Diagnosis and management of thrombosis in critically ill patients with COVID-19

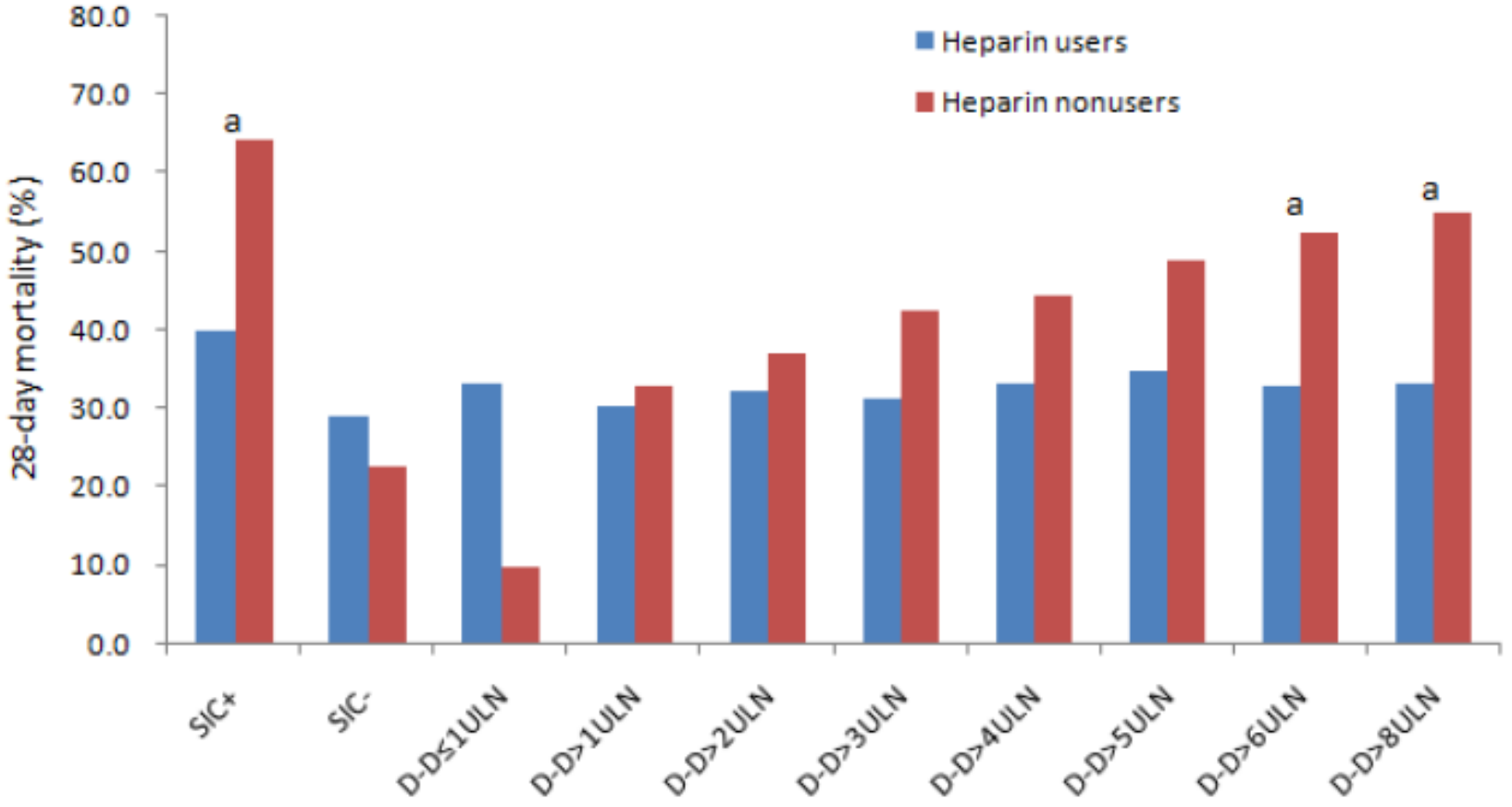
Nicole Juffermans

Laboratory of Experimental Intensive Care and Anesthesiology (L.E.I.C.A.)

of the Amsterdam Univeristy Medical Center and

Department of Intensive Care Medicine, OLVG Hospital

Use of heparin associated with lower mortality in COVID-19



Patient type?
Dose?
VTE or not?

Tang, 27th March JTH

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

Symptomatic approach. 184 patients; incidence 31%

Type of event	Number of cases	Relevant details
Pulmonary embolism	25	– 18 cases with at least PE in segmental arteries, 7 cases PE limited to subsegmental arteries
Other venous thromboembolic events	3	– 1 proximal deep-vein thrombosis of the leg – 2 catheter related upper extremity thrombosis
Arterial thrombotic events	3	– All ischemic strokes

Klok, Thromb Res 5th April

preprints.org > medicine & pharmacology > general medical research > doi: 10.20944/preprints202004.0345.v1

Preprint **Article** *Version 1* This version is not peer-reviewed

Incidence of Venous Thromboembolism in Hospitalized Patients with COVID-19

Version 1 : Received: 18 April 2020 / Approved: 19 April 2020 / Online: 19 April 2020 (13:08:16 CEST)

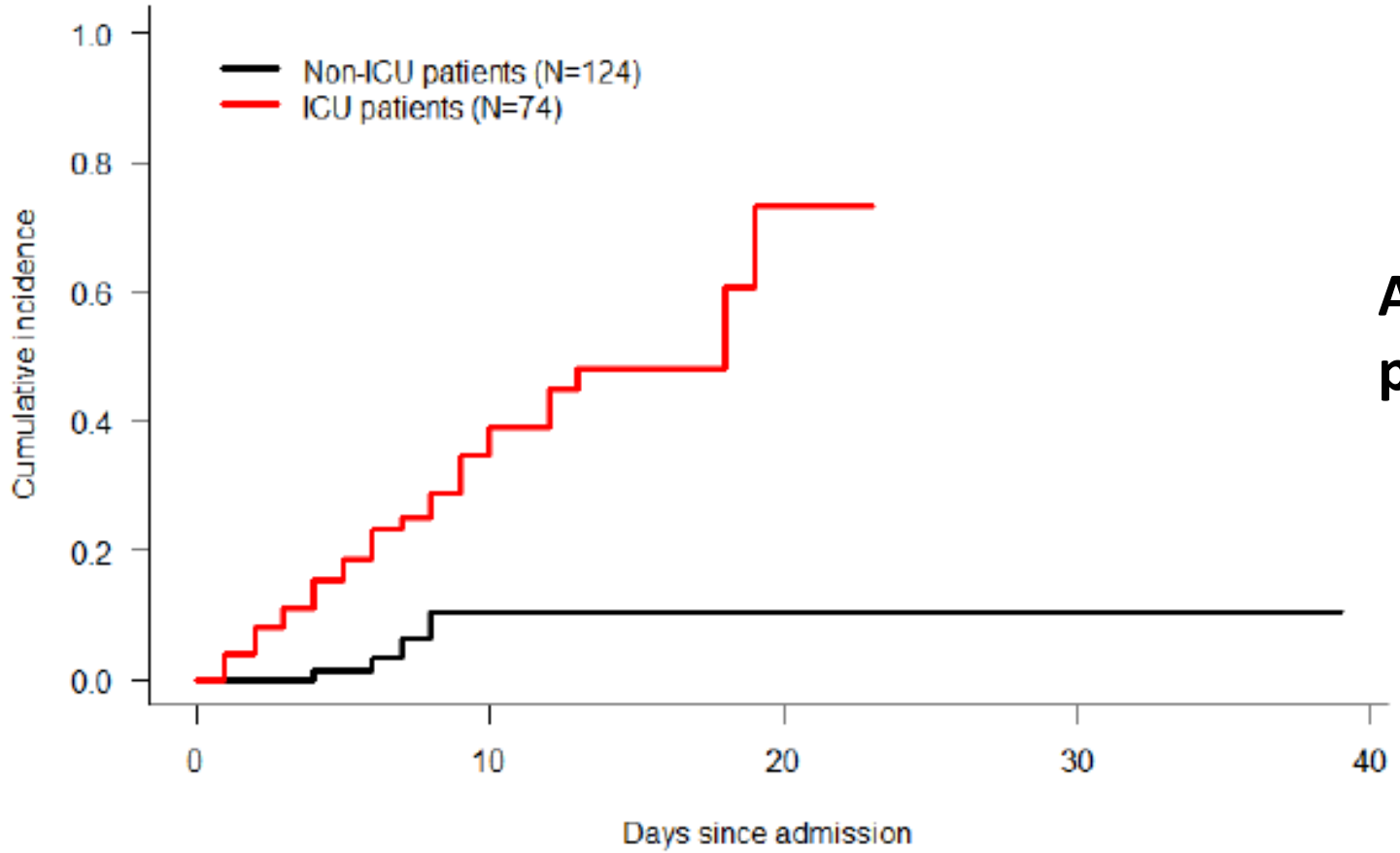
Screening approach

	All patients (N=198) n (%)	ICU patients (N=74) n (%)	Patients in wards (N=124) n (%)
Venous thromboembolism	33 (17)	29 (39)	4 (3.2)
Pulmonary embolism	11 (5.6)	9 (12)	2 (1.6)
Central or lobar	0	0	0
Segmental	9 (4.5)	8 (11)	1 (0.8)
Subsegmental	2 (1.0)	1 (1.4)	1 (0.8)
Deep-vein thrombosis	22 (11)	20 (27)	2 (1.6)

Amsterdam UMC
Universitair Medische Centra

Middeldorp, Preprint 18th April

Incidence of VTE in ICU increases over time

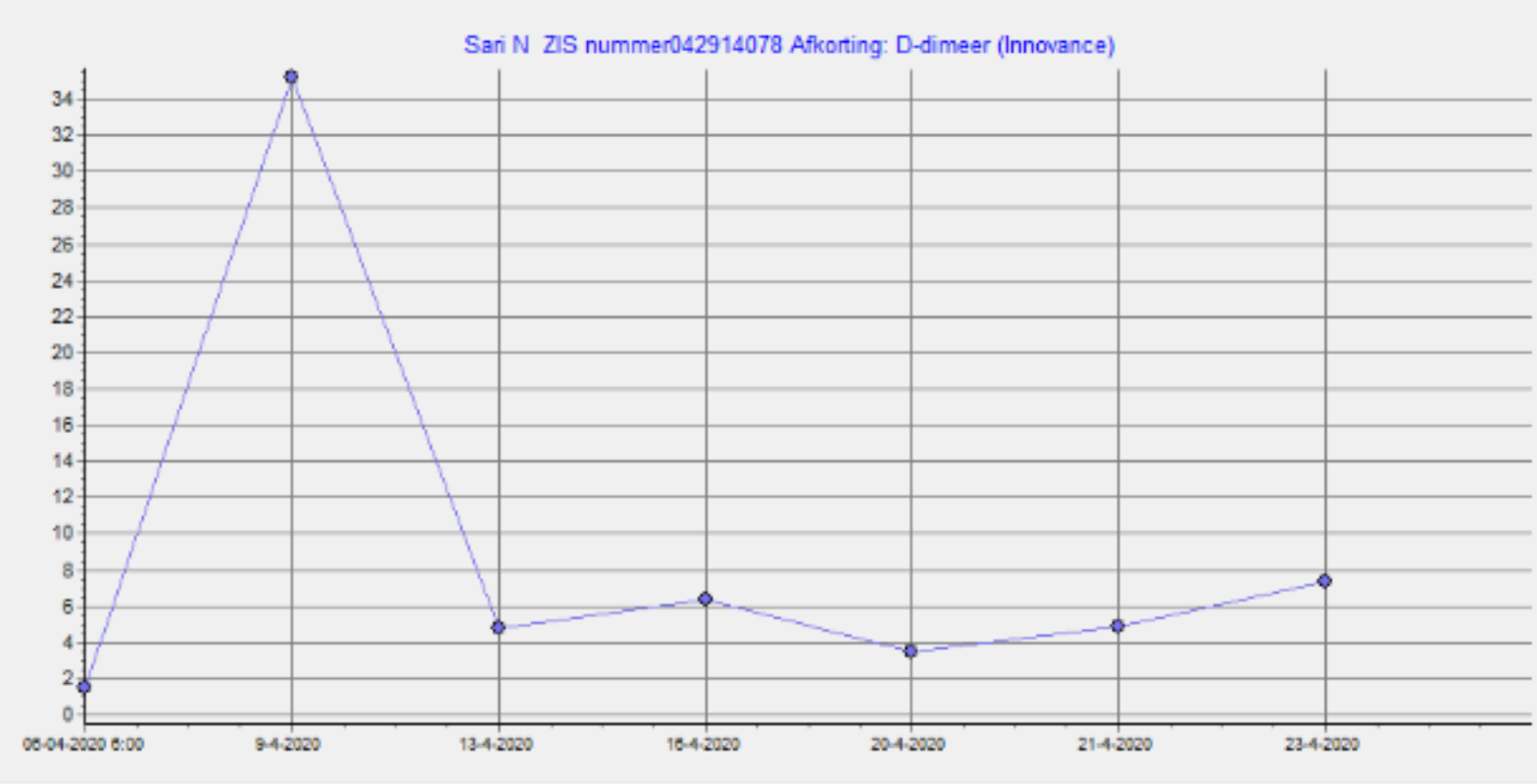


All patients were on prophylactic LMWH

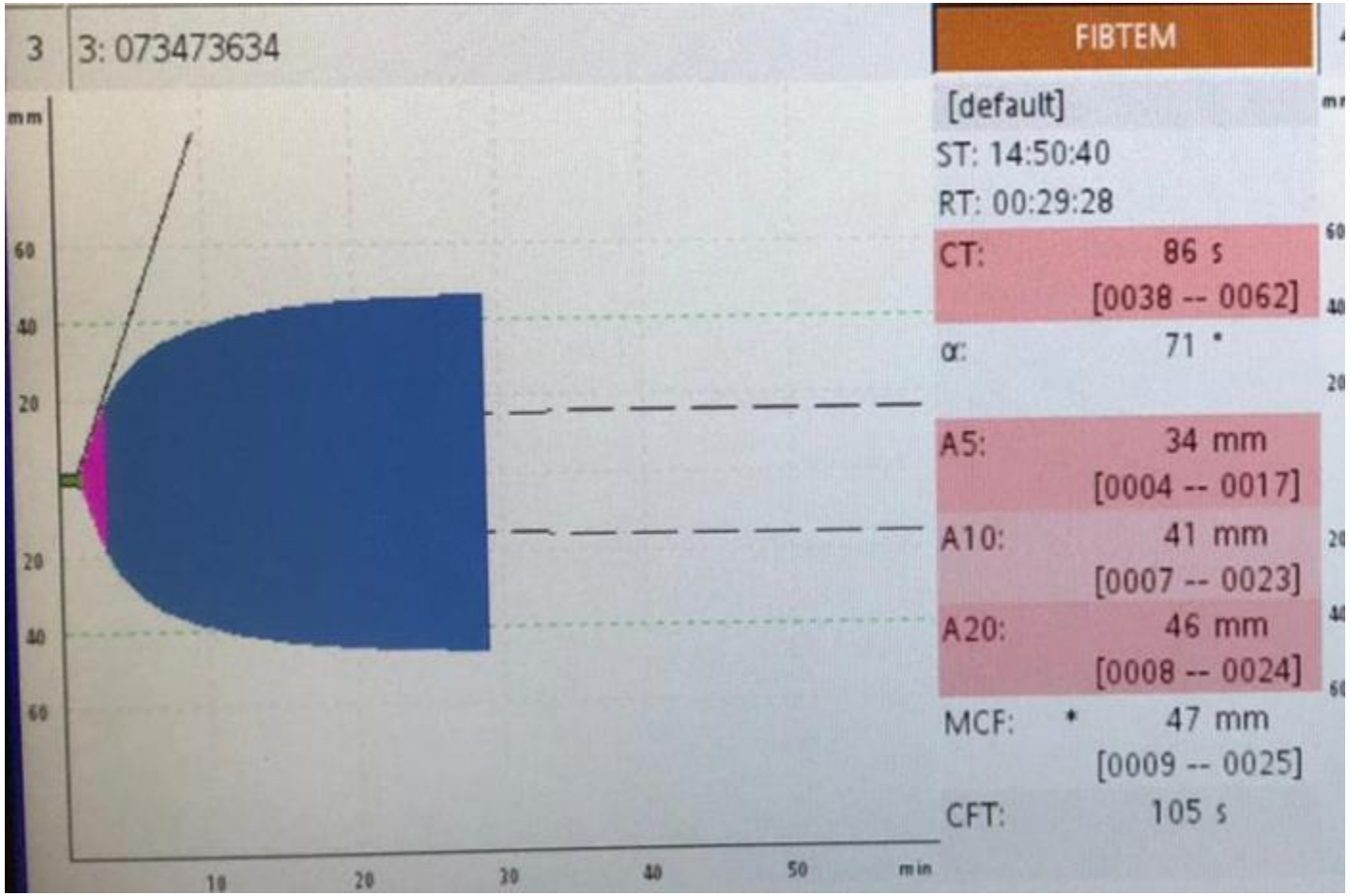
Give prophylactic heparin.
To everybody with COVID.

Data hidden at the request of the presenter.

Diagnosis of VTE. Is D-dimer helpful?



Visco elastic test helpful in diagnosis?



Visco elastic testing in 16 COVID patients: concordance with other tests

Standard tests	Normal range	Baseline
aPTT (sec)	24 – 35	36.4 (29-41.6)
INR		1.08 (0.98-1.11)
Fibrinogen (mg/dL)	200 - 400	794 (583-933)
Platelet count (x1,000 cells/µL)	150 - 450	271 (192-302)
Antithrombin (%)	80 - 120	85 (65-91)
D-dimer (µg/mL)	< 0.5	3.5 (2.5-6.5)
Interleukin-6 (pg/mL)	0 - 10	218 (116-300)

Viscoelastic tests	Normal range	Baseline
Clotting time (sec)	103 - 153	139 (133-155)
Clot strenght (hPa)	13 - 33.2	55 (35-63)
Platelet contribution to clot strength (hPa)	11.9 – 20.8	43 (24-45)
Fibrinogen contribution to clot strength (hPa)	1 – 3.7	12 (6-13.5)

Ranucci , 17th April JTH

Coag tests improve (in time) with increasing dose of LMWH and adding clopidogrel

Standard tests	Normal range	Baseline	Follow-up 7 days	P
aPTT (sec)	24 – 35	36.4 (29-41.6)	44.1 (42.1-47.4)	0.012
INR		1.08 (0.98-1.11)	1.13 (1.08-1.19)	0.500
Fibrinogen (mg/dL)	200 - 400	794 (583-933)	582 (446-621)	0.001
Platelet count (x1,000 cells/µL)	150 - 450	271 (192-302)	320 (308-393)	0.463
Antithrombin (%)	80 - 120	85 (65-91)	107 (81-130)	0.018
D-dimer (µg/mL)	< 0.5	3.5 (2.5-6.5)	2.5 (1.6-2.8)	0.017
Interleukin-6 (pg/mL)	0 - 10	218 (116-300)	-	-

Viscoelastic tests	Normal range	Baseline	Follow-up 14 days	P
Clotting time (sec)	103 - 153	139 (133-155)	135 (125-151)	0.058
Clot strenght (hPa)	13 - 33.2	55 (35-63)	34 (17-54)	0.013
Platelet contribution to clot strength (hPa)	11.9 – 20.8	43 (24-45)	29 (14-44)	0.035
Fibrinogen contribution to clot strength (hPa)	1 – 3.7	12 (6-13.5)	6.2 (3-9.9)	0.038

Heparin resistance in COVID-19

- Due to large amounts of acute phase reactants (fibrinogen !)
- Increased factor VIII levels
- (low levels of AT but in COVID-19 these are always > 80%)

- If > 25IE/kg/hr heparine and no prolongation of APTT: monitor on antiXa.
- Target (top) antiXa between 0.3-0.7 IE/ml

tPA in COVID? Case series of 3 patients

- 2 x 25 mg Alteplase, while withholding heparin.
- Transient increase in P/F ratio, returning to baseline within hours
- No bleeding events

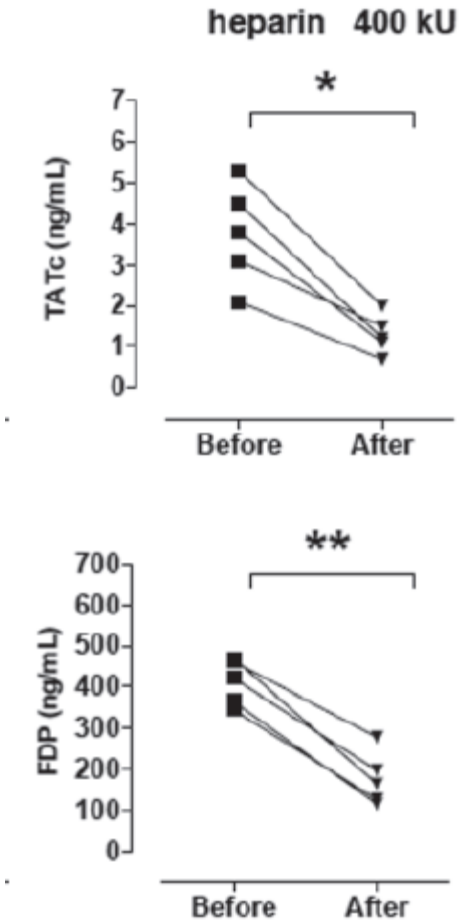
- Higher dose? Combine with heparin?

Wang, 8th April JTH

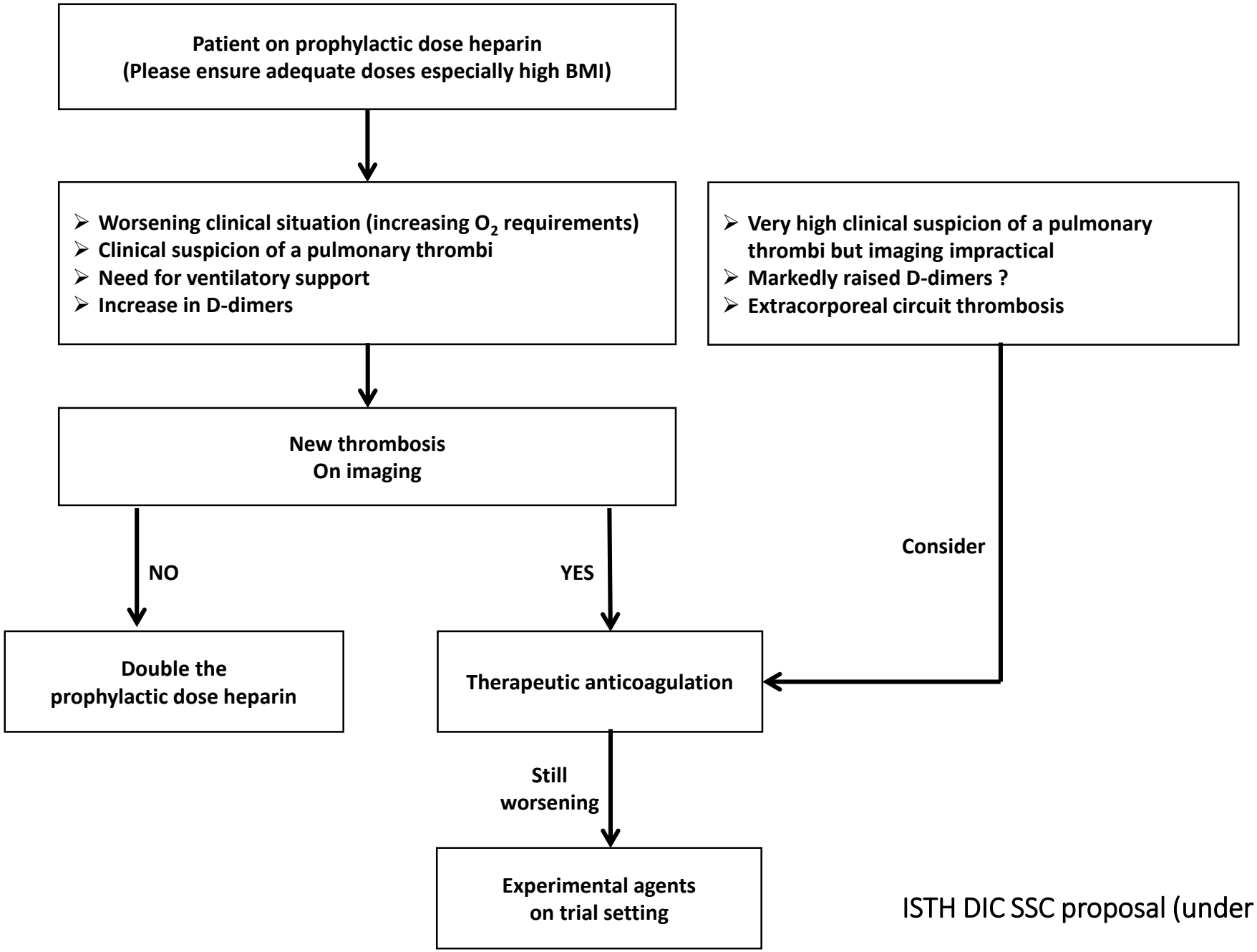
LETTER

Nebulized heparin reduces levels of pulmonary coagulation activation in acute lung injury

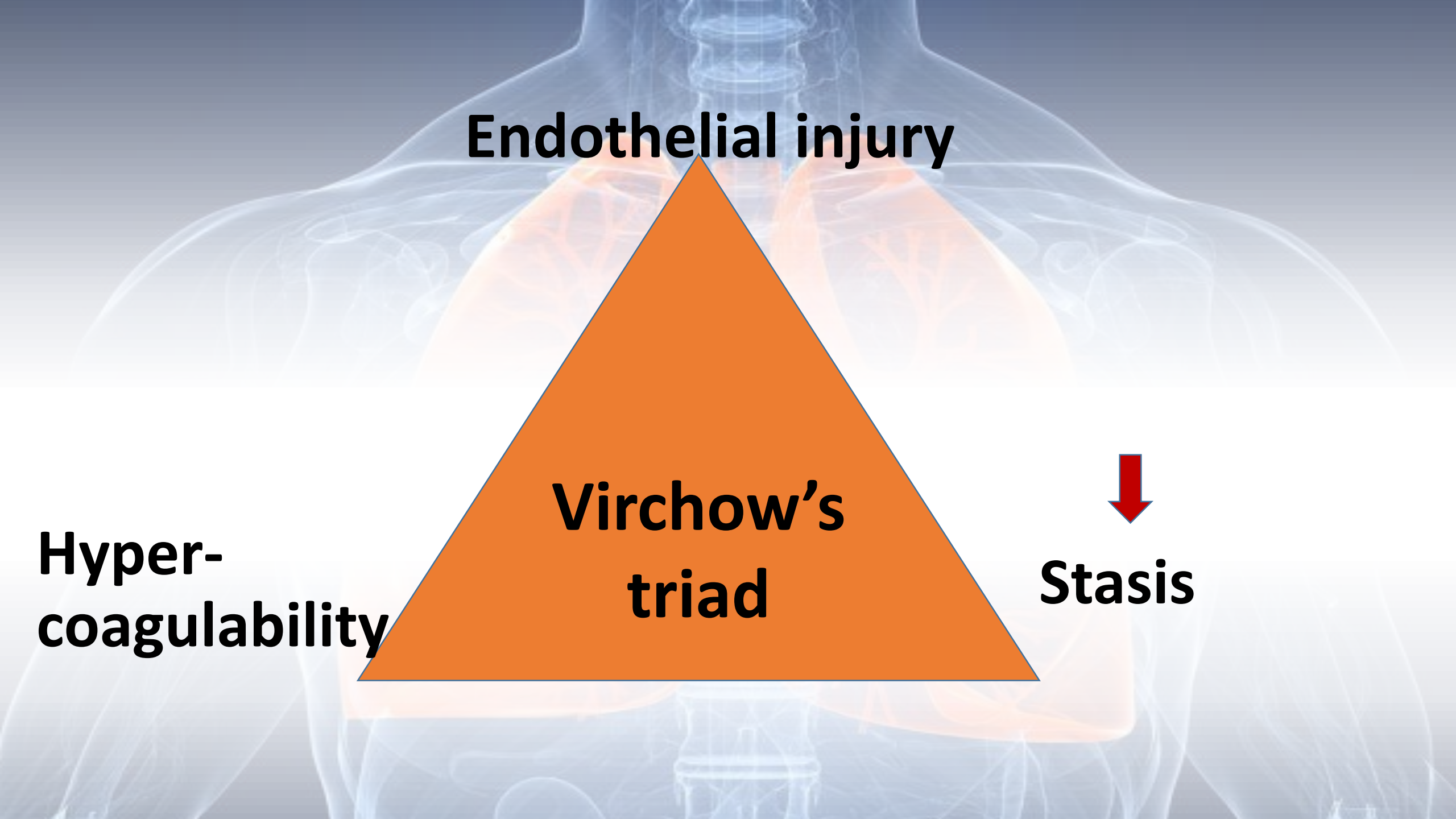
Barry Dixon*[1], Marcus J Schultz[2], Jorrit J Hofstra[2], Duncan J Campbell[3,4] and John D Santamaria[1]



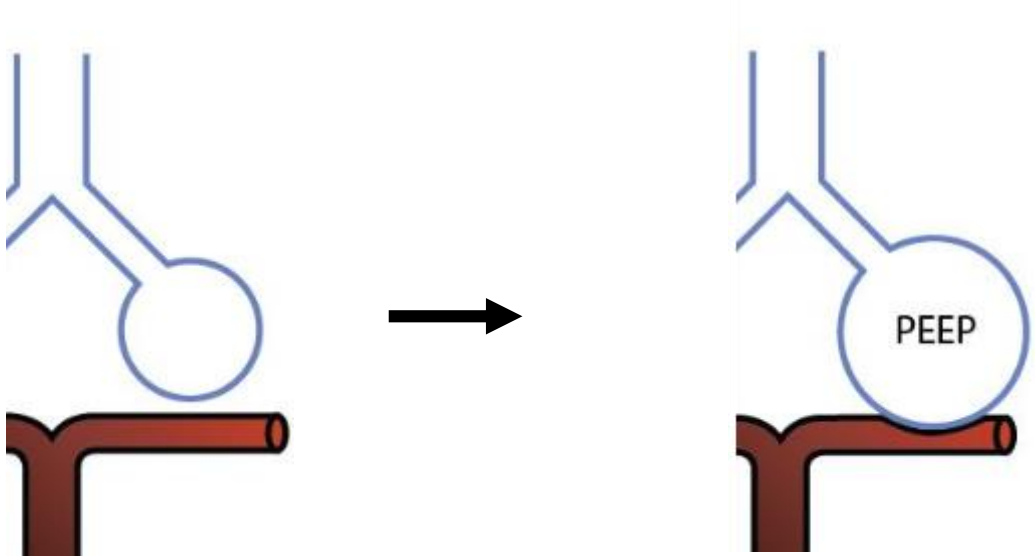
Dixon, Crit Care 2010



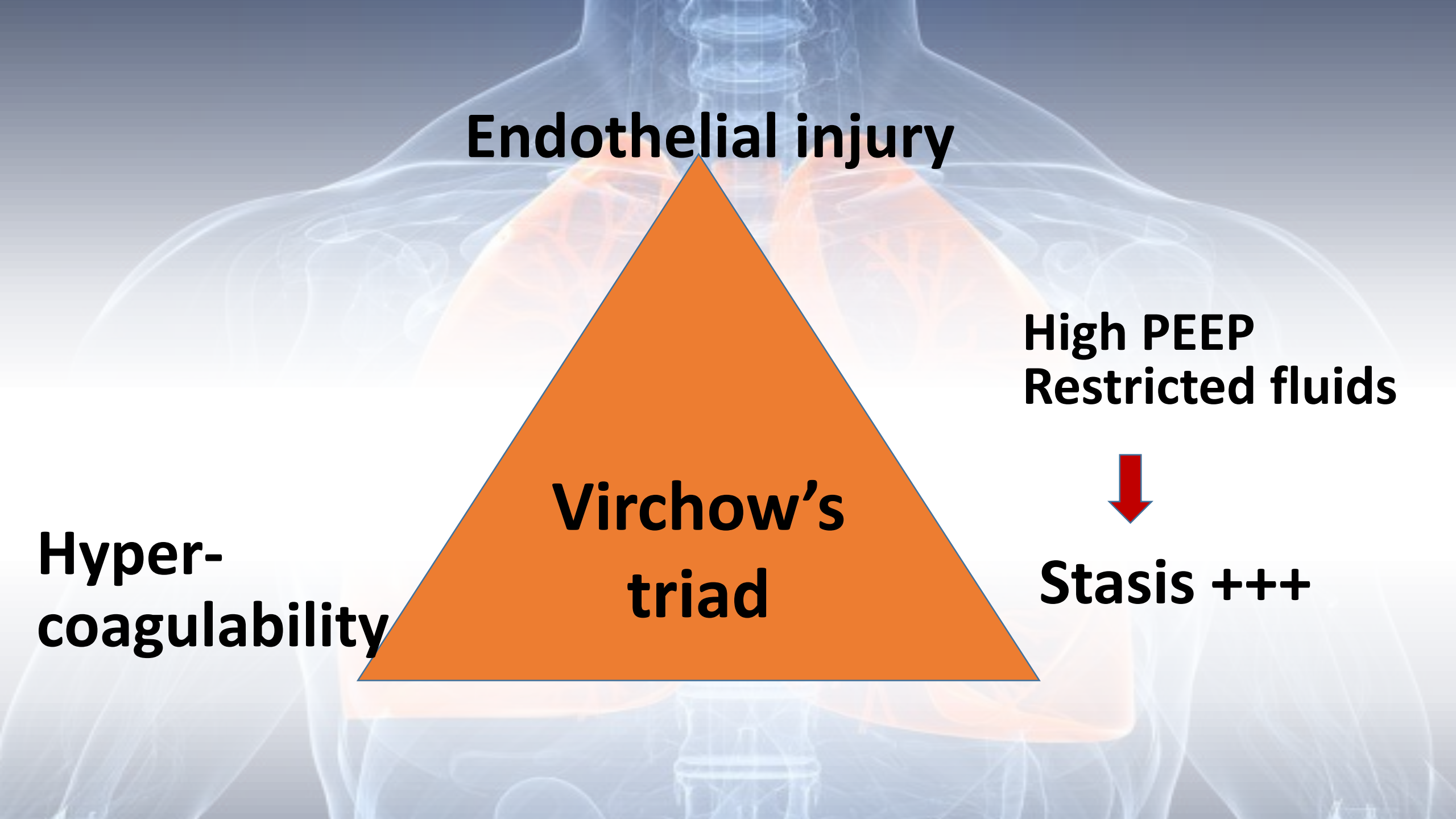
ISTH DIC SSC proposal (under review)

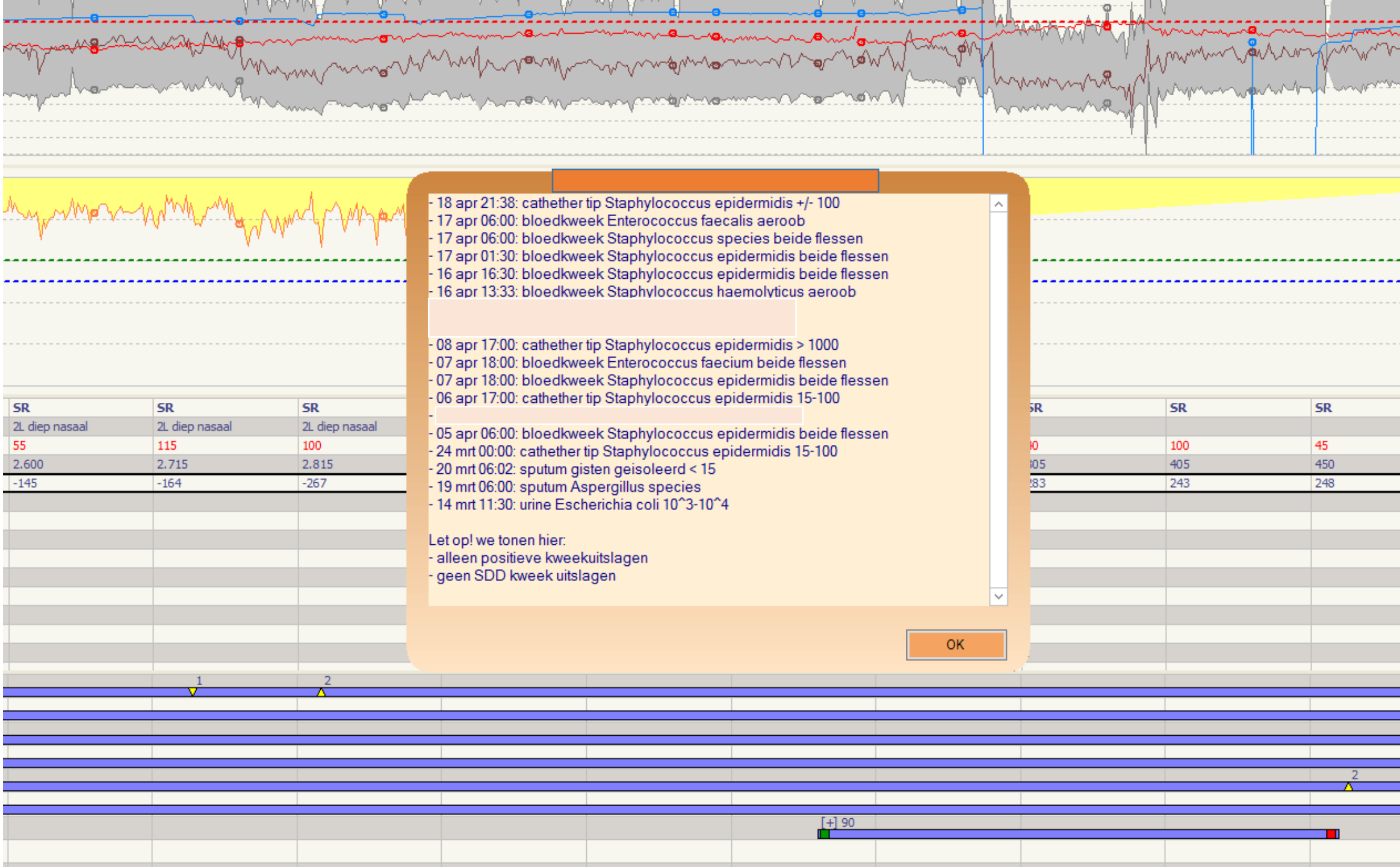

Endothelial injury
Virchow's triad
Hyper-coagulability
Stasis

ARDS: PEEP improves oxygenation, but also increases intrathoracic pressure

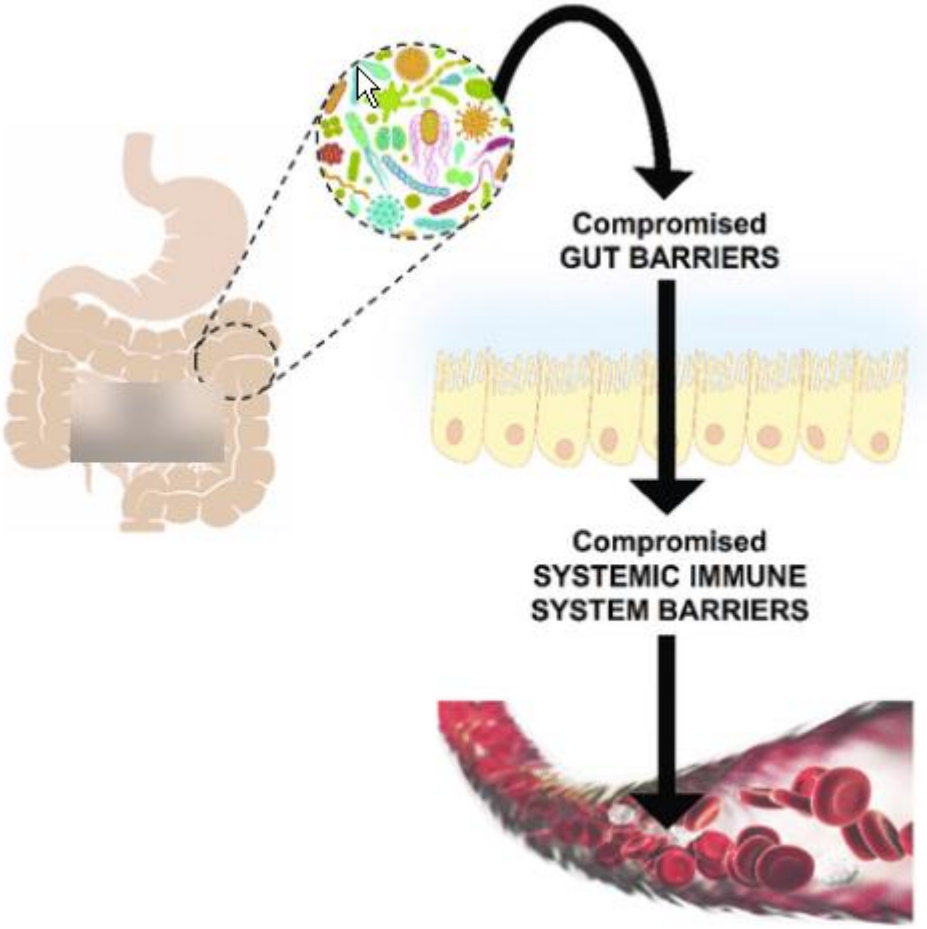


pulmonary perfusion ↓


Endothelial injury
Virchow's triad
High PEEP
Restricted fluids
Stasis +++
Hyper-coagulability


- 18 apr 21:38: cathether tip Staphylococcus epidermidis +/- 100
- 17 apr 06:00: bloedkweek Enterococcus faecalis aeroob
- 17 apr 06:00: bloedkweek Staphylococcus species beide flessen
- 17 apr 01:30: bloedkweek Staphylococcus epidermidis beide flessen
- 16 apr 16:30: bloedkweek Staphylococcus epidermidis beide flessen
- 16 apr 13:33: bloedkweek Staphylococcus haemolyticus aeroob
- 08 apr 17:00: cathether tip Staphylococcus epidermidis > 1000
- 07 apr 18:00: bloedkweek Enterococcus faecium beide flessen
- 07 apr 18:00: bloedkweek Staphylococcus epidermidis beide flessen
- 06 apr 17:00: cathether tip Staphylococcus epidermidis 15-100
- 05 apr 06:00: bloedkweek Staphylococcus epidermidis beide flessen
- 24 mrt 00:00: cathether tip Staphylococcus epidermidis 15-100
- 20 mrt 06:02: sputum gisten geisoleerd < 15
- 19 mrt 06:00: sputum Aspergillus species
- 14 mrt 11:30: urine Escherichia coli 10^3-10^4
Let op! we tonen hier:
- alleen positieve kweekuitslagen
- geen SDD kweek uitslagen
OK
SR
2L diep nasaal
55
2.600
-145
SR
2L diep nasaal
115
2.715
-164
SR
2L diep nasaal
100
2.815
-267
SR
100
405
243
SR
45
450
248
1
2
2
[+] 90

Bacterial translocation in COVID, resulting in infected thrombi?



Viral gastro-enteritis
(Shock)

Post viral immune paralysis ?

Low amount of CFU
can grow in thrombi ?

To summarize

- Give prophylaxis to everybody with COVID
- Consider double dose of prophylaxis in ICU
- Have a low threshold for CT imaging. Consider screening with US.
- Ddimer can be useful for monitoring but no clear cut off value known
- In case of heparin resistance, monitor with anti Xa levels
- In patients with PE, consider a PEEP trial
- In patients with VTE and persistent fever, look for infected thrombi