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Morning Brief : Scientific Review

17 June 2020

The purpose of the Morning Brief is to summarize and present key information, research articles and other relevant publications pertaining to critical care and COVID-19.

Stellenbosch University Research Response Team

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Content

Statistics
Topic: Coagulopathy

JOHNS HOPKINS UNIVERSITY & MEDICINE | CORONAVIRUS RESOURCE CENTER

Home | Maps & Trends | Testing | Tracing | News & Information | COVID-19 Basics | Videos & Live Events

World Map | U.S. Map | Critical Trends

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

Total Confirmed

8,075,962

Confirmed Cases by Country/Region /Sovereignty

- 2,119,912 US
- 888,271 Brazil
- 544,725 Russia
- 343,091 India
- 299,594 United Kingdom
- 244,328 Spain
- 237,500 Italy
- 232,992 Peru
- 194,305 France
- 192,439 Iran

Admin0 | Admin1 | Admin2

Last Updated at (M/D/YYYY)
6/16/2020, 6:33:16 PM

Esri, FAO, NOAA

Cumulative Confirmed Cases | Active Cases | Incidence Rate | Case-Fatality Ratio | Testing Rate | Hospitalization Rate

188
countries/regions

Lancet Inf Dis Article: Here. Mobile Version: Here.
Lead by JHU CSSE. Technical Support: Esri Living Atlas team and JHU APL. Financial Support: JHU and NSF. Click *here* to **donate** to the CSSE dashboard team, and other JHU COVID-19 Research

Global Deaths

438,171

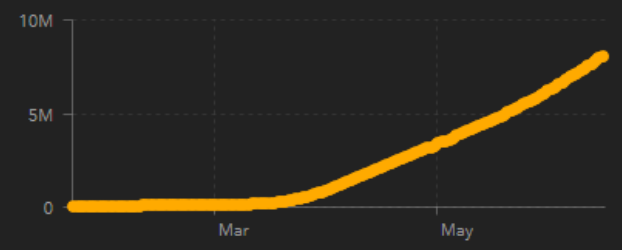
- 116,341 deaths US
- 43,959 deaths Brazil
- 42,054 deaths United Kingdom
- 34,405 deaths Italy
- 29,439 deaths France

Global Deaths

US State Level
Deaths, Recovered

- 30,856 deaths, 68,851 recovered New York US
- 12,708 deaths, 28,819 recovered New Jersey US
- 7,647 deaths, recovered Massachusetts US
- 6,326 deaths, recovered Illinois US

US Deaths, Recove...



Confirmed | Logarithmic | Daily Cases

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1 148 933	73 533	39 867	1 568	3 495
TESTS CONDUCTED	POSITIVE CASES IDENTIFIED	TOTAL RECOVERIES	TOTAL DEATHS	NEW CASES

MONDAY 15 JUNE 2020

Province	Deaths	Recoveries
Eastern Cape	236	5331
Free State	9	222
Gauteng	87	3348
KwaZulu Natal	69	1810
Limpopo	4	199
Mpumalanga	1	138
North West	5	152
Northern Cape	1	52
Western Cape	1156	28615
Total	1568	39867

Age Distribution Deaths:

Age	Deaths	Percentage
0-9	3	0,2
10-19	5	0,3
20-29	21	1,3
30-39	94	6,0
40-49	200	12,8
50-59	386	24,6
60-69	422	27,0
70-79	272	17,3
80-89	122	7,8
90-99	35	2,2
Uknown	8	0,5
1568	100	

Western Cape Government

Number of COVID-19 Cases in the Western Cape

1165	30236	43602	710	248739
Total Deaths	Total Recovered*		Last 24 Hours*	Tests Done

WC Department of Health
Last Updated:
Tuesday, June 16, 2020
13:00

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RECOVERY
Randomised Evaluation of COVID-19 Therapy

HOME FOR PATIENTS FOR SITE STAFF RESULTS NEWS

Results

Results

In March 2020, the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone (a steroid treatment). Over 11,500 patients have been enrolled from over 175 NHS hospitals in the UK.

On 8 June, recruitment to the dexamethasone arm was halted since, in the view of the trial Steering Committee, sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit.

A total of 2104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomised to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).

Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).

Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.

PRESS RELEASE

16 June 2020

Statement from the Chief Investigators: low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

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Current background

- COVID-19-associated coagulopathy (CAC) - Anticoagulation data emerging fast
- Much discussion & debate currently around antiplatelets as directed therapy for COVID-19
  - Mostly for improvement of oxygenation
  - Several hypotheses regarding pulmonary and systemic thrombi

Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study

Luca Carsana, Aurelio Sonzogni, Ahmed Nasr, Roberta Simona Rossi, Alessandro Pellegrinelli, Pietro Zerbi, Roberto Rech, Riccardo Colombo, Spinello Antinori, Mario Corbellino, Massimo Galli, Emanuele Catena, Antonella Tosoni, Andrea Gianatti, Manuela Nebuloni

Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum

Geoffrey D. Barnes[1] · Allison Burnett[2] · Arthur Allen[3] · Marilyn Blumenstein[4] · Nathan P. Clark[5] · Adam Cuker[6] · William E. Dager[7] · Steven B. Deitelzweig[8] · Stacy Ellsworth[9] · David Garcia[10] · Scott Kaatz[9] · Tracy Minichiello[11]

COVID-19 update: Covid-19-associated coagulopathy

Richard C. Becker[1]

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Pharmacological Research 158 (2020) 104950

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study

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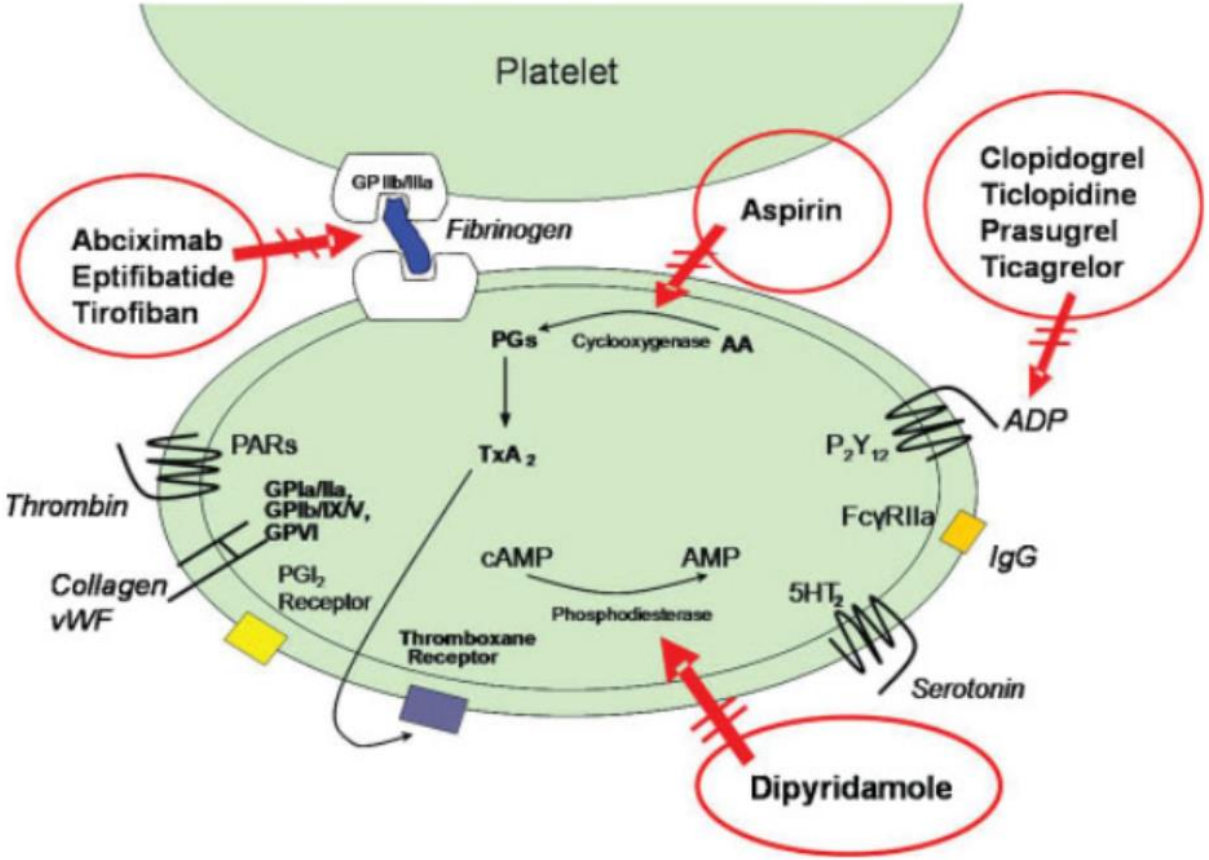
Background & Hypothesis

- Study hypothesis
  - Tirofiban + dual antiplatelet therapy (DAPT) beneficial to improve oxygenation and outcomes
  - Severe COVID-19 + confirmed prothrombotic state (D-dimer ≥ 3x ULN)



Walenga JM et al. Nonhemostatic adverse effects of anticoagulants and antiplatelet agents. Seminars in thrombosis and hemostasis 2012 Nov; 38(8):884-892.

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Design

- Design
  - Investigator-initiated, single center, compassionate use, phase IIb, open-label, case control, proof of concept
  - Respiratory Care Unit in Milan, Italy

- Inclusion criteria
  - Hospitalised
  - Severe hypoxaemic respiratory failure (P/F ratio < 250) requiring helmet continuous positive airway pressure (CPAP)
  - Bilateral pulmonary infiltrates
  - Laboratory confirmed positive nasal swab for SARS-CoV-2
  - D-dimer value ≥ 3 ULN

- Controls
  - Hospitalised patients with COVID-19-related pneumonia and severe respiratory failure
  - Matched for age, D-dimer value and Sequential Organ Failure Assessment (SOFA) Score

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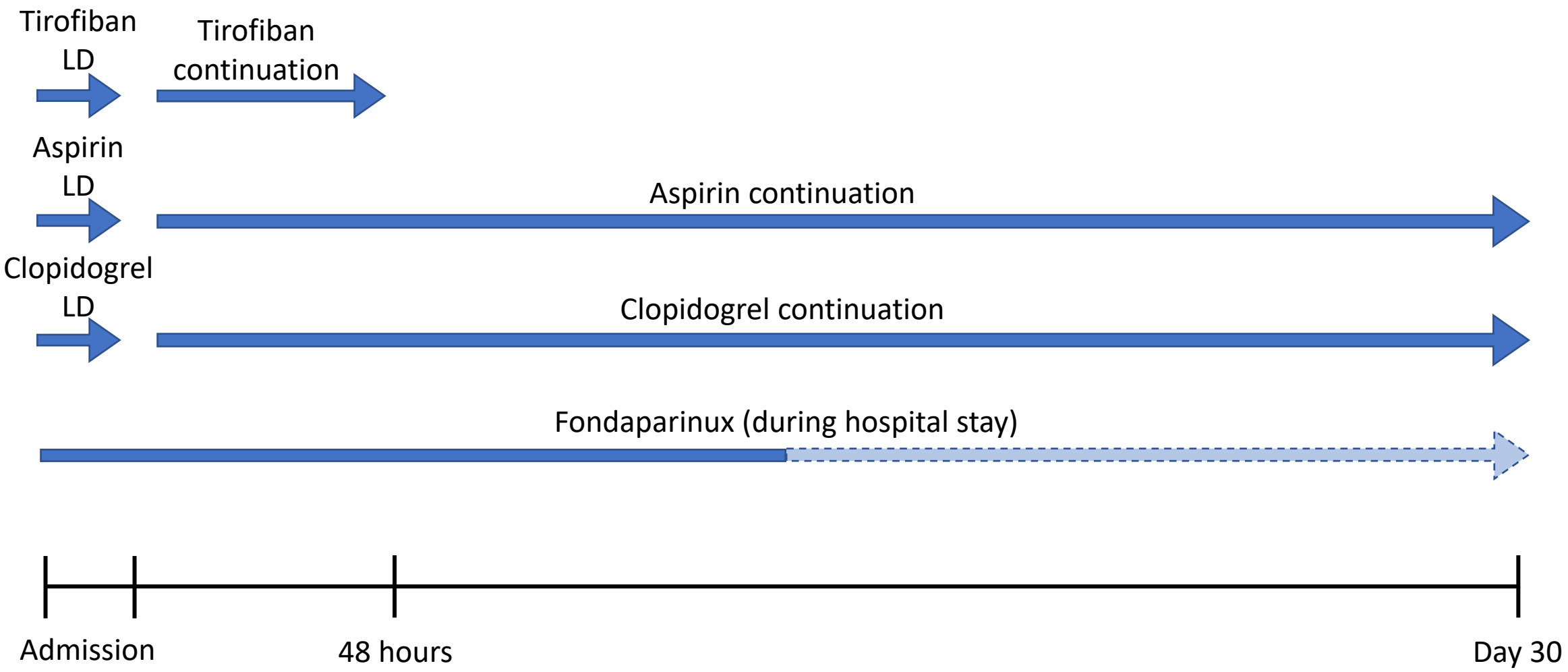
Interventions

Matched controls received prophylactic or therapeutic dose of LMWH according to local standard of care



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Other characteristics

- Comorbidities:
  - Cancer
  - Type II DM
  - Hypertension
  - Obesity
  - Asthma
  - COPD

Relating to cases. Not reported for controls.

- Other treatments:
  - Hydroxychloroquine
  - Steroids

Relating to 1 case. Not reported for controls.

- DVT & PE ruled out before enrolment
- No patients were on antiplatelets or NSAIDs

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Outcomes

- Primary outcomes
  - Effects of antiplatelets on hypoxaemia
  - Clinical outcomes

- Co-primary exploratory outcomes after 1, 2, & 7 days
  - Change in PaO_2
  - Change in P/F ratio
  - Change in arterial/alveolar oxygen gradient (A-a O_2)

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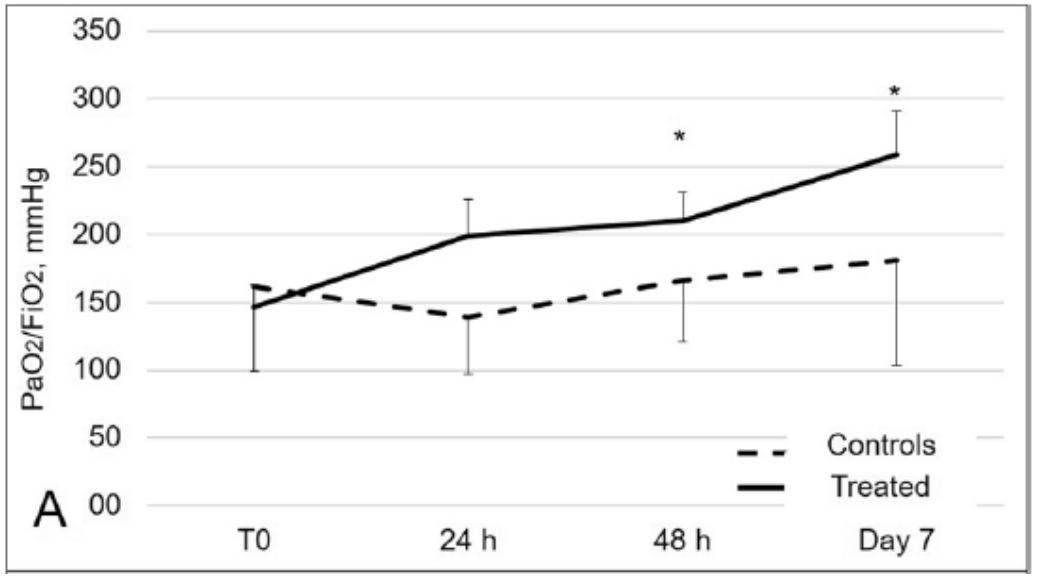
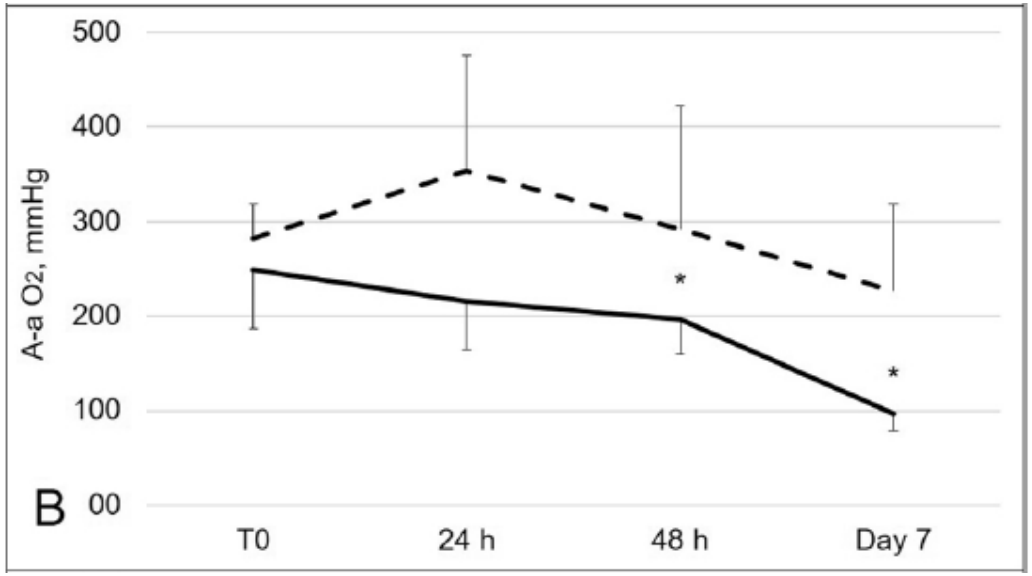
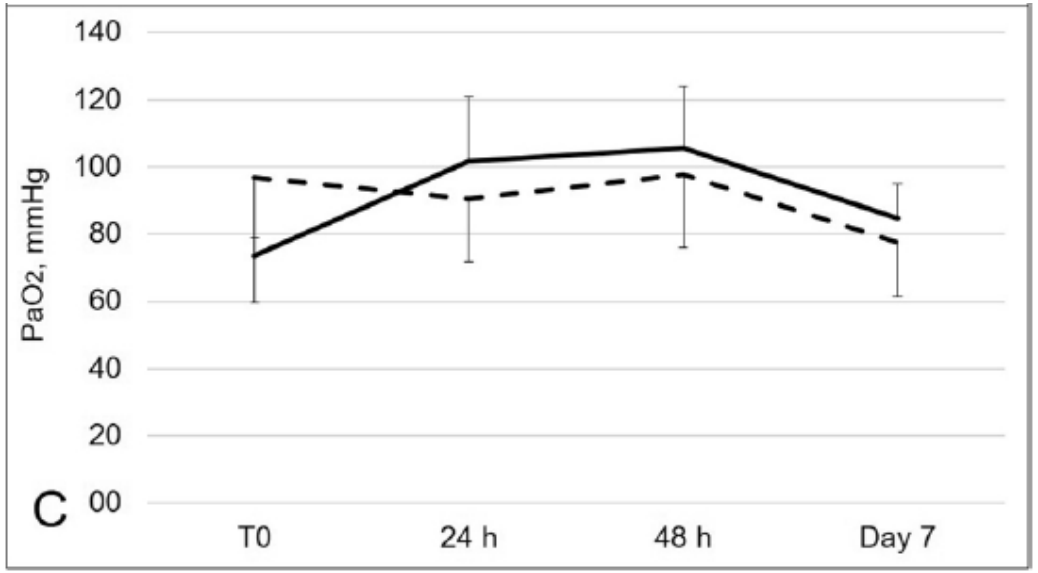
Results







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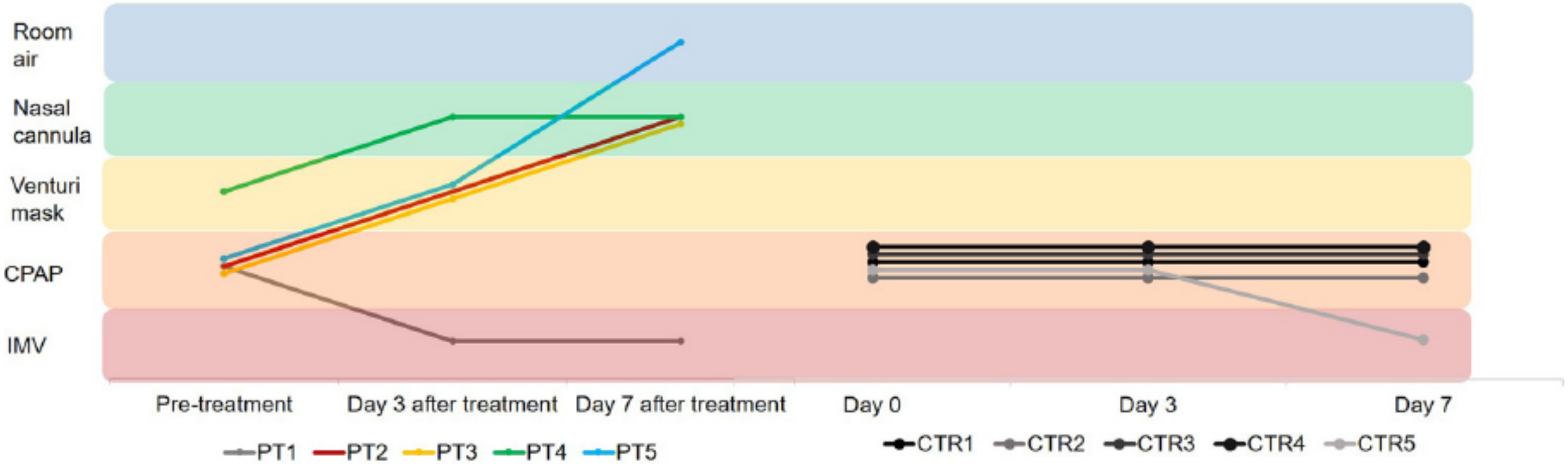
Results



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Results

- 30-day outcome
  - 4/5 patients were discharged without major or minor AEs
  - 1/5 patient died in-hospital

- Effect hypothesis
  - Aspirin & clopidogrel impede consolidation of forming thrombi (predominantly affecting **platelet activation**)
  - Tirofiban might prevent formation of newly assembling clots promoted by the dysfunctional endothelium of lung capillaries (predominantly affecting **platelet aggregation**)

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Limitations

- Very small sample size (compassionate use) → Stats of limited use
- Selection bias
- Not all moderate-severe COVID-19 patients will have hypercoagulable state
  - Authors note that triple antiplatelet therapy must be weighed against bleeding risk
- Demographics similar, but baseline bloods differed in absolute terms for esp. CRP (62 vs 150 mg/L) and D-dimer (3038 vs 4038 mcg/L) for intervention vs controls, respectively
  - CRP ↓ in both groups by 7 days, but only treatment group D-dimer ↓ by 7 days (↑ in controls)
- Controls did not receive the same anticoagulation (Fondaparinux vs LMWH) or indication doses (treatment vs prophylactic doses)

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Conclusions

- Well conducted trial with pragmatic design as proof-of-concept

- Small sample size does not allow for statistical interpretation
- But study highlights need for urgent further research into role of antiplatelets
- Even with triple antiplatelet therapy, no significant drop in platelet count compared to baseline or controls
- Addition of anticoagulant did not result in clinical bleeding during stay or at 30 day F/U

- Cannot currently recommend antiplatelets ± anticoagulants to all COVID-19 patients, as risk/benefit ratio might be skewed in less severe cases

- We urgently need larger RCTs to evaluate role and patient selection of antiplatelets + anticoagulants in moderate-severe COVID-19

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References

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This summary was prepared by Dr Roland van Rensburg as part of the daily brief to the TBH ICU team.