Hospital and ICU management of COVID-19

- This webinar will start at 8.30pm IST / 4pm UK.
- You can watch the recording on the AHSN Network and SAHF YouTube channels afterwards.
- Please use the chat to submit your questions.

Panellists

- **Dr Sanjay Bhagani,** Consultant Physician/Associate Professor, Royal Free Hospital

- **Professor Ramani Moonesinghe,** National Clinical Director for Critical and Perioperative Care, NHSE England/NHS Improvement. Honorary Consultant in Anaesthesia and Perioperative Medicine, University College Hospital

- **Professor Kamlesh Khunti,** Professor of Primary Care Diabetes & Vascular Medicine, GP and SAHF Trustee

- **Professor Wasim Hanif,** Professor of Diabetes & Endocrinology, Consultant Physician, & Head of Service and SAHF Trustee

- **Dr Pratima Chowdary,** Consultant Haematologist, Royal Free Hospital

- **Dr Tara Sood,** Consultant, Royal Free Hospital and National Clinical Lead – Same Day Urgent Care

- **Dr Nikhil Tandon,** Consultant Endocrinologist and Head of Department of Endocrinology, Metabolism and Diabetes at All India Institute of Medical Sciences (AIIMS).

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UK-INDIA COVID-19 RESPONSE

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Welcome

The webinar is about to begin.

Dr Harpreet Sood

GP and SAHF Trustee

Overview of webinar

- Hospital therapies for COVID-19
- Glycaemic management
- ICU management
- Anticoagulation therapy
- Question and answer session

Hospital management of COVID-19

Dr Nikhil Tandon

Professor and Head Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, New Delhi

Moderate disease
RR ≥ 24 / breathlessness
SpO2: 90% to ≥ 93% on room air

Admit in ward:

- *Oxygen Support*
  - Target SpO2: 92-96%
  - Preferred device: Non-rebreathing face mask
  - Awake proning
- *Anti-inflammatory or immunomodulatory therapy*
  - Inj Methylpred 0.5-1 mg/kg in 2 doses
- *Anti-coagulation*
  - Conventional dose prophylactic unfractionated heparin or LMWH (e.g 0.5 mg/kg/d enoxaparin)

Monitoring

- *Clinical*:
  - work of breathing; haemodynamic stability; change in O_2 requirement
- *Radiology*:
  - Serial CXR; HRCT – only if worsening
- *Lab monitoring*:
  - CRP, D-dimer (48-72 hrly)
  - CBC, KFT, LFT (24-48 hrly)
  - IL-6 in case of deterioration (subject to availability)

https://www.icmr.gov.in/pdf/covid/techdoc/COVID19_Management_Algorithm_22042021_v1.pdf

EUA / Off-label use (Specific circumstances)

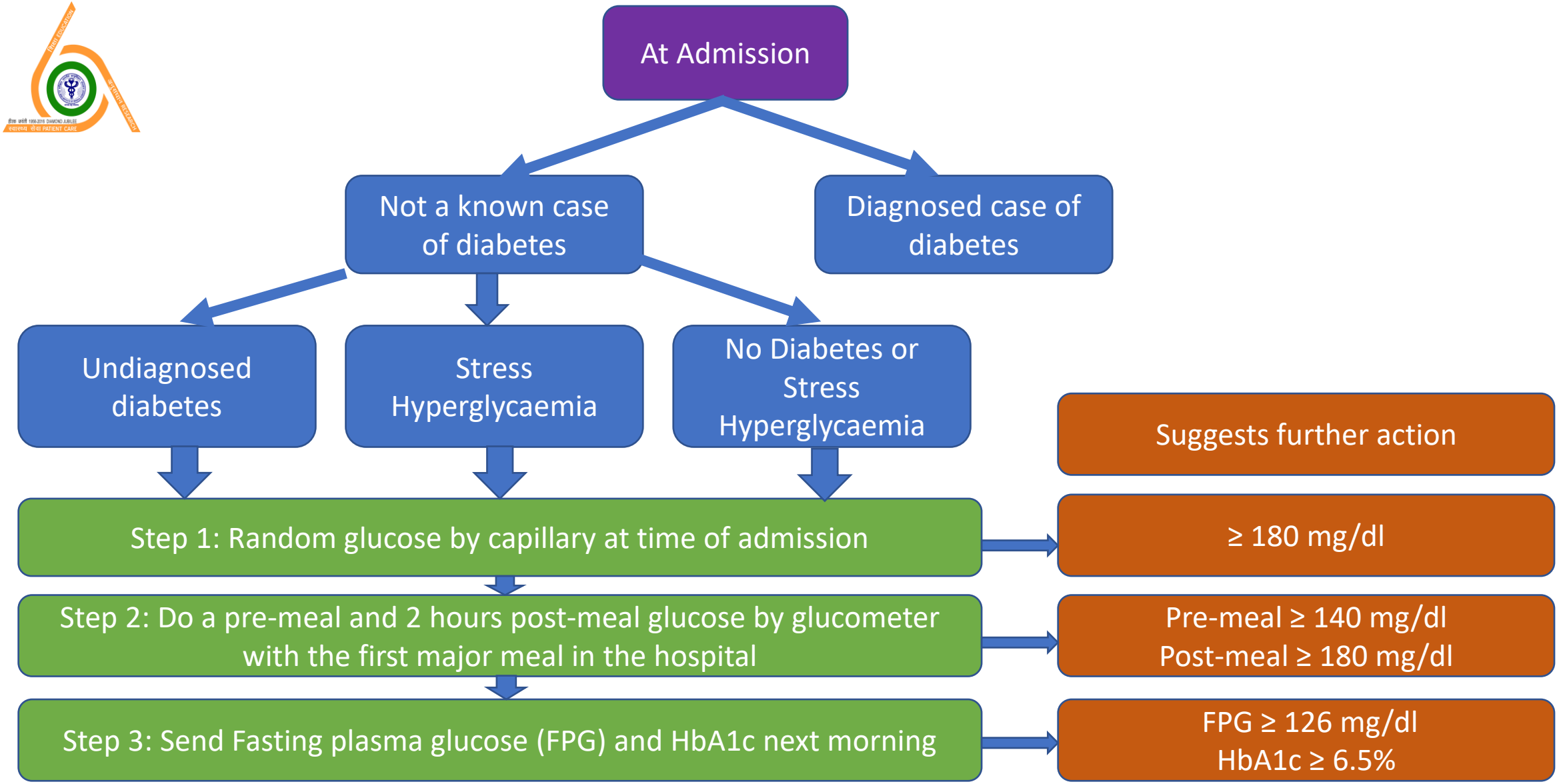
- **Remdesivir (EUA)** – to be considered ONLY in patients with
  - Moderate-severe disease requiring supplemental oxygen
  - No renal / hepatic dysfunction [eGFR < 30; AST/ALT > 5x ULN] **AND**
  - Within 10 days of symptom onset

- **Tocilizumab (Off-label)** – consider when **ALL** criteria listed below are met:
  - Severe disease (preferably within 24-48 hrs of onset)
  - Significantly elevated inflammatory markers: CRP, IL-6
  - Not improving despite steroids

- **Convalescent plasma (Off label)** – when ALL following criteria are met:
  - Early moderate disease (within 7 days of symptom onset)
  - Availability of high titre donor plasma (signal: cut-off ratio ≥ 3.5)

Diabetes management in COVID facilities

https://www.mohfw.gov.in/pdf/ClinicalGuidanceonDiabetesManagementatCOVID19PatientManagementFacility.pdf


At Admission
Not a known case of diabetes
Diagnosed case of diabetes
Undiagnosed diabetes
Stress Hyperglycaemia
No Diabetes or Stress Hyperglycaemia
Suggests further action
Step 1: Random glucose by capillary at time of admission
≥ 180 mg/dl
Step 2: Do a pre-meal and 2 hours post-meal glucose by glucometer with the first major meal in the hospital
Pre-meal ≥ 140 mg/dl
Post-meal ≥ 180 mg/dl
Step 3: Send Fasting plasma glucose (FPG) and HbA1c next morning
FPG ≥ 126 mg/dl
HbA1c ≥ 6.5%

Known case of diabetes on Oral glucose lowering agents

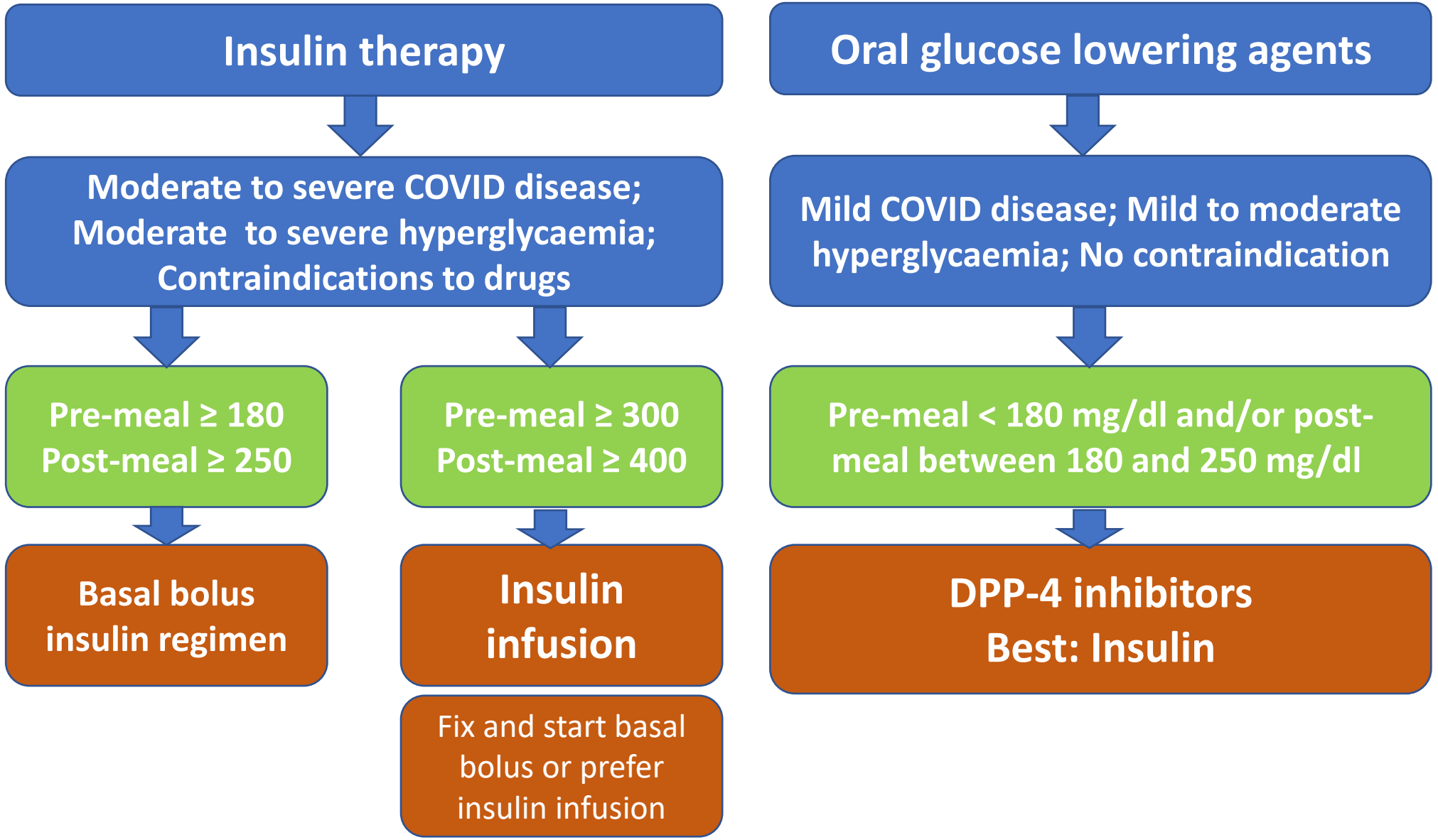
Stop
SGLT-2 inhibitors
Pioglitazone

Mild COVID disease; No contraindication

Pre-meal < 180 mg/dl and/or post-meal < 250 mg/dl

Caution
Metformin
Sulfonylureas

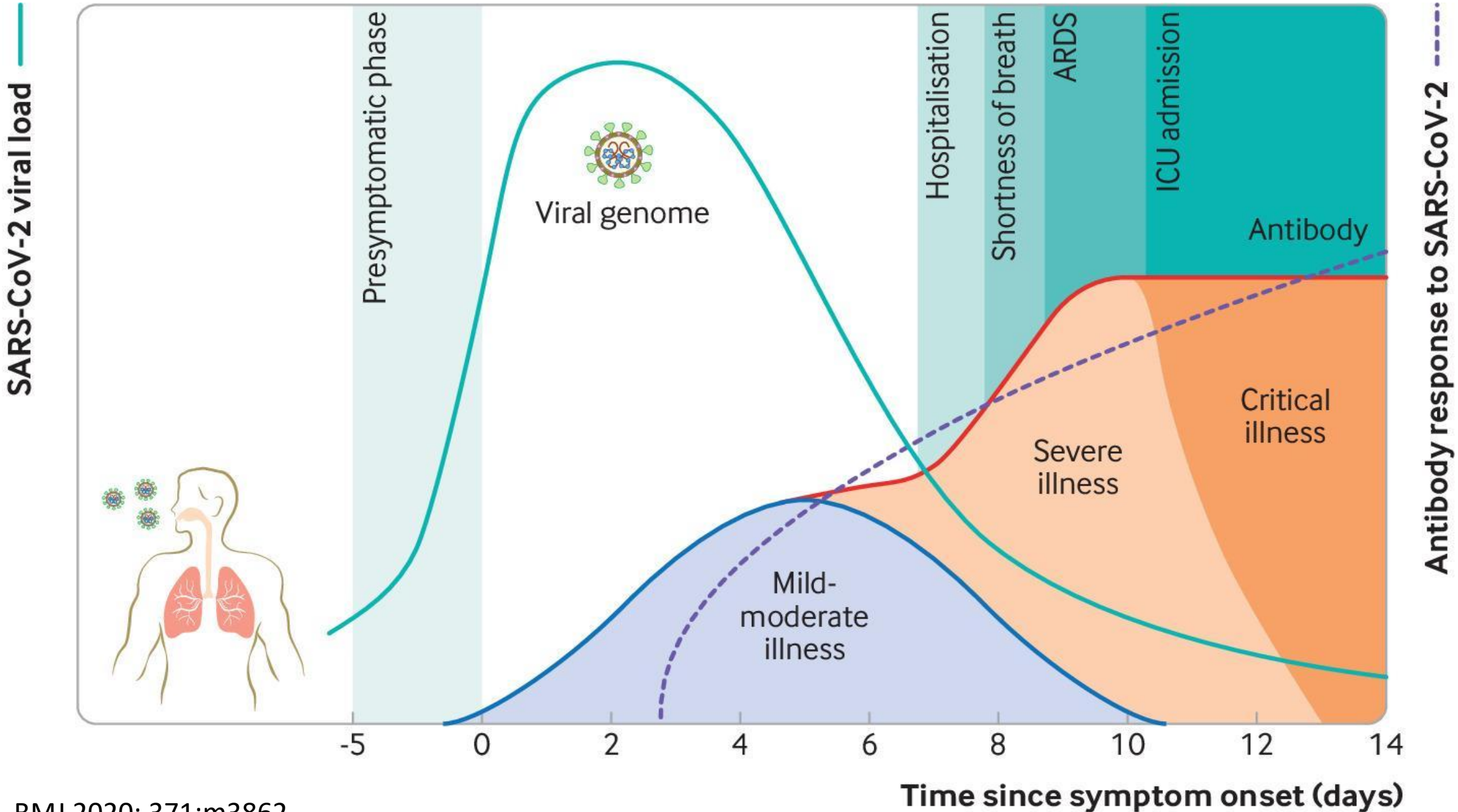
DPP-4 inhibitors (Relatively safe)
Vildagliptin/Teneligliptin (Low cost)
Sitagliptin/linagliptin (High cost)


Insulin therapy
Oral glucose lowering agents
Moderate to severe COVID disease; Moderate to severe hyperglycaemia; Contraindications to drugs
Mild COVID disease; Mild to moderate hyperglycaemia; No contraindication
Pre-meal ≥ 180 Post-meal ≥ 250
Pre-meal ≥ 300 Post-meal ≥ 400
Pre-meal < 180 mg/dl and/or post-meal between 180 and 250 mg/dl
Basal bolus insulin regimen
Insulin infusion
DPP-4 inhibitors Best: Insulin
Fix and start basal bolus or prefer insulin infusion

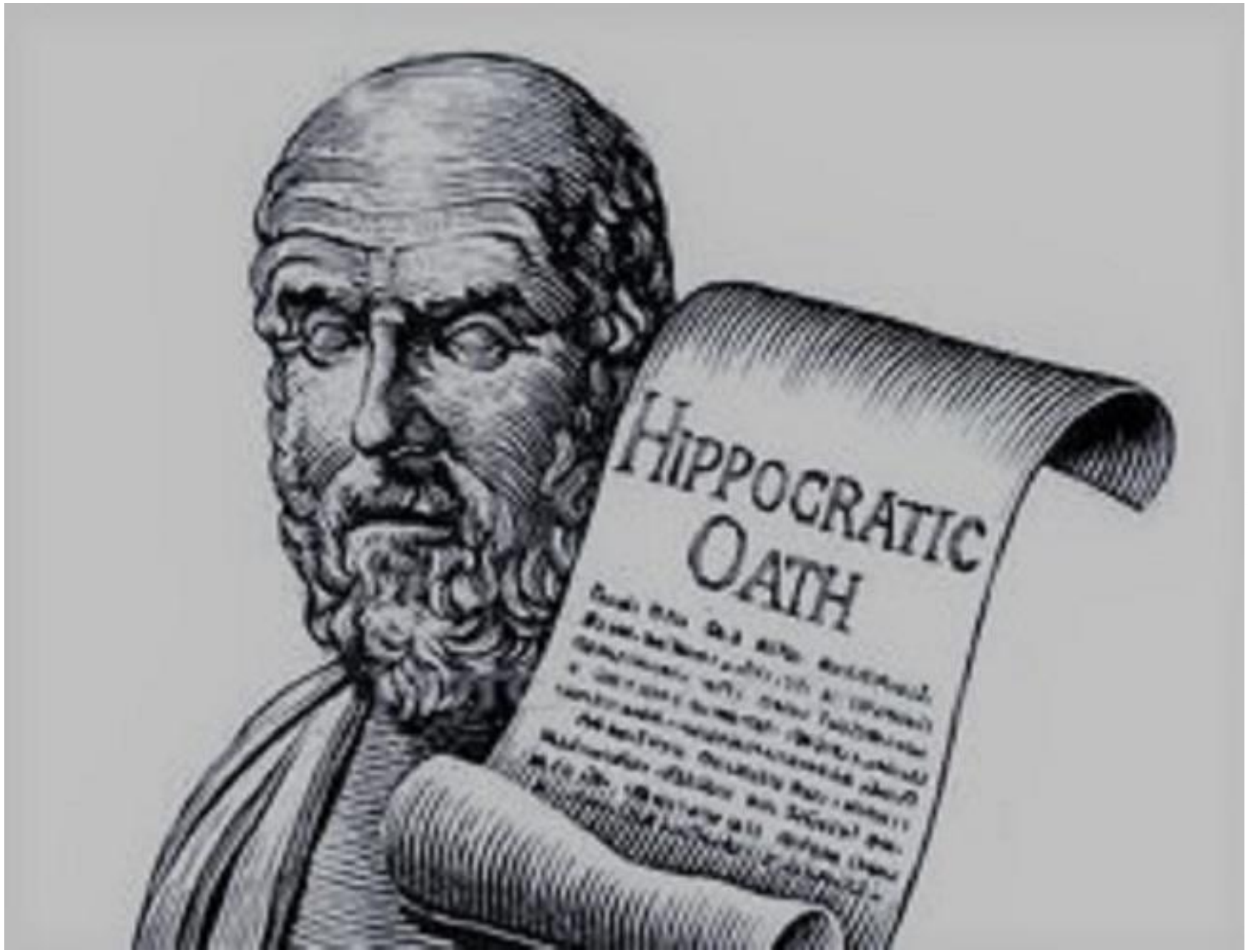
Hospitalised patients with COVID-19: evidence-based therapies

Dr Sanjay Bhagani

Consultant Physician / Associate Professor,
Royal Free Hospital / UCL, London



BMJ 2020; 371:m3862

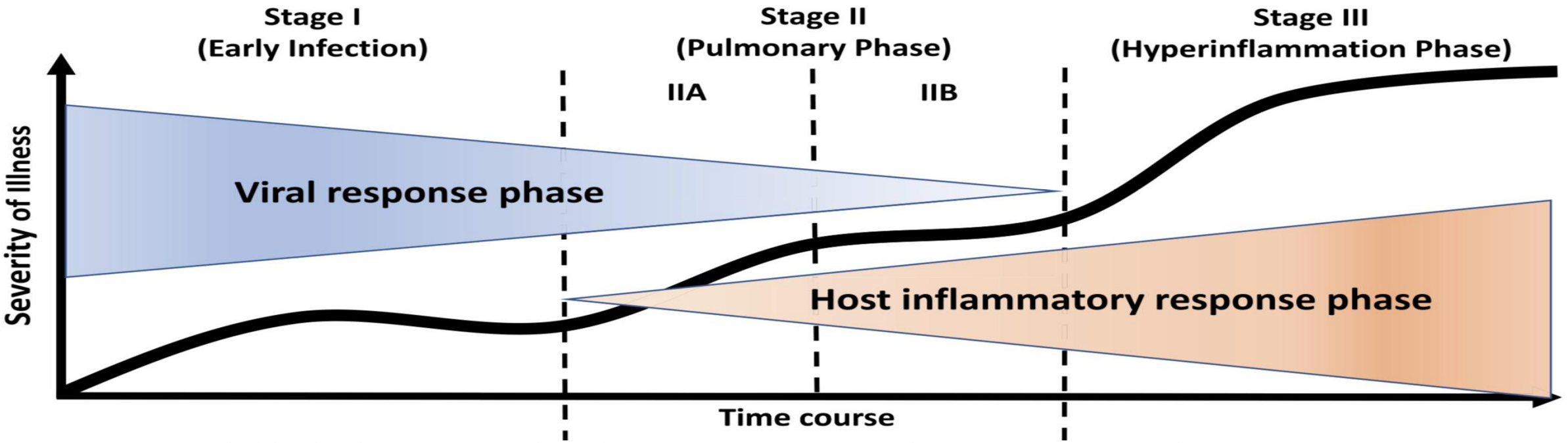


“First Do No Harm”

Hierarchy of the strength of evidence for recommendation of an intervention

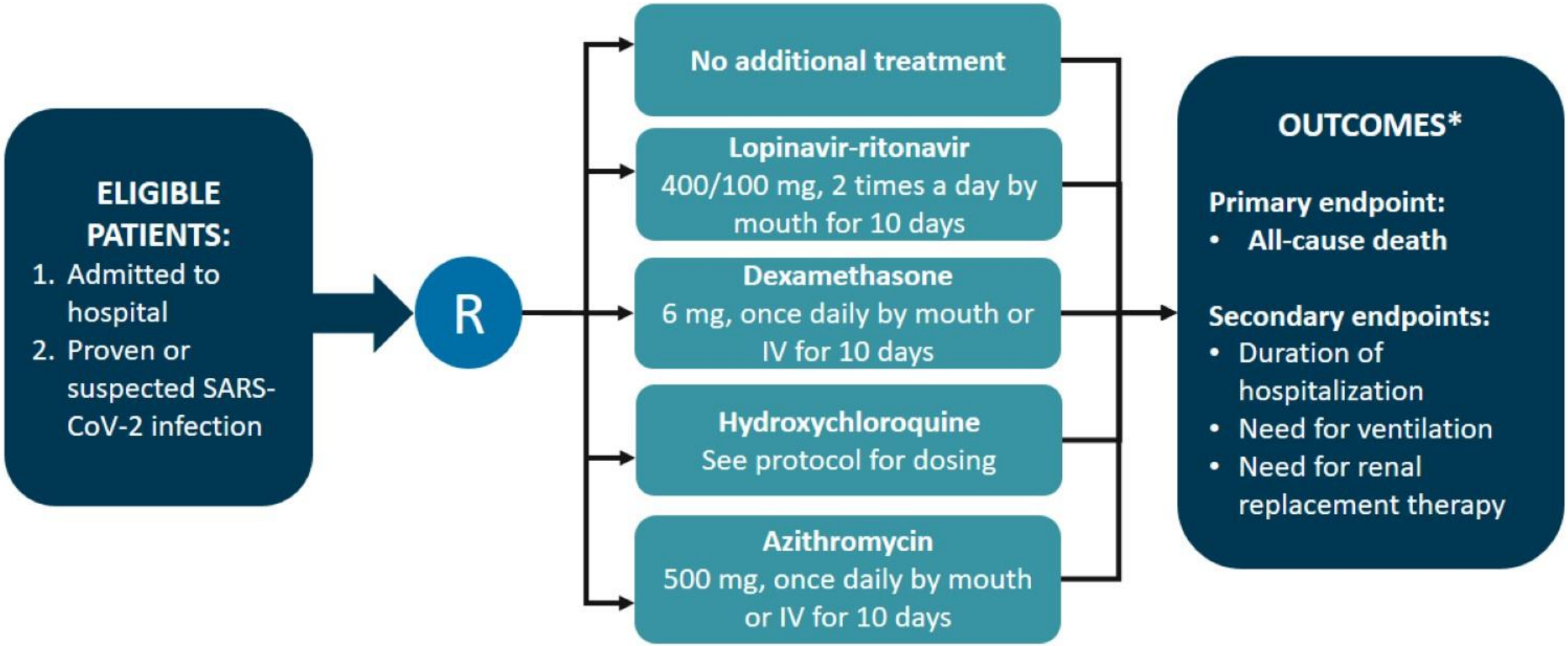
- Expert recommendation
- Case-series/case-reports
- Case-Control studies
- Cohort studies
- Randomised-Control Trials
- Systematic Review / Meta-analyses

Increasing Certainty



Antivirals/neutralising antibodies	Immunomodulators
• Remdesivir • Lopinavir/ritonavir • Favipiravir • Hydroxy/Chloroquine • Interferon-beta • Ivermectin • Convalescent plasma and hIVIG • Neutralising monoclonal antibodies (LY-CoV555, REGN COV2, AZD7442, ViR7831, BRII 196/198) • New antivirals (Molnupiravir, PF CL-PIs)	• Corticosteroids • IL-6 inhibiters (e.g. tocilizumab, sarilumab) • IL-1 inhibitors (e.g. anakinra, canakinumab) • anti-TNF (e.g. Infliximab) • Janus kinase (JAK) inhibitors (e.g. baricitinib) • anti-GM-CSF (e.g. Mavrilimumab) • C-C chemokine receptor type 5 (CCR5) antagonist (e.g. leronlimab)

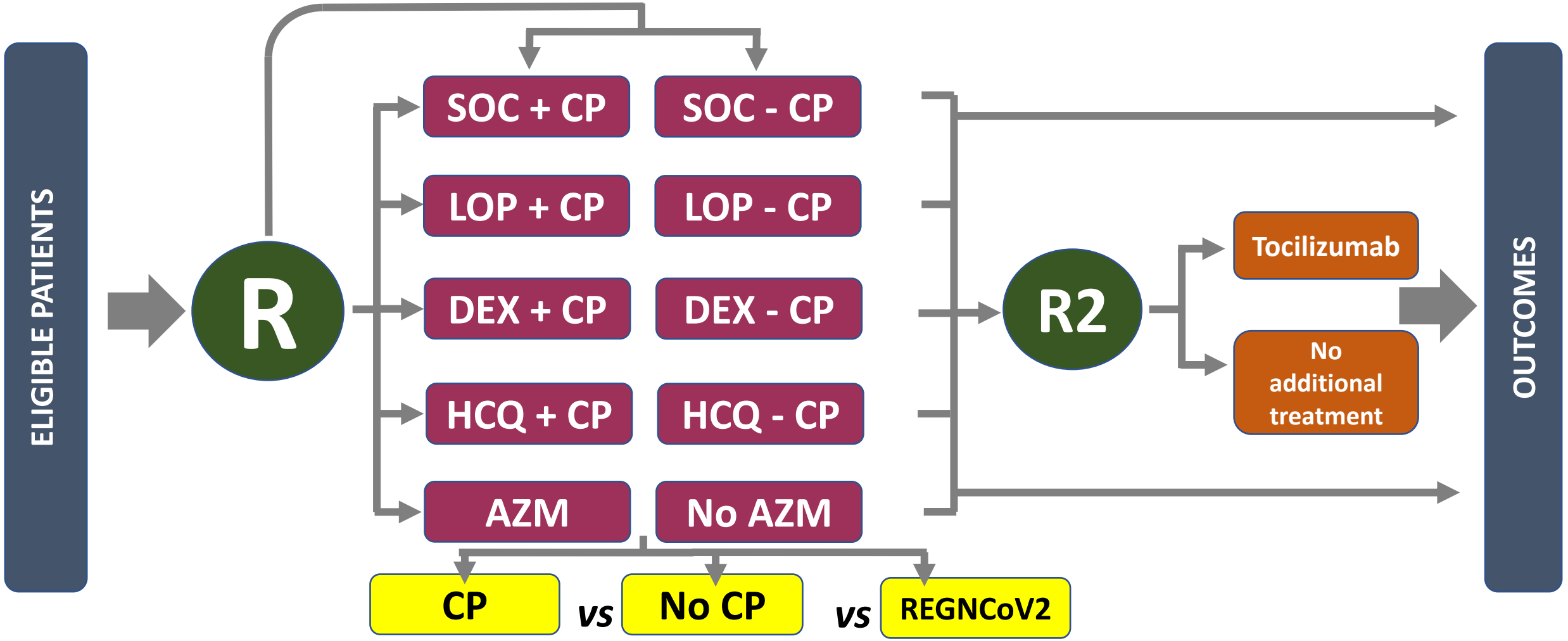
RECOVERY Trial Design[a,b]



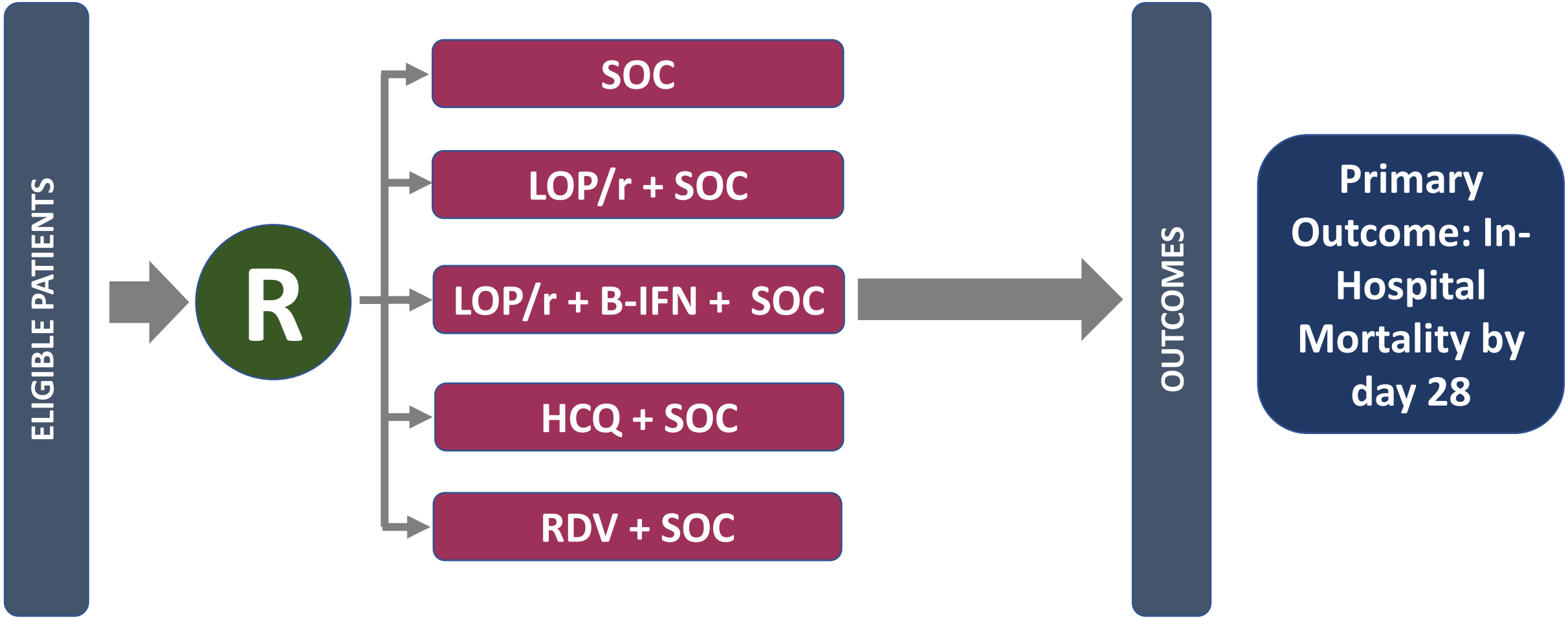
*Second randomization includes convalescent plasma and tocilizumab.

a. Recovery Trial website. Treatments/beneficial COVID-19. 2020; b. RECOVERY Collaborative Group. *N Engl J Med.* 2020. [Epub ahead of print]

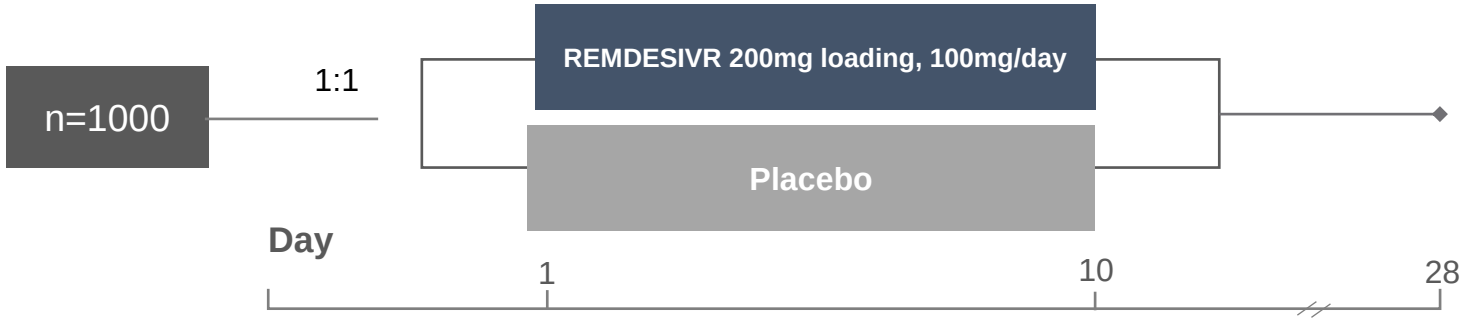
RECOVERY – an evolving 'platform' trial



SOLIDARITY TRIAL - WHO



Adaptive COVID-19 Treatment Trial 1 (ACCT-1)



Primary Outcome

Time to recovery

[Time Frame: Day 1 through Day 29]

Clinical status ordinal scale
1: Not hospitalised, no limitations on activities
2: Not hospitalised, limitation on activities, home oxygen requirement
3: Hospitalised, not requiring supplemental oxygen and no longer requires ongoing medical care (used if hospitalization was extended for infection-control reasons)
4: Hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or medical conditions)
5: Hospitalised, requiring supplemental oxygen
6: Hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices
7: Hospitalised, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8: Death

Phase 3 randomised, double-blind, placebo-controlled, multicentre global trial

Primary Outcome analysis stratified by

a) **Age**
b) **Clinical Severity**
c) **Length of Sx (> 10 vs. <10 days)**

Secondary Outcomes

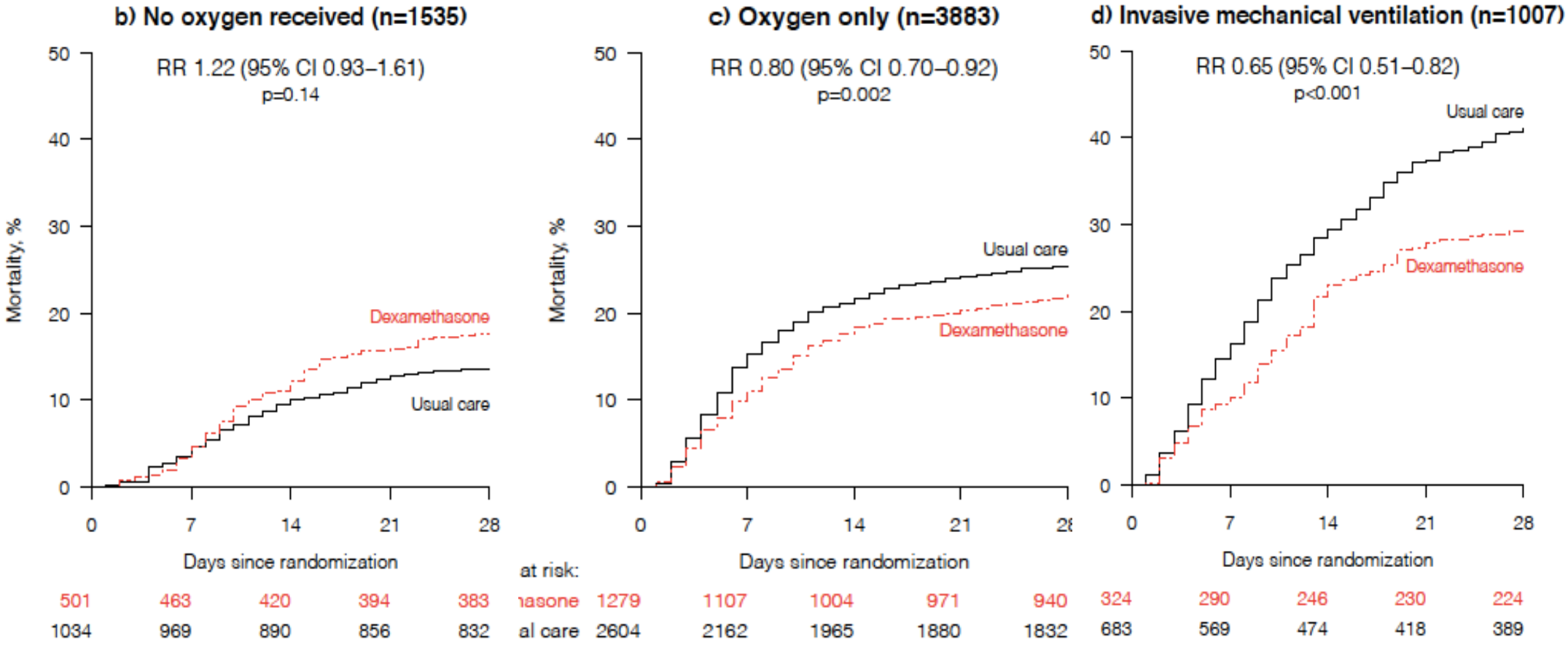
a) **Mortality at Day 14, day 28**

What doesn't work in RCTs (for hospitalized patients)

- Hydroxychloroquine
- Lopinavir/r
- Lopinavir/r plus injectable IFN-B
- Azithromycin
- Convalescent Plasma and hIVIG
- Neutralising monoclonal Abs (LyCoV55, ViR7831, BRII 196/198)
  - Data on REGN CoV2 awaited

RECOVERY – Low-dose Dexamethasone works

– sub-group analysis by baseline clinical status



Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), no antiviral agents have yet been shown to be efficacious.

METHODS

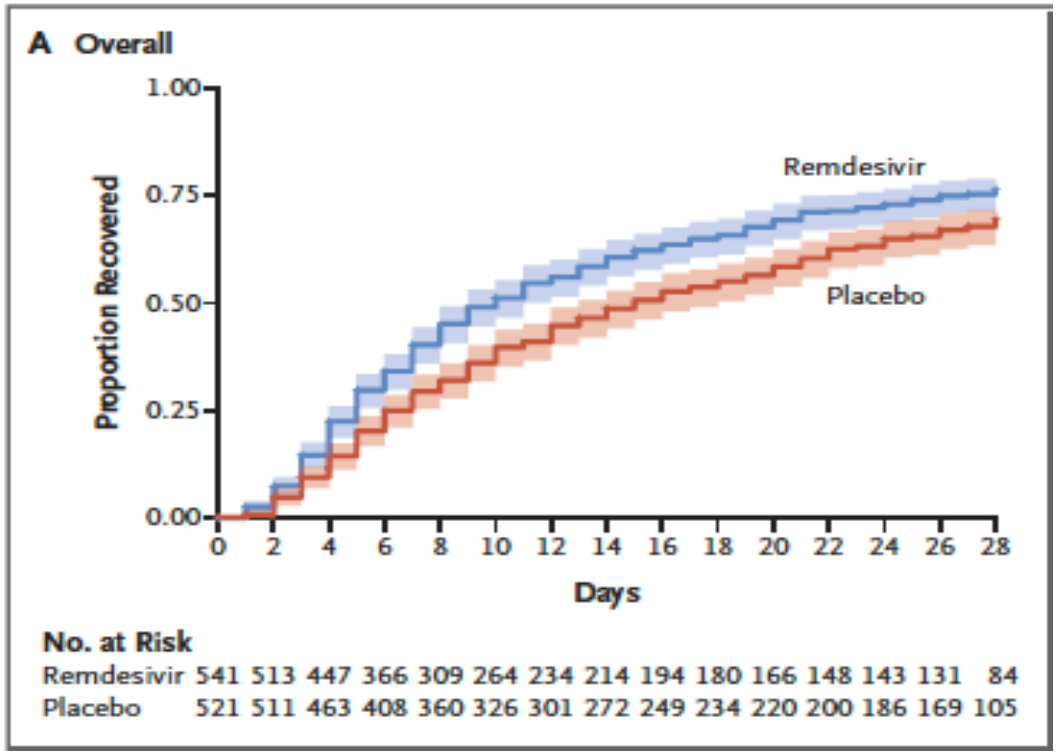
We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS

A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportional-

Beigel et al. N Engl J Med. 2020 October 10

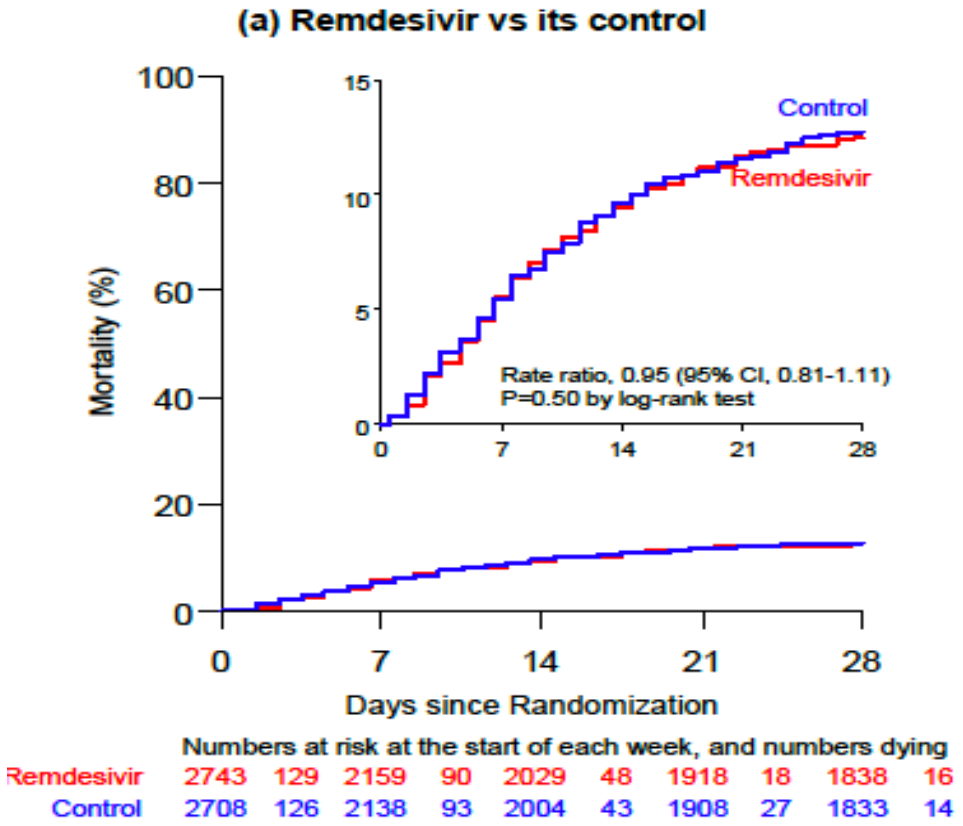
Adaptive Covid-19 Treatment trial (ACTT-1)

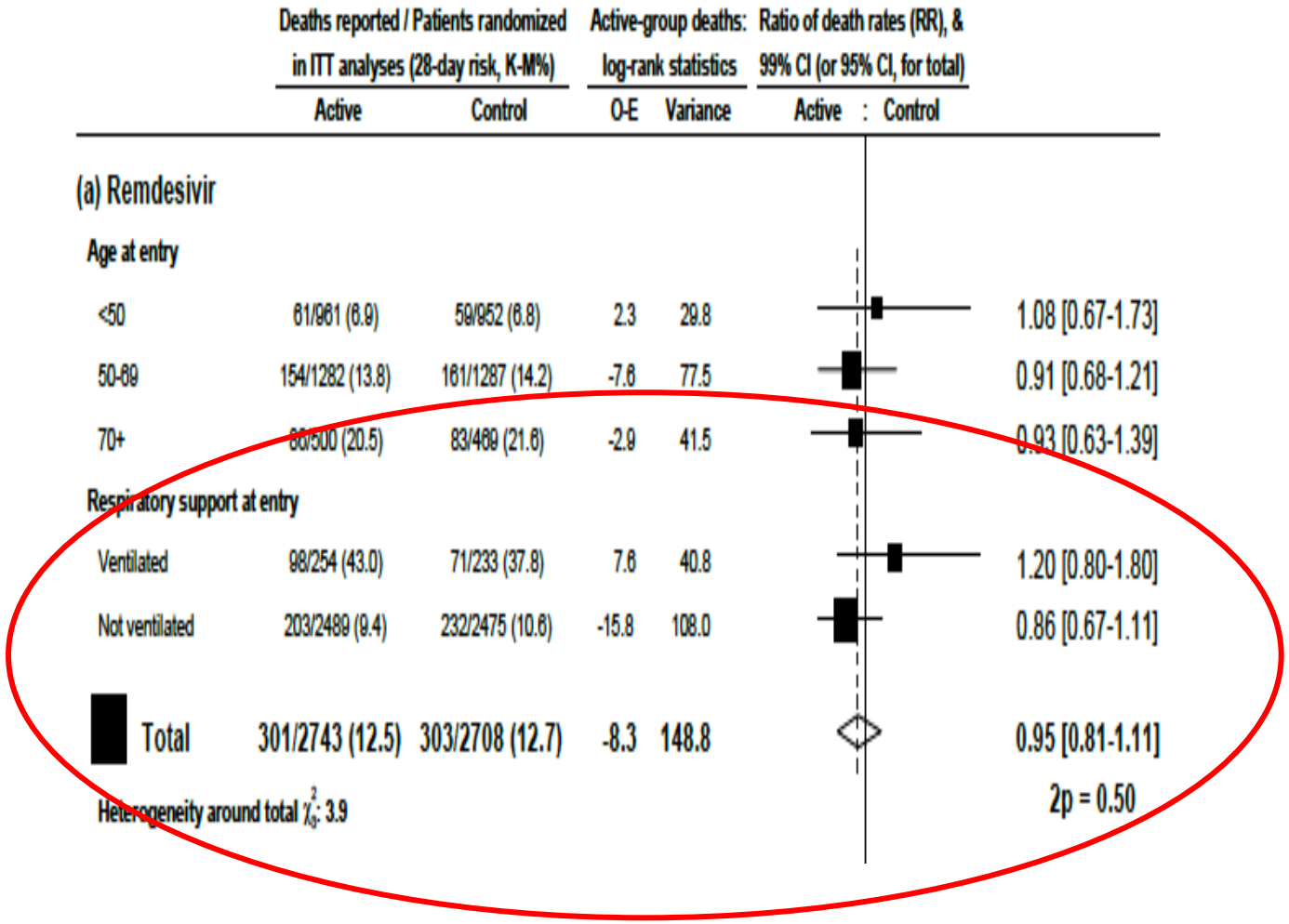


- Median time to recovery*: 10 days remdesivir arm (95% CI 9-11) vs 15 days placebo (95% CI, 13-18).
- OR 1.5, 95% CI 1.2 – 1.9
- 29 day mortality 6.7% (RDV) vs 11.9% (HR, 0.73; 95% CI, 0.52 to 1.03)

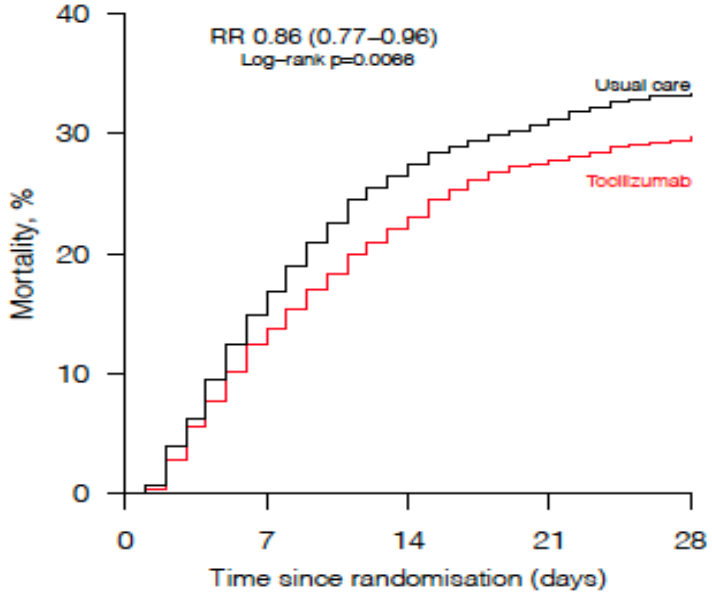
* first day satisfied categories 1, 2, or 3 on the 8 category ordinal scale

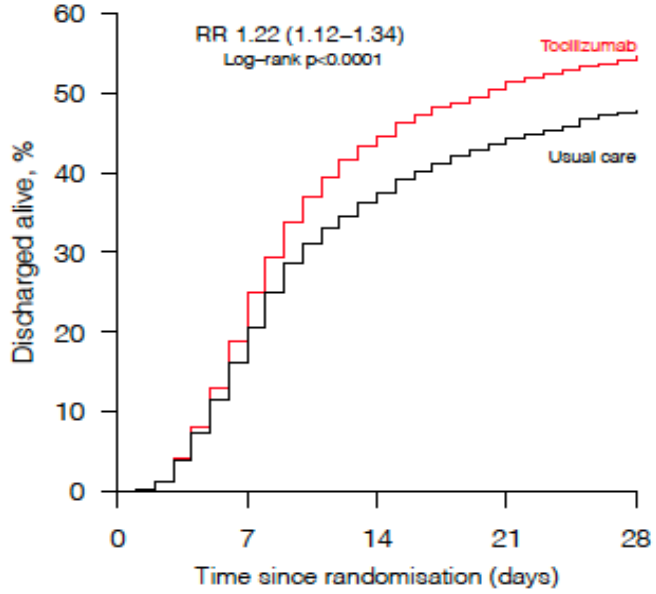
Solidarity – RDV does NOT reduce in-hospital mortality by day 28



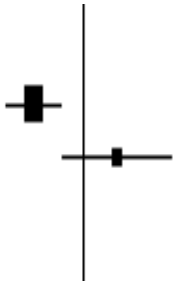


RECOVERY: Tocilizumab – final results





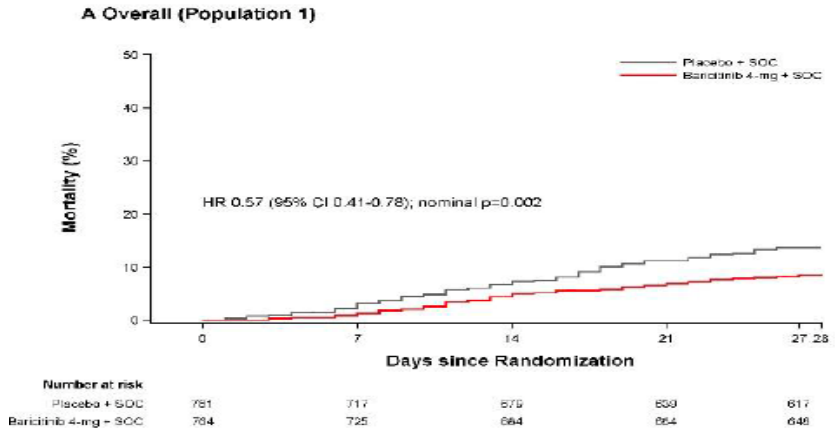
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70–0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91–1.48)
Unknown	0/1 (0%)	2/6 (33%)	

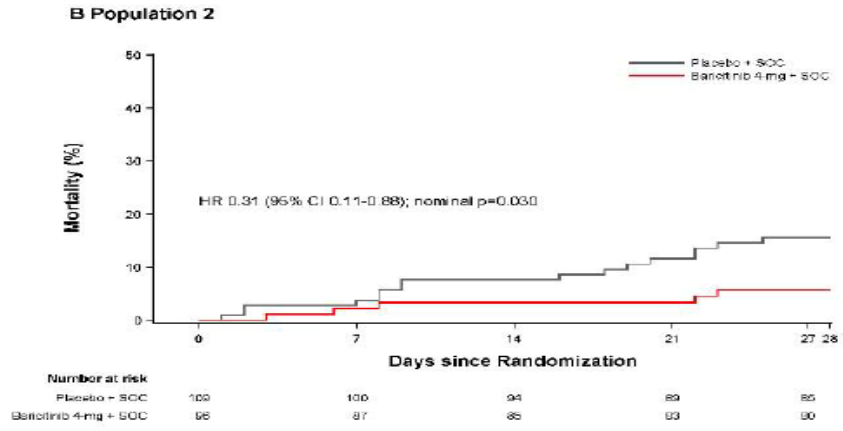


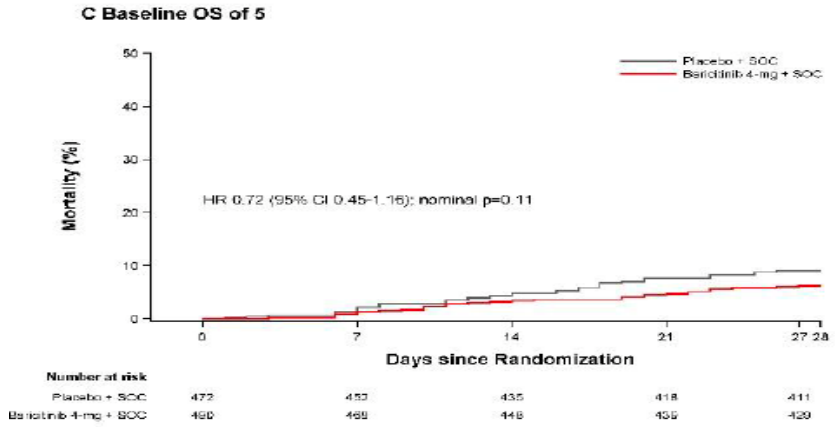
RECOVERY Randomised Evaluation of COVID-19 Therapy

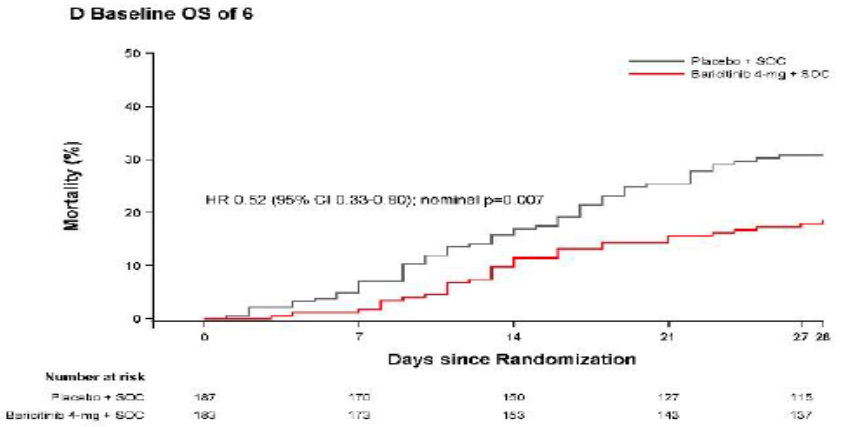
UNIVERSITY OF OXFORD

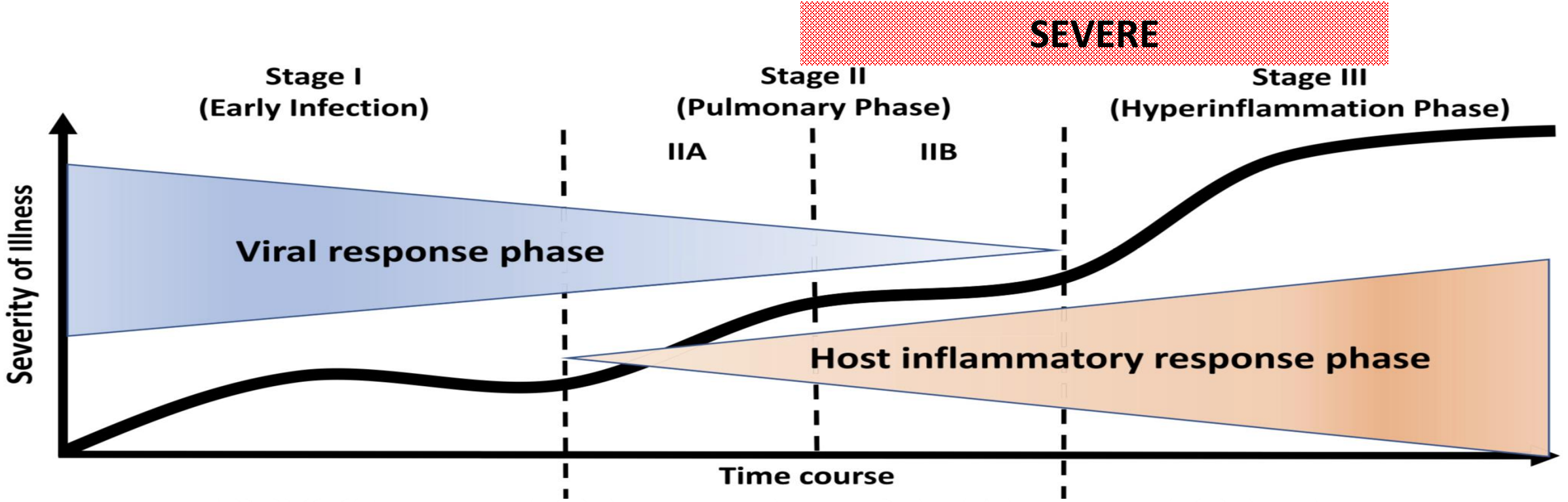
COV-BARRIER – Baricitinib may prevent mortality in hospitalized patients requiring high-flow O2 or NIV











Antivirals/neutralising antibodies

- Remdesivir
- Lopinavir/ritonavir
- Favipiravir
- Hydroxy/Chloroquine
- Interferon-beta
- Ivermectin
- Convalescent plasma and hIVIG
- Neutralising monoclonal antibodies (REGN COV2, LY-COV555, ViR7831, Brii-196/198, AZD7442)
- New antivirals (MK 4482, PF CL-PIs)

Immunomodulators

- Corticosteroids
- IL-6 inhibiters (e.g. tocilizumab, sarilumab)
- IL-1 inhibitors (e.g. anakinra, canakinumab)
- anti-TNF (e.g. Infliximab)
- Janus kinase (JAK) inhibitors (e.g. baricitinib)
- anti-GM-CSF (e.g. Mavrilimumab)
- C-C chemokine receptor antagonists type 5 (CCR5) (leleronlimab) and type 2 (Cenciviroc)
- Anticoagulation/antiplatelets

So what do we do at the Royal Free Hospital for hospitalized patients with moderate/severe COVID-19?

(SaO2<945 RA, or requiring supplementary O2)

- Low-dose corticosteroids – 10 days maximum
- If Sx onset <10 days (and eGFR>30) – Remdesivir – 5 days maximum
- If CRP >75, or within 48hrs of HFNO/NIV/Mechanical ventilation – single-dose iv tocilizumab or sarilumab
- Anticoagulation
- Enrol on to ongoing clinical trials……
  - NIH ACTIV3
  - RECOVERY

Inpatient diabetes in COVID times

Prof Kamlesh Khunti

Professor of Primary Care Diabetes & Vascular Medicine, GP and SAHF Trustee

Prof Wasim Hanif

Professor Diabetes & Endocrinology

Consultant Physician University Hospital Birmingham, UK

Board of Trustee Diabetes UK

Board of Trustee SAHF

Diabetes guidelines

NHS
University Hospitals Birmingham
NHS Foundation Trust

Birmingham Health Partners

All patients require documentation regarding CPR and escalation to ITU

Key Advice on admission

- **Check blood glucose** (capillary, lab, blood gas) **in ALL patients presenting to hospital**
- **Check capillary ketones in ALL patients with known diabetes** – *even if blood glucose levels are normal*
- **STOP SGLT-2 inhibitor therapy** *(canagliflozoin, dapagliflozin, empagliflozin, sotagliflozin)* **in ALL unwell patients**
- Consider stopping metformin if patient is dehydrated, has a raised lactate or is in AKI
- **Never stop background insulin** *(Lantus, Levemir, Tresiba, Humulin I)* in patients with T1DM or T2DM
- Treat DKA and HHS as per protocol **BUT give IV fluids much more slo**wly in COVID19 suspected or positive patients
- **Examine the feet in ALL patients with diabetes** - *in particular for acute ulceration, infection or ischaemia*

Rationale

- **Up to 20% of hospital beds are occupied by someone with diabetes**
- People with diabetes are more likely to have **severe manifestations of COVID19 infection** and this percentage is expected to increase over the next few weeks and months

NHS
University Hospitals Birmingham
NHS Foundation Trust

Key Advice for patients on the wards

- Encourage patients to self-manage where possible *(including doing self-glucose testing)* as per existing Trust policy
- Aim for a safe **blood glucose target of 110 to 270 mg/dl (6 – 15 mmol/l)**while in hospital
- **Limit the use of VRII** *(insulin sliding scale)* in patients – *use Trust guidelines to convert to subcutaneous insulin*

Key Advice for patients in Critical Care

- Ventilated patients with COVID19 infection have been found to be **highly insulin resistant** and requiring exceptionally high rates of insulin infusion (>20 units/hr) – *involve Diabetes Team early*
- Atypical diabetes presentations such as **euglycaemic DKA can occur in the setting of COVID19 infection** *(even as a first presentation)* as well as in patients on **SGLT-2 inhibitor therapy**
- This manifests as profound ketosis *(ketones >3.0)* and acidosis *(PH < 3.0)* at normal blood glucose levels *(<11 mmol/l) – treat as per Trust DKA guidelines*
- Please refer to **Diabetes Team via PICS** for further advice

Medications to Stop Temporarily when unwell *(SADMAN)*

- ***Diuretics*:** frusemide, bendroflumethiazide, indapamide, bumetanide
- ***ACE inhibitors:*** ramipril, lisinopril, perindopril ***/ ARBs:*** candesartan, losartan, irbesartan
- ***Metformin***
- ***NSAIDs:*** ibuprofen, naproxen, diclofenac
- ***GLP1 analogues****:* exenetide, liraglutide, dulaglutide, lixisenatide, semaglutide
- ***SGLT inhibitors:*** canagliflozin, dapagliflozin, empagliflozin, sotagliflozin

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RECOVERY trial

- Dexamethasone reduces risk of death by one third
- Steroid Protocol for Managing Diabetes
- Measure BMs if elevated start Gliclazide 40 mg at 8AM add in needed at 12 PM titrate dose
- Add in Medium acting insulin like Humulin-I, Insultard, Levemir at 8 AM once a day
- Measure BMs regularly and check for ketones in more than 300

Diagnostic criteria

1. Blood glucose greater than or equal to 11 mmol/L or history of diabetes[+]
(glucose will be less than 11mmol/L in euglycaemic ketoacidosis)*
2. Blood ketones greater than or equal to 3 mmol/L or urine ketones greater than or equal to 2+
3. pH less than 7.3 or bicarbonate less than 15 mmol/L

Consider ITU referral if any of the following:

1. Young or elderly (decided at the discretion of treating physician) or pregnant **2.** Heart or liver or kidney failure **3.** Severe DKA judged by: blood ketones greater than 6mmol/L **or** bicarbonate less than 5mmol/L **or** pH less than 7.1 **or** potassium less than 3.5 mmol/L or GCS less than 12 **or** persistent hypoxia or persistent brady/ tachycardia **or** anion gap greater than 16 mEq/L

Time since diagnosis of DKA

0 min to 60 min

Restore circulatory volume

- Give 500ml of 0.9% sodium chloride every 15-30 min until systolic BP greater than 90 mmHg (recheck BP after each 500ml infusion)
- Then give 1000ml 0.9% sodium chloride over 1 hr

Start insulin therapy

- Start insulin infusion at 0.1ml/kg/hr
- Continue patient's long-acting insulin

60 min to 6 hrs

Continue fluid replacement

- 1 litre of 0.9% sodium chloride with potassium*, over 2 hr
- Then,1 litre of 0.9% sodium chloride with potassium*,over 2 hr
- Then,1 litre of 0.9% sodium chloride with potassium*,over 4 hr

*** Potassium replacement**

- Less than 3.5- senior review
- 3.5-5.5- 40 mmol/l
- >Greater than 5.5- no replacement

6 hrs to 12 hrs

Continue fluid replacement

- 1 litre of 0.9% sodium chloride with potassium*, over 4 hr
- Then,1 litre of 0.9% sodium chloride with potassium*,over 6 hr
- **Senior review if DKA persists beyond 12 hours**

Monitor for hypoglycaemia

- Start 500ml 10% glucose at 125ml/hr when glucose less than or equal to 14 mmol/L

Monitoring

- Hourly glucose and **hourly ketones**
- Bicarbonate & potassium at 1 hr & 2 hr after diagnosis & 2 hourly thereafter

Check infusion rate if:

- Ketones not reducing by 0.5mmol/hr
- Bicarbonate not increasing by 3mmol/hr
- Glucose not reducing by 3mmol/hr

If glucose less than or equal to 4 mmol/L, stop insulin infusion and follow hypoglycaemia guidelines Restart infusion when hypoglycaemia resolves and if DKA still persists

DKA Resolution and further management

- DKA is resolved when ketones less than 0.6 mmol/L and ph greater than 7.3 or bicarbonate greater than 15 mmol/L
- If DKA is resolved, switch to variable rate insulin infusion and seek diabetes specialist review for further management

† Rule out **Euglycaemic ketoacidosis** and **Hyperglycaemic Hyperosmolar State** (HHS) in high risk acutely unwell patients with diabetes (Eg: Pregnancy, those on SGLT-2 inhibitors (gliflozins)

For more information, please review the management of diabetic ketoacidosis in adults by Joint British Diabetes Societies Inpatient Care Group

University Hospitals Birmingham NHS
NHS Foundation Trust

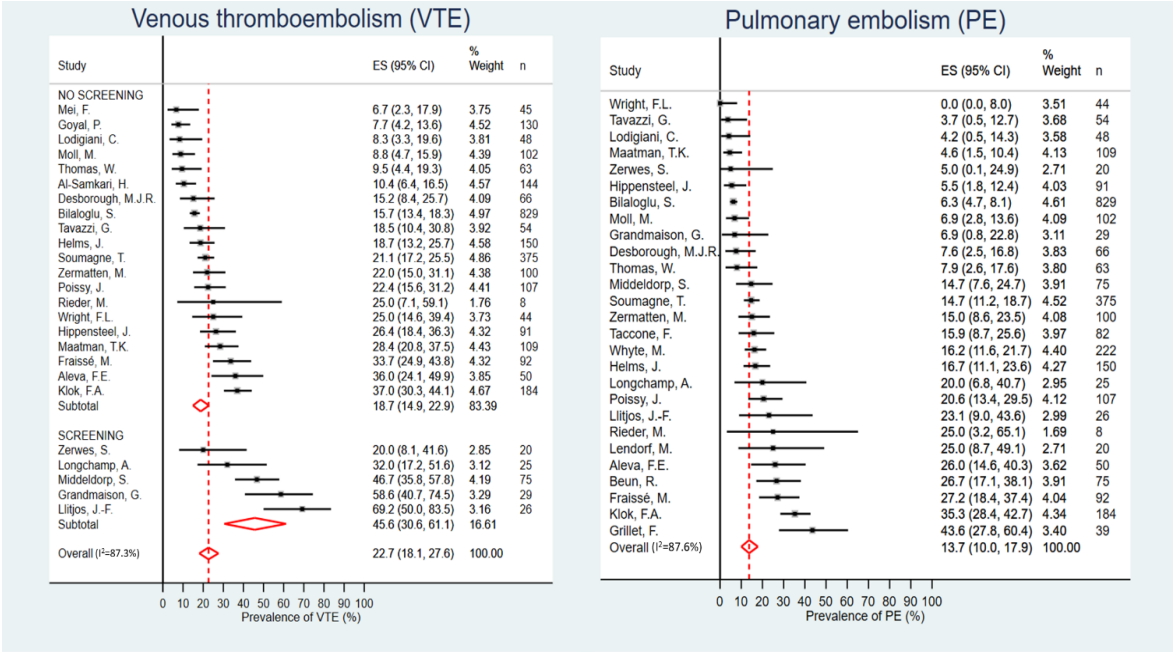
Anticoagulation and COVID-19

Dr Pratima Chowdary

Professor of Haemophilia and Haemostasis, KD Haemophilia and Thrombosis Centre, Royal Free Hospital, London

D-dimer and COVID- 19

- Elevated D-dimer is associated with increased risk of thrombosis and mortality
- Venous thrombosis
  - Systematic review and meta-analysis (66 studies (28,173 patients)
  - Non – ICU: VTE - 7.9%; PE – 3.5%
  - ICU: VTE – 22.7%; PE – 13.7%
- Mortality
  - Four to eight fold increase in D-dimer above upper limit of normal



Stephan Nopp et al. Res Pract Thromb Haemost Sep 2020; Tang N et al. J Thomb Haemost. 2020;18:844-7; Thachil J et al. J Thromb Haemost. 2020;18:1023-6; Yao et al. Journal of Intensive Care, 2020

Short et al. Crit Care Med, May 2021.

Endothelial cell infection and endothelitis in COVID-19

Post-mortem analysis of the transplanted kidney by electron microscopy

Apoptosis of endothelial cells secondary to infection

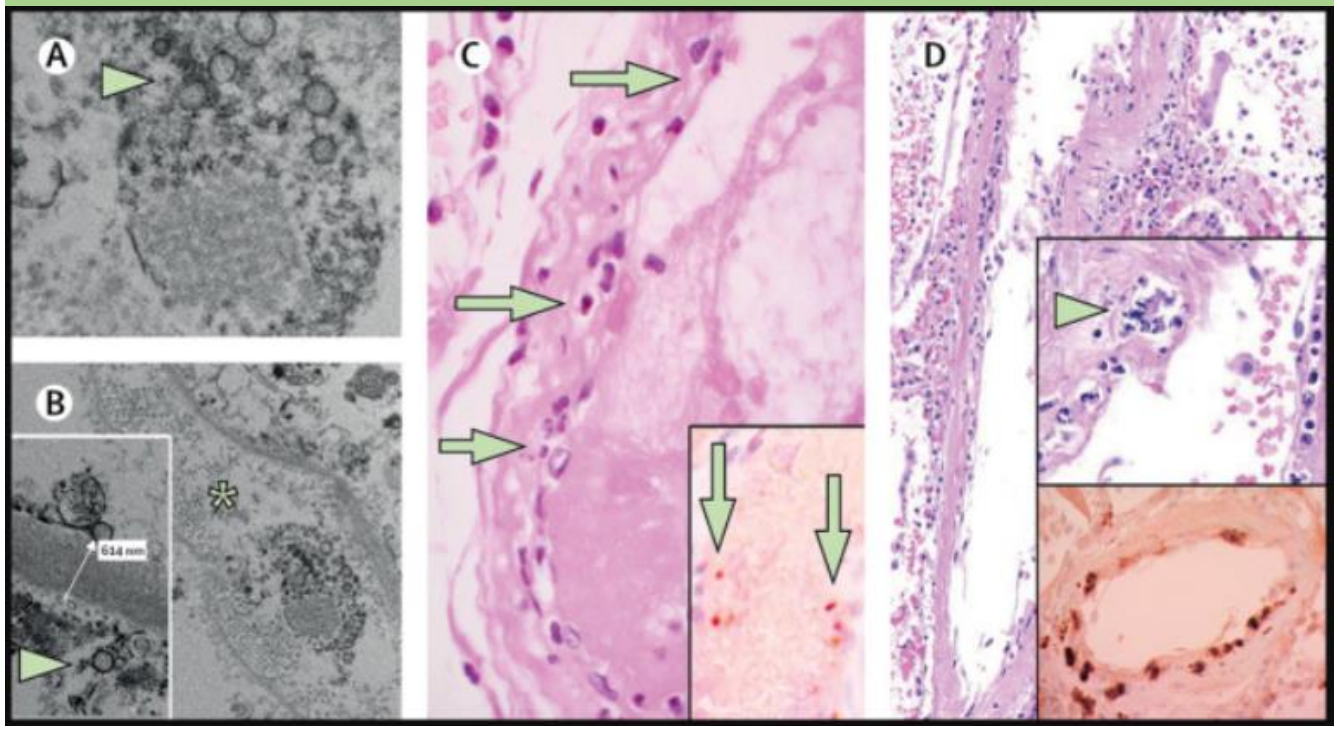


Figure A, B - Viral inclusion structures in endothelial cells.

Figure C (small bowel) - accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies.

Figure D (lung) Accumulation of mononuclear cells was found in the lung, and most small lung vessels appeared congested.

Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, Mandeep R Mehra, Reto A Schuepbach, Frank Ruschitzka, Holger Moch; The Lancet, 20 April 2020

Hypercoagulability is multifactorial

Procoagulants - increased

↑ Tissue factor expression

- EC damage
- Monocytes

↑ FVIII, von Willebrand factor, fibrinogen

↑ Contact pathway activation – polyphosphate / NETosis

Platelet activation

Polyphosphate secretion – contact pathway activation

Anticoagulant – impaired

Endothelial damage – loss of normal anticoagulant surface

Cytokine-induced shedding of Thrombomodulin and endothelial protein C receptor

Fibrinolysis - Inhibition

↑ PAI – 1 levels

NETosis

When to consider investigations for PE?

- Ventilated patients
  - Failure to improve after 48 hrs of proning
  - Sudden worsening Pa02/Fio2 ratio
  - Sharp elevation of d-dimer levels (more than a two-fold increase)
- Non ventilated patients
  - Absolute d-dimer > 5000 ng/mL at presentation
  - Sudden deterioration in saturation, with a sharp increase in d-dimer level (more than a two-fold)
- First surge @ Royal Free over 11 weeks (March 16th and May 31st, 2020)
  - ~20% had d-dimer > 5000 ng/mL at admission; 25% of this group had a PE

Antithrombotic strategy - what are we trying to achieve?

Decreased need for oxygen support and ventilation

- Decreased duration of oxygen support
- Decreased need for ventilation

Decrease in symptomatic venous and arterial thrombosis

- Fewer symptomatic events
- Fewer asymptomatic events

Overall decrease in mortality

- Mortality at day 30 and day 90

Multiplatform RCT – therapeutic anticoagulation vs usual care in severe COVID-19 suggested futility

	Therapeutic anticoagulation	Usual care pharmacological thromboprophylaxis
Number of patients	N=532	N=557
Events (No. of patients/total no. (%))		
Major thrombotic events	27/471 (5.7%)	49/476 (10.3%)
Death in hospital	189/529 (35.7%)	189/545 (34.7%)
Major thrombotic events or death	200/483 (41.4%)	211/494 (42.7%)
Adjusted odds ratio (95% CrI)[a]	1.05 (0.79-1.40)	
Major bleeding	15/482 (3.1%)	12/495 (2.4%)
Odds ratio (95% CrI)[a]	1.19 (0.57-2.49)	

Severe Covid-19

requirement for organ support

- high flow nasal cannula
- non-invasive ventilation
- invasive ventilation
- vasopressors
- Inotropes

a, Composite ordinal scale

Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report. medRXiv; DOI: https://doi.org/10.1101/2021.03.10.21252749
Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)
Anti-thrombotics for Adults Hospitalized With COVID-19 (ACTIV-4)

Moderate COVID-19

Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]

Anticoagulation and COVID-19 in the absence of documented VTE

Prophylactic dose	Treatment dose	Intermediate dose
• Inpatient with a bleeding risk identified	• Patients requiring supplemental oxygen • Essentially patients for whom steroids have been initiated	• Ventilated patients – ICU • High flow nasal oxygen, Continuous positive airway pressure (CPAP) or non invasive ventilation
Product	**Product**	**Product**
• Low molecular weight heparins , prophylactic dose	• Low molecular weight heparin, therapeutic doses • Direct oral anticoagulants	• Prophylactic dose of low molecular weight heparins twice a day

https://www.nice.org.uk/guidance/ng191/resources/fully-accessible-version-of-the-guideline-pdf-pdf-9078468301

Summary

- Elevated d-dimers related to the disease severity and a prognostic marker for mortality
- Venous thrombosis is a combination in situ pulmonary artery thrombosis and / or embolisation of deep vein thrombi
- Review bleeding risks before embarking on therapeutic anticoagulation in the absence of VTE

- Therapeutic anticoagulation is not beneficial when initiated in patients requiring high oxygen support
- Therapeutic anticoagulation is beneficial in patients requiring supplemental oxygen

Intensive Care Management of COVID-19

Prof Ramani Moonesinghe

National Clinical Director for Critical and Perioperative Care, NHS England, and Professor and Honorary Consultant, University College London (UCL) and UCL Hospitals

Summary

- Best practice in COVID19 is well described and there are multiple sources of information:
  - https://icmanaesthesiacovid-19.org/covid-cc-guideline-update
  - https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-66142077109189
  - WHO website
- Challenges will be related to surge and how to deal with demand exceeding supply of:
  - Workforce
  - Oxygen
  - Equipment
  - Medicines
- The greatest ‘pinch point’ will determine the compromises which might be required

Choice of ventilatory support

- If a patient does not have an immediate indication for intubation, there is equipoise over whether a trial of CPAP or HFNO may be of benefit
- In the UK, clinical experience is very divided – some units intubated everyone early, some units tried CPAP on everyone and had lots of patients avoid mechanical ventilation
- RECOVERY-RS trial was trying to evaluate this but has stopped recruiting and is unlikely to give us an answer

Choice of ventilatory support – general considerations

- CPAP:
  - Requires lower level of nursing and monitoring (good if workforce is an issue)
  - Generally well tolerated apart from usual issues (mask fit, pressure ulcers)
  - Most CPAP devices are very oxygen ‘hungry’ – a big problem if oxygen is a limited resource
  - Some CPAP devices dispense large volumes of oxygen into the environment which can be a fire risk in poorly ventilated or very enclosed spaces
- HFNO
  - Very well tolerated and low level of nursing and monitoring required
  - Hugely oxygen hungry – again, not suitable for settings where oxygen is a limited resource
- IPPV:
  - Invasive and requires sedation (medicines and feeding) and higher levels of nursing and monitoring
  - Fully sedated patients may be easier to manage than weaning patients

Using anaesthetic machines to ventilate patients

- May be used to ventilate patients in surge conditions
- Not ideal but definitely better than nothing!
- Higher flows than usual may be required to avoid build up of condensation within the circle system
- Issues specific to anaesthetic machines:
  - In-line suction triggering anaesthesia ventilators to stop (beware)
  - Ensure CO2 sampling is ‘ventilator side’ of the viral filter (separated from patient expired gas by a viral filter).
  - Heat and Moisture Exchange (HME) filters may become rapidly saturated with water vapour when used with anaesthetic machines with a circle system.

CPAP: when to give up and intubate?

- Signs of CPAP failure may include:
  - Increased work of breathing, deteriorating oxygenation, high expired tidal volume, high minute ventilation persistently rising inflammatory markers and D-dimers, agitation and distress, and failure to tolerate rest periods on HFNO. Such markers of potential deterioration should be taken in context of the patient's overall clinical condition.
  - Pneumomediastinum, pneumothoraces and surgical emphysema are a feature of COVID pneumonitis and may be exacerbated by a high spontaneous minute ventilation (i.e. self-induced lung injury).
- No specific absolute duration of non-invasive respiratory support has been identified as detrimental in an individual COVID patient who may remain stable for days before eventual improvement. It is thus crucial to individualise care, including the types of non-invasive support offered, alone or in combination, to find which approach best suits any particular patient.
- Prediction of failure is complex but may be assisted by a scoring system taking into account age, GCS, respiratory rate-oxygenation index, comorbidities and vasopressor use: https://www.thelancet.com/action/showPdf?pii=S2589-7500%2820%2930316-2

Principles of ventilation

- Usual best practice in ventilation:
  - 6-8ml tidal volume
  - Avoidance of high airway pressures
  - Permissive hypercapnia may be fine
  - Avoidance of hyperoxia:
    - 92-96% if oxygen supply no problem
    - 90-93% fine oxygen supply is a problem and patient monitored
    - >88% sufficient for patients with chronic respiratory disease

Proning

- Awake prone positioning may improve V/Q mismatch, oxygenation and work of breathing and may be combined with HFNO, CPAP or NIV.
- Early application of prone positioning in severe ARDS (ventilated patients) is associated with a significant reduction in both 28 and 90-day mortality. No studies in COVID, but clinical experience suggests an improvement in gas exchange is often seen in ventilated patients in both early and later phases of the disease. The benefit may wear off after several hours or days for some patients.
- If proning is used, it is recommended for 16-18 hours per day (longer may be acceptable) and may continue to show benefit for > 7 days.

Risks:

- Potential injury to eyes: Turn head regularly, e.g. 3 hourly
- Be careful about pressure areas (chest, nose, cheeks),
- Brachial plexus injury is a risk – careful position of shoulders important
- Obstruction/displacement of tracheal tube/tracheostomy. Significant haemodynamic and/or respiratory decompensation can occur during the act of proning or deproning. Be prepared! (availability of 100% O2, vasopressors etc). Patients usually recovery quickly.

Thromboprophylaxis

- Potentially confusing…
- Summary:
  - Lower acuity patients (oxygen therapy only): therapeutic anticoagulation
  - Higher acuity patients (high flow oxygen, CPAP or mechanical ventilation): reduce this to an intermediate dose (i.e. twice normal prophylactic dose)
- Start anticoagulation asap (within 14h of hospital admission)
- Check balance of risk/benefit regularly
- Do not base dosing on D-dimer level
- Might need to add in further anticoagulation to patients on renal replacement therapy and problems with filter clotting

Cardiovascular

- Cardiovascular disease and its antecedent risk factors are associated with greater risk of death from Covid-19.
- Raised cardiac troponin T (TnT) and/or NT-proBNP levels may occur and are strongly associated with poorer outcome. Myocarditis uncommon
- Right sided cardiac dysfunction due to pulmonary hypertension and/or pulmonary embolism may occur. It is associated with increased mortality risk and appears more common than left sided heart failure.
- Acute pericarditis can occur but cardiac tamponade is rare.
- Remember: acute coronary syndromes can still occur. Diagnosis can be difficult given that raised TnT is common. Echocardiography (regional wall motion abnormality) and ECG may help. Seek expert cardiology advice.
- Arrhythmias are common, e.g. AF and bradycardia, and should be managed in a normal fashion.

Fluid management

- We probably got this a bit wrong in our first wave
- Temptation is to go super-dry
- Renal failure a real risk and puts patients in a v poor prognostic category: plus renal replacement support may become a rare resource
- Top tips:
  - Don’t go super-dry
  - Consider insensible losses (ambient temperature)
  - Remember that high airway pressures and PEEP can compromise renal perfusion pressure

If renal replacement therapy is required….

- If using conventional haemofiltration:
  - Intermittent filtration should be fine in most patients
  - Preserve sets (if possible use a set on a patient for maximum time then move machine onto a different patient)
  - Filter clot is a problem: consider higher dose thromboprophylaxis or heparin via the circuit
- If your hospital has renal physician support:
  - Consider if dialysis can be used if a water supply is available or can be plumbed
  - Either slow low efficiency dialysis (SLED) or intermittent haemodialysis
  - A handful of UK centres used peritoneal dialysis - tricky (especially in proned patients) but possible

Treatments

- Dexamethasone: 6mg daily for 10 days
- Remdesivir – do not start in ICU; if patient on it already, continue for 5 days then stop
- Tociluzimab – single dose will suffice

- Nothing else is evidence based
- Do not feel bad if the fancy drugs are not available
- The biggest impact will be the staffing, infrastructure and organisation of your workforce – and much of this will be out of your control

Consider this:

- There is equipoise on choice of ventilatory support – so do what best fits your infrastructure:
  - Think about staffing
  - Think about oxygen demand
  - Think about medicines / feeding etc
  - Think about equipment (not just hardware but also consumables)

- Do the simple things as well as you can:
  - Give every patient a daily FASTHUG:
    - Feeding
    - Analgesia
    - Sedation
    - Thromboprophylaxis
    - Hydration
    - Ulcer prophylaxis
    - Glycaemic control

Use your team as effectively as you can

- Proning teams (including surgeons)
- Line teams (including radiologists / cardiologists)
- Intubation teams (anaesthetists, theatre support staff)
- FAST HUG / housekeeping teams – non intensive care staff
- Communications teams (with families) – non intensive care staff

The key to good critical care is…

The staff

- We are all in this together
  - It's hard, but flattened hierarchies can help
  - Everyone must feel empowered to speak up (in this setting, patient harm very likely to occur due to human factors / accidental mistakes)
- Look after 'surge staff'
  - Resources are available to help train surge staff
  - Try to allocate them in a way which maximises benefit of their existing experience (e.g. surgeons on proning teams)
- Look after each other:
  - Psychological harm common and most likely to occur in core ICU staff, particularly senior staff with senior responsibility (and especially nurses)
  - Long haul not short sprint
  - Take time, spend time with your loved ones, eat, sleep

Q&A session

Led by Dr Alison Tavaré, West of England Regional Clinical Lead for COVID Oximetry @home

Please ask any questions using the chat function.

SAHF/AHSN UK-India COVID-19 webinar series

FLYERS TO UPDATE

HOSPITAL AND ICU MANAGEMENT OF COVID-19

Friday 7 May, 8.30-9.30pm (India Standard Time) / 4-5pm (UK BST)

This is the second in a series of UK-India COVID-19 webinars from the South Asian Health Foundation, Academic Health Science Network (AHSN Network) and Learn with Nurses, sharing NHS experiences of COVID-19 specifically regarding hospital and ICU management with health and care professionals in other countries.

- Hospital therapies for COVID-19
- Glycaemic management
- ICU management
- Anticoagulation therapy
- Question and answer session

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Further information:

Panellists will include:

- **Dr Sanjay Bhagani,** Consultant Physician/Associate Professor, Royal Free Hospital

- **Professor Ramani Moonesinghe,** National Clinical Director for Critical and Perioperative Care, NHSE England/NHS Improvement. Honorary Consultant in Anaesthesia and Perioperative Medicine, University College Hospital

- **Professor Kamlesh Khunti,** Professor of Primary Care Diabetes & Vascular Medicine, GP and SAHF Trustee

- **Professor Wasim Hanif,** Professor of Diabetes & Endocrinology, Consultant Physician, & Head of Service and SAHF Trustee

- **Dr Pratima Chowdary,** Consultant Haematologist, Royal Free Hospital

- **Dr Tara Sood,** Consultant, Royal Free Hospital and National Clinical Lead – Same Day Urgent Care

- **Dr Nikhil Tandon,** Consultant Endocrinologist and Head of Department of Endocrinology, Metabolism and Diabetes at All India Institute of Medical Sciences (AIIMS).

Register:

TO REGISTER FOR THIS SEMINAR CLICK HERE OR GO TO: https://zoom.us/webinar/register/WN_Wsg4G5k7TgO2ob6AL5UZjw

If the Zoom webinar has reached capacity, you can also watch a livestream of the webinar on YouTube at: https://www.youtube.com/c/AHSNNetwork/live

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Thank you