Peer reviewed version

Link to published version (if available):
[10.1007/s00134-021-06448-5](#)

Link to publication record in Explore Bristol Research
PDF-document

University of Bristol - Explore Bristol Research
General rights

Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19:

REMAP-CAP randomized control trial

Running Head

REMAP-CAP COVID-19 Antiviral Therapy RCT

The REMAP-CAP Investigators

Yaseen M. Arabi, MD[1,2,3,]; Anthony C. Gordon, MBBS, MD[4,5]; Lennie P.G. Derde, MD, PhD.[6,7]; Alistair D. Nichol, PhD[8,9,10]; Srinivas Murthy, MDCM, MHSc[11]; Farah Al Beidh, PhD[4]; Djillali Annane, MD,PhD[12, 13, 14]; Lolowa Al Swaidan, M.Sc, [02, 03,15,] Abi Beane, PhD[16]; Richard Beasley,DSc[17]; Lindsay R. Berry, PhD[18]; Zahra Bhimani, MPH[19]; Marc J.M. Bonten, PhD[7,20]; Charlotte A. Bradbury, MD, PhD, FRCPath[21,22]; Frank M. Brunkhorst, MD[23]; Meredith Buxton,PhD[24]; Adrian Buzgau,MSc[25]; Allen Cheng,PhD[25,26]; Menno De Jong, MD, PhD[27]; Michelle A. Detry, PhD[18]; Eamon J. Duffy, BPharm[28]; Lise J. Estcourt, MD, DPhil[29,30]; Mark Fitzgerald, PhD[18]; Rob Fowler, MDCM[31,32,33]; Timothy D. Girard, MD,MSCI[34,35] Ewan C. Goligher, MD, PhD[36]; Herman Goossens, PhD[37]; Rashan Haniffa, PhD[38,39,40]; Alisa M. Higgins, PhD[9]; Thomas E. Hills, PhD[17,41]; Christopher M. Horvat, MD, MHA[34,35,42]; David T. Huang, MD, MPH[34,35]; Andrew J. King, PhD[35]; Francois Lamontagne, MD[43,44]; Patrick R. Lawler, MD, MPH[31,36,45] Roger Lewis, MD, PhD[18,46]; Kelsey Linstrum, MS[34,35]; Edward Litton, PhD[47,48,49]; Elizabeth Lorenzi, PhD[18]; Salim Malakouti, BCompSc[34,50]; Daniel F. McAuley, MD[51,52]; Anna McGlothlin, PhD[18]; Shay Mcguinness, MB ChB,[17,25,53]; Bryan J. McVerry, MD[34,35]; Stephanie K. Montgomery, MSc[34,35]; Susan C. Morpeth, MBChB, PhD[54]; Paul R. Mouncey, MSc[55]; Katrina Orr, BPharm, PGCert Clin Trial[56]; Rachael Parke, PhD[17,53,57]; Jane C. Parker, B.N[09]; Asad E. Patanwala, PharmD, MPH[58,59]; Kathryn M. Rowan, PhD[60]; Marlene S. Santos, MD, MSc.[19]; Christina T. Saunders., PhD[18]; Christopher W. Seymour, MD[34,35]; Manu Shankar-Hari, PhD[61,62]; Steven Y. C. Tong, MBBS,[63,64]; Alexis F. Turgeon, MD, MSc[65,66]; Anne M. Turner, MPH[17]; Frank Leo Van de Veerdonk, MD, PhD[67]; Ryan Zarychanski, MD, MSc,[68]; Cameron Green, MSc[09]; Scott Berry, PhD[18]; John C. Marshall, MD[19,69]; Colin McArthur, MBChB[70]; Derek C. Angus, MD,MPH[34,35]; Steven A. Webb, MBBS, PhD, MPH, FRACP, FCICM, FAAHMS,[09,49]

1. Intensive Care Department, Ministry of the National Guard - Health Affairs, Riyadh, Kingdom of Saudi Arabia
2. King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia
3. King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia
4. Imperial College London, Division of Anaesthetics, Pain Medicine and Intensive Care, London, United Kingdom
5. Imperial College Healthcare NHS Trust, Intensive Care Unit, London, United Kingdom
6. University Medical Center Utrecht, Intensive Care Center, Utrecht, The Netherlands
7. University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands
8. University College Dublin Clinical Research Centre at St Vincents University Hospital, Dublin, Ireland
9. The Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia
10. The Alfred Hospital, Melbourne, Australia
11. University of British Columbia, Department of Pediatrics, Vancouver, Canada
12. Department of Intensive Care, Hôpital Raymond Poincaré (APHP), 92380 Garches

1

13. Laboratory of Infection & Inflammation ; U1173, School of Medicine Simone Veil, University Versailles Saint Quentin & University Paris Saclay, INSERM, 78423 Montigny le Bretonneux
14. FHU SEPSIS (Saclay and Paris Seine Nord Endeavour to PerSonalize Interventions for Sepsis) and RHU RECORDS (Rapid rEcognition of CORticosteroiD resistant or sensitive Sepsis), ANR-18-RHUS60004 Garches 92380, France
15. Pharmaceutical Care Services, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia
16. University of Oxford, Nuffield Department of Clinical Medicine, Oxford, United Kingdom
17. Medical Research Institute of New Zealand, Wellington, New Zealand
18. Berry Consultants, Austin, TX, United States
19. St. Michael's Hospital Unity Health Toronto, Critical Care Department, Toronto, Canada
20. Department of Medical Microbiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
21. University of Bristol, Faculty of Health Sciences, Bristol, United Kingdom
22. University Hospitals Bristol and Weston NHS Foundation Trust, Bristol Hematology and Oncology Centre, Bristol, United Kingdom
23. Jena University Hospital, Anesthesiology and Intensive Care Medicine, Jena, Germany
24. Global Coalition for Adaptive Research, San Francisco, California, United States of America
25. Monash University, Melbourne, Australia
26. Alfred Health, Department of Infectious Diseases, Melbourne, Australia
27. Department of Medical Microbiology & Infection Prevention, Amsterdam University Medical Centers, Amsterdam, The Netherlands
28. Infectious Disease, Auckland City Hospital, Auckland, New Zealand
29. NHS Blood and Transplant, Oxford, United Kingdom
30. University of Oxford, Radcliffe Department of Medicine, Oxford, United Kingdom
31. University of Toronto, Ontario, Canada
32. Sunnybrook Health Sciences Centre, Toronto, Canada
33. Canadian Critical Care Trials Group, Canada
34. UPMC Health System, Pittsburgh, PA, United States of America
35. University of Pittsburgh Schools of the Health Sciences, Pittsburgh, PA, United States of America
36. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada
37. University of Antwerp, Wilrijk, Belgium
38. National Intensive Care Surveillance- Mahidol Oxford Research Unit, Colombo, Sri Lanka
39. University of Oxford, Centre for Tropical Medicine and Global Health, Oxford, United Kingdom
40. University College Hospital, Critical Care Department, London, United Kingdom
41. Auckland District Health Board, Auckland, New Zealand
42. UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, United States of America
43. Université de Sherbrooke, Sherbrooke, Canada
44. Centre de recherche du CHU de Sherbrooke, Sherbrooke, Canada
45. Peter Munk Cardiac Centre at University Health Network, Toronto, Canada
46. Harbor-UCLA Medical Center, Torrance, California, United States of America
47. Fiona Stanley Hospital, Intensive Care Unit, Perth, Australia
48. St. John of God Hospital Subiaco, Intensive Care Unit, Perth, Australia
49. University of Western Australia, School of Medicine, Perth, Australia
50. Computer Science, University of Pittsburgh, Pittsburgh, PA, United States of America
51. Queen's University Belfast, Wellcome-Wolfson Institute for Experimental Medicine, Belfast, Northern Ireland
52. Royal Victoria Hospital, Regional Intensive Care Unit, Belfast, Northern Ireland
53. Auckland City Hospital, Cardiothoracic and Vascular Intensive Care Unit, Auckland, New Zealand
54. Middlemore Hospital, Microbiology Laboratory, Auckland, New Zealand
55. Intensive Care National Audit & Research Centre, Clinical Trials Unit, London, United Kingdom
56. Fiona Stanley Hospital, Pharmacy Department, Perth, Australia
57. The University of Auckland, School of Nursing, Auckland, New Zealand
58. University of Sydney, School of Pharmacy, Sydney, Australia
59. Department of Pharmacy, Royal Prince Alfred Hospital, Sydney, Australia
60. Intensive Care National Audit & Research Centre (ICNARC), London, United Kingdom
61. Guy's and St Thomas' NHS Foundation Trust, Critical Care Medicine, London, United Kingdom
62. King's College London, School of Immunology and Microbial Sciences, London, United Kingdom
63. Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
64. Department of Infectious Diseases, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
65. Laval University, Department of Anesthesiology and Critical Care Medicine, Division of Critical Care Medicine, Québec City, Québec, Canada
66. CHU de Québec - Université Laval Research Center, Population Health and Optimal Health Practices Research Unit, Trauma - Emergency - Critical Care Medicine, Québec City, Québec, Canada
67. Radboudumc, Dept Internal Medicine, Nijmegen, The Netherlands
68. University of Manitoba, Winnipeg, Canada

69. Department of Surgery, University of Toronto, Toronto, Canada
70. Auckland City Hospital, Department of Critical Care Medicine, Auckland, New Zealand

Word Count: Summary: 250 words, Text: 3207

Corresponding Author:

Yaseen M. Arabi, MD, FCCP, FCCM, ATSF

ORCID: 0000-0001-5735-6241
Intensive Care Department, Ministry of the National Guard Health Affairs, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia
P.O. Box 22490 Riyadh 11426, ICU 1425
E-mail: arabi@ngha.med.sa
Telephone: +966-11-8018855
Fax: +966-11-80-18880

Abstract

Purpose: To study the efficacy of lopinavir-ritonavir and hydroxychloroquine in critically ill patients with coronavirus disease 2019 (COVID-19)

Methods: Critically ill adults with COVID-19 were randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir, and hydroxychloroquine or no antiviral therapy (control). The primary endpoint was an ordinal scale of organ-support free days. Analyses used a Bayesian cumulative logistic model and expressed treatment effects as an adjusted odds ratio (OR) where an OR >1 is favorable.

Results: We randomized 694 patients to receive lopinavir-ritonavir (n=255), hydroxychloroquine (n=50), combination therapy (n=27) or control (n=362). The median (IQR) organ support-free days among patients in lopinavir-ritonavir, hydroxychloroquine, and combination therapy groups was 4 (–1 to 15), 0 (–1 to 9) and –1 (–1 to 7), respectively, compared to 6 (–1 to 16) in the control group with in-hospital mortality of 88/249 (35%), 17/49 (35%), 13/26 (50%), respectively, compared to 106/353 (30%) in the control group. The three interventions decreased organ support-free days compared to control (OR [95% credible interval]: 0.73 [0.55, 0.99], 0.57 [0.35, 0.83] 0.41 [0.24, 0.72]), yielding posterior probabilities that reached the threshold futility (≥99.0%), and high probabilities of harm (98.0%, 99.9% and >99.9%, respectively). The three interventions reduced hospital survival compared with control (OR [95% CrI]: 0.65 [0.45, 0.95], 0.56 [0.30, 0.89], and 0.36 [0.17, 0.73]), yielding high probabilities of harm (98.5% and 99.4% and 99.8%, respectively).

Conclusion: Among critically ill patients with COVID-19, lopinavir-ritonavir, hydroxychloroquine, or combination therapy worsened outcomes compared to no antiviral therapy.

Trial registration Clinicaltrials.gov identifier: NCT02735707

Keywords

Adaptive platform trial; intensive care; pneumonia; pandemic; COVID-19; lopinavir-ritonavir, hydroxychloroquine

Declaration

adaptive and platform clinical trials, received support for its role in the design, conduct, and analysis of REMAP-CAP. Dr. Lewis is the Senior Medical Scientist at Berry Consultants, LLC; **EL** reports grants from EU, grants from Australian National Health and Medical Research Council , grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; **DFM** reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis and Eli Lilly, and from sitting on a DMEC for a trial undertaken by Vir Biotechnology. In addition his institution has received funds from grants from several funders for studies in patients with ARDS and COVID-19. In addition, DFM has a patent (US8962032) issued to his institution for a treatment for inflammatory disease. He is a Director of Research for the Intensive Care Society and NIHR EME Programme Director; **AM** reports grants from EU-PREPARE, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; B JM reports grants from Translational Breast Cancer Research Consortium, grants from UPMC Learning While Doing Program, during the conduct of the study; grants from NIH/NHLBI, grants from Bayer Pharmaceuticals, Inc, outside the submitted work; **SCM** reports grants from Health Research Council of New Zealand, during the conduct of the study; **PRM** reports grants from National Institute for Health Research, grants from European Union FP7 (PREPARE), during the conduct of the study; **RP** reports grants from Fisher and Paykel Healthcare NZ Ltd, outside the submitted work; **KMR** reports grants from European Union, grants from UK National Institute for Health Research, during the conduct of the study**; CTS.** reports grants from EU PREPARE, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; **CWS**. reports grants from NIH, personal fees from Beckman Coulter, outside the submitted work; **MSH** reports other from National Institute For Health Research, outside the submitted work; **AMT** reports grants from Health Research Council of New Zealand, during the conduct of the study; **FVV** reports personal fees from Gilead, personal fees from Sobi, outside the submitted work; **SB** reports personal fees from Berry Consultants, during the

Availability of data and material

Qualified researchers registered with an appropriate institution can request access to deidentified patient data after 9 months of publication through submission of a proposal to the corresponding author. The proposal will be reviewed and approved by the REMAP-CAP ITSC to ensure that any proposed publication is of high quality, honours the commitments made to the study patients in the consent documentation and ethical approvals, and is compliant with sponsor restrictions and relevant legal and regulatory requirements (eg, relating to data protection and privacy). The ITSC committee will have the right to review and comment on any draft manuscripts before publication. A contract will also be signed.

*Authors Contributions***:**

Project Administration: YMA, ACG, LPGD, ADN, SM, FAB, ZB, ECG, HG, DTH, AJK, KL, SSM, SKM, PRM, JCP, KMR, MSS, CG, SB, JCM, CM, DA, SAW.

Resources: ACG, LPGD, ADN, SM, RB, MJMB, FMB, MB, KMR, JCM, CM, DA, SAW.

Software: LRB, AB, MF, AMH, CMH, DTH, RJL, E Lorenzi, SSM, AM, SKM, PRM, JCP, KMR, CTS, CG, SB, CM, SAW.

Supervision: YMA, ACG, LPGD, ADN, SM, MJMB, FMB, HG, BJM, KMR, SB, JCM, CM, DA, SAW.

Validation: FAB, AB, TDG, AMH, CMH, DTH, KL, BJM, SKM, PRM, JCP, CTS, AMT, CG, CM.

Visualization: LRB, MAD, MF, RJL, E Lorenzi, AM, CTS, SB.

Writing –Draft: YMA, ACG, LPGD, ADN, SM, SB, JCM, CM, DA, SAW.

Writing – Review & Editing: YMA, ACG, LPGD, ADN, SM, FAB, DA, LAS, AB, RB, LRB, ZB, MJMB, CAB, FMB, MB, AB, AC, ADJ, MAD, EJD, LJE, MF, RF, TDG, ECG, HG, RH, AMH, TEH, CMH, DTH, AJK, FL, PRL, RJL, KL, E Litton, E Lorenzi, SSM, DFM, AM, SMC, BJM, SKM, SCM, PRM, KO, RP, JCP, AEP, KMR, MSS, CTS, SWS, MSH, SYCT, AFT, AMT, FVV, RZ, CG, SB, JCM, CM, DA, SAW.

Ethics approval

The trial was approved by the relevant ethics committees in all regions.

Consent to participate

Written or verbal informed consent, in accordance with regional legislation, was obtained

from all patients or from their surrogates

Consent for publication

All authors approved the manuscript for submission

Introduction

In less than 18 months~~one year~~, Coronavirus disease 2019 (COVID-19), caused by the

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has infected more than

~~163~~ 167 million people across the globe and caused more than 3.~~8~~9 million deaths.[1] Given

the emerging nature of the virus, several repurposed agents were considered as potential

antiviral agents for COVID-19.[2] Lopinavir-ritonavir and hydroxychloroquine were proposed

based on data from Severe Acute Respiratory Syndrome (SARS) and Middle East

Respiratory Syndrome (MERS).[3-8] In vitro, lopinavir and hydroxychloroquine inhibit SARS-

CoV-2 replication.[9-11] A pharmacokinetic analysis predicted that therapeutic doses of

lopinavir, ritonavir, and hydroxychloroquine would achieve concentrations in both plasma

and lungs that are inhibitory of SARS-CoV-2 [12] In a ferret infection model for SARS-CoV-2

infection, lopinavir-ritonavir or hydroxychloroquine resulted in improved clinical scores

compared to the control group, although the virus titers were not different.[13]~~[13]~~ The two

agents became widely used.[14-16] Several national guidelines for treatment of COVID-19

listed lopinavir-ritonavir and hydroxychloroquine (or chloroquine) as therapeutic options,[17]

and in March 2020, the US Food and Drug Administration (FDA) issued an Emergency Use

Authorization for hydroxychloroquine, which was revoked later in June 2020[18].

Subsequently, clinical trials were published, including the RECOVERY and Solidarity trials,

demonstrating lack of benefit of lopinavir-ritonavir and hydroxychloroquine in hospitalized

patients with COVID-19, although the proportions of critically ill patients were small.[19-23] In

addition, most trials tested individual interventions, therefore, the effect of the combination of

lopinavir-ritonavir and hydroxychloroquine and the interaction with other agents used for the

treatment of COVID-19 such as corticosteroids and interleukin-6 (IL-6) receptor antagonists

are unknown.

The objective of this trial was to evaluate the effects of lopinavir-ritonavir,

hydroxychloroquine, and combination therapy of lopinavir-ritonavir and hydroxychloroquine

compared to no COVID-19 antiviral therapy on organ support-free days in critically ill patients with COVID-19.

Methods

Study Design

The Randomized, Embedded, Multifactorial Adaptive Platform trial (NCT02735707) is an ongoing international adaptive platform trial designed to determine the best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings.[24] In the pandemic stratum, patients requiring organ support in an intensive care unit were enrolled as Severe State, and hospitalized patients not receiving organ support in the intensive care unit (ICU) were enrolled as Moderate State. Within the COVID-19 Antiviral Therapy Domain, patients were randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir, and hydroxychloroquine or control (no antiviral agents against COVID-19). The pandemic stratum included other domains each with multiple interventions, and patients could be randomized to interventions in multiple domains (Statistical Analysis Committee Primary Analysis Report, Supplementary Appendix). This report describes the results of the patients in the Severe State in the COVID-19 Antiviral Therapy Domain (Table S1). Some sites also enrolled patients in the Moderate State. These patients (n=32) are not included in the current analysis, though descriptive data are reported in the Supplementary Appendix.

The trial's protocol documents (REMAP-CAP Core Protocol, REMAP-CAP Pandemic Appendix to the Core Protocol, COVID-19 Antiviral Therapy Domain-Specific Appendix) and statistical analysis plans (REMAP-CAP Statistical Analysis Appendix, COVID-19 Antiviral Domain Statistical Analysis Plan) were posted online (www.remapcap.org) before analysis and are available in the Supplementary Appendix. The trial is managed by a blinded International Trial Steering Committee and is overseen by an unblinded Data and Safety Monitoring Board (DSMB).

The trial was approved by the relevant ethics committees in all regions. Written or verbal informed consent, in accordance with regional legislation, was obtained from all patients or their surrogates.

Patients

Patients were eligible for the COVID-19 Antiviral Therapy Domain- Severe State if they were ≥18-years old, admitted with suspected or confirmed COVID-19, and were receiving respiratory or cardiovascular organ failure support in an intensive care unit (ICU). Organ support included the provision of invasive mechanical ventilation, non-invasive mechanical ventilation, high-flow nasal cannulae with a flow rate of at least 30 liters per minute and a fractional inspired oxygen concentration of 0.4 or higher, or the infusion of vasopressor or inotropes for shock. In addition to patients enrolled in the COVID-19 Antiviral Therapy Domain, the primary model included patients enrolled in other domains in Severe State, for covariate adjustment. Patients were excluded from the platform if 1) death was deemed to be imminent during the next 24 hours AND one or more of the patient, substitute decision-maker, or attending physician are not committed to full active treatment, 2) expected to be discharged from hospital the same day or the following day, 3) more than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection, or 4) previous participation in this REMAP-CAP within the last 90 days. Additionally, patients were excluded from the COVID-19 Antiviral Therapy Domain in the presence of any of the following exclusion criteria 1) known hypersensitivity to lopinavir-ritonavir and hydroxychloroquine, 2) receiving lopinavir-ritonavir and hydroxychloroquine as a usual medication prior to this hospitalization, 3) known human immunodeficiency (HIV) infection (an exclusion criterion from receiving lopinavir-ritonavir), 4) severe liver failure (an exclusion criterion from lopinavir-ritonavir), 5) known or suspected pregnancy, 6) receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to the assessment of eligibility (an exclusion criterion from lopinavir-ritonavir), 7) high clinical risk of sustained ventricular dysrhythmia (an

exclusion criterion from hydroxychloroquine). Detailed platform and COVID-19 Antiviral

Therapy Domain-specific inclusion and exclusion criteria are listed in Table S2 in the

Supplementary Appendix.

Randomization and masking

Using a concealed online randomization system, patients were randomized to receive

lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir, and

hydroxychloroquine or control (no antiviral agents against COVID-19). Based on local

equipoise and drug availability, investigators at each participating site selected a priori two or

more interventions, one of which had to be control, to which patients could be randomized.

The REMAP-CAP platform uses response-adaptive randomization; however, the allocation

in the COVID-19 Antiviral Therapy Domain did not deviate from the starting equal ratio

before enrollment was halted. Although the interventions were given as open-label drugs,

neither the clinical staff nor the ITSC were provided any information about aggregate patient

outcomes.

Interventions

Lopinavir-ritonavir was administered for 5 days minimum, up to a maximum of 14 days or

until ICU discharge whichever occurred first. Lopinavir–ritonavir was administered at a dose

of 400 mg of lopinavir and 100 mg of ritonavir (Kaletra, AbbVie) every 12 hours. For patients

with a gastric tube who were unable to swallow tablets, lopinavir-ritonavir (at the same dose)

was administered as a 5-ml suspension every 12 hours or alternatively as two dissolved

tablets or four crushed tablets (double dose), noting that systemic absorption is reduced by

approximately 50% for crushed tablets.[25] Hydroxychloroquine was administered as two

loading doses of 800 mg, 6-hours apart, followed 6 hours later by 400 mg 12-hourly for 12

doses. This dose regimen was supported by pharmacokinetic modelling and by guidance

regarding safety from clinicians with experience with the use of hydroxychloroquine for the

treatment of severe malaria.[26] If a patient was unable to swallow, crushed

hydroxychloroquine tablets were administered via an enteral tube. The study protocol

provided guidance for monitoring for drug interactions and QTc prolongation (Supplementary

Appendix). Other aspects of care were provided as per each site's standard of care.

Outcomes

The primary outcome was a composite ordinal scale of the number of respiratory and

cardiovascular organ support-free days (OSFD) and in-hospital mortality with death assigned

the worst outcome (–1). Among survivors, respiratory and cardiovascular organ support-free

days are calculated up to day 21, such that a higher number represents faster recovery. The

definitions of respiratory and cardiovascular organ support were the same as in the inclusion

criteria. This outcome was used in a recent FDA-approved registration trial, with a 1.5-day

difference considered to be the minimal clinically important difference.[27][27] Each

component of the composite, organ support free-days in survivors and in-hospital mortality,

are reported separately. Secondary a priori outcomes were 90-day survival, respiratory

support-free days, cardiovascular support-free days, time to ICU and hospital discharge, a

composite outcome of progression to invasive mechanical ventilation, extracorporeal

membrane oxygenation (ECMO), or death among those not ventilated at baseline, the World

Health Organisation ordinal scale assessed at 14 days and SARS-CoV-2 RNA clearance

from respiratory specimens (COVID-19 Antiviral Therapy Domain-Specific Appendix and

COVID-19 Antiviral Domain SAP, Supplementary Appendix).[28] The WHO scale is a clinical

progression scale that reflects patient trajectory and resource use over the course of clinical

illness and ranges from 0 (no disease) to 8 (death). Safety a priori outcomes included

serious adverse events and serious ventricular arrhythmia or sudden unexpected death

while not receiving continuous cardiac monitoring (COVID-19 Antiviral Therapy Domain-

Specific Appendix and COVID-19 Antiviral Domain SAP, Supplementary Appendix).

Statistical Analysis

REMAP-CAP uses a Bayesian design with no prespecified sample size; enrollment in any intervention continues until a pre-defined statistical trigger is met at an adaptive analysis. Detailed statistical analysis plan is provided in the Supplementary Appendix (COVID-19 Antiviral Domain SAP). The primary model was run by an unblinded Statistical Analysis Committee, who conduct all protocol-specified trial update analyses independently of the ITSC, reporting results directly to the DSMB (Supplementary appendix).

The primary analysis was intention-to-treat, with a Bayesian cumulative logistic model with neutral prior distributions for treatment effects. The model estimated the proportional odds ratio for the ordinal primary outcome of organ support-free days. The primary analysis was adjusted for location (site, nested within country), age (categorized into 6 groups), sex, and time period (2-week calendar epochs). The primary analysis was conducted on the REMAP-CAP Severe State cohort, including any patient randomized to at least one domain as of November 19, 2020 (Supplementary Appendix, Table S3). This approach allowed maximal incorporation of all information, providing a robust estimation of the coefficients of all covariates, as per the REMAP-CAP design.[24] Lopinavir-ritonavir and hydroxychloroquine were modeled hierarchically to allow for borrowing among the interventions' effect estimates. This meant that the effects of lopinavir-ritonavir and hydroxychloroquine shared a mean representing a common "antiviral effect". Distinct intervention-specific effects were estimated but the effects of lopinavir-ritonavir and hydroxychloroquine were shrunk toward the overall estimate of antiviral effect based on the heterogeneity of effects in the data.[15] The combination therapy effect was estimated as the sum of the lopinavir-ritonavir and hydroxychloroquine and effects with an interaction effect between lopinavir-ritonavir and hydroxychloroquine.

The analysis of the primary outcome was repeated in models restricted to patients in the Unblinded cohort, which included severe COVID-19 patients randomized to the COVID-19

Antiviral Therapy Domain or other previously reported interventions and domains (Corticosteroid Domain and reported arms of the Immune Modulation Therapy Domain). We conducted additional analyses restricting to patients who were randomized concurrently with the lopinavir-ritonavir group or with hydroxychloroquine and combination therapy groups. Other analyses were conducted excluding those who tested negative for SARS-CoV-2, those in the COVID-19 Antiviral Therapy Domain cohort with no adjustment for assignment to interventions in other domains, and on the per-protocol cohort (Supplementary Appendix, Table S3). Additional secondary and sensitivity analyses of the primary outcome are described in the Supplementary Appendix.

Similar primary, secondary, and sensitivity analyses were conducted to estimate the effect on hospital survival. Interactions of antiviral interventions with corticosteroid therapy and with IL-6 receptor antagonists (tocilizumab, sarilumab) were modeled. The effect of antiviral interventions on secondary outcomes was assessed using the Unblinded cohort (defined above).

The Bayesian analysis models result in posterior distributions for parameters of interest including proportional odds ratios. Results from models of ordinal and dichotomous endpoints are reported as posterior median odds ratios (OR) and 95% credible intervals. Results from models of time-to-event endpoints are reported as posterior median hazard ratios (HR) and 95% CrIs. For consistency of interpretation, all models are parameterized so that an OR/HR greater than 1 indicates patient benefit relative to the control group, and an OR/HR less than 1 indicates patient harm relative to the control group. The model allows the calculation of the posterior probability that each COVID-19 Antiviral Therapy Domain intervention (including the control group) was optimal, superior to control (OR/HR>1), harmful (OR/HR<1) or futile (OR/HR<1.2). In this manuscript, we present the posterior probabilities of futility for the primary models and harm for all models; the posterior probabilities of being optimal or superior are available in the Statistical Analysis Committee Primary Analysis Report and ITSC Secondary Analysis Report in the Supplementary

Appendix. An intervention was deemed harmful if the posterior probability of harm compared to control was greater than 90% (REMAP-CAP Pandemic Appendix to the Core Protocol-Supplementary Appendix). There was no imputation of missing primary (or secondary) outcomes.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The unblinded Statistical Analysis Committee had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Patients

Enrollment into the REMAP-CAP pandemic stratum started on March 9, 2020, and into the four arms of the COVID-19 Antiviral Therapy Domain on April 8, 2020, with patients enrolled from 99 sites across 8 countries (Table S1, Supplementary Appendix). Enrollment into the hydroxychloroquine and combination therapy arms was halted temporarily on May 23, 2020, based on published concerns regarding the safety and efficacy of hydroxychloroquine, but resumed later in a few sites, although only 3 patients (2 in the hydroxychloroquine arm and 1 in the combination therapy arm) were enrolled after May 23, 2020, from one site. The hydroxychloroquine and combination therapy arms were closed completely on July 13, 2020. Enrollment into the lopinavir-ritonavir arm was halted on November 19, 2020, after reaching the prespecified futility threshold. Enrollment into the Corticosteroid Therapy Domain was halted on June 17-2020, while the COVID-19 Antiviral Therapy Domain was actively enrolling into the lopinavir-ritonavir and control groups, and enrollment into no immune modulation intervention in the Immune Modulation Domain was halted on November 19, 2020, simultaneously with lopinavir-ritonavir based on the results of the adaptive analysis.

The reports of corticosteroids and IL-6 receptor antagonists (tocilizumab and sarilumab) have been published.[29, 30] [24]

During the study period, 2046 patients with suspected or confirmed COVID-19 were enrolled in one or more REMAP-CAP domains (Figure 1, Table S1, Supplementary Appendix), with 726 patients randomized within the COVID-19 Antiviral Therapy Domain (268 assigned to lopinavir-ritonavir, 52 to hydroxychloroquine, 29 to combination therapy of lopinavir-ritonavir and hydroxychloroquine and 377 to control). Within this domain, there were 32 patients for whom consent was withdrawn or not obtained and 17 patients with unavailable follow-up data on the primary outcome. As a result, 694 were included in this report, of whom 677 were analyzed for the primary outcome. Of the included patients, 502/694 (72.3%) were enrolled from the United Kingdom, 100/694 (14.4%) from Saudi Arabia, 42/694 (6.1%) from Canada, and remaining from other countries (Table S1).

The baseline characteristics were balanced across patients randomized concurrently with lopinavir-ritonavir (Table 1) and across patients randomized concurrently with hydroxychloroquine and combination therapy (Table S4). Of enrolled patients, 689/693 (99.4%) were receiving respiratory support (high-flow nasal cannula, noninvasive or invasive ventilation or ECMO) and 137/693 (19.8%) were receiving vasopressor support.

Intervention Fidelity

Information on lopinavir-ritonavir and hydroxychloroquine dosing during the study period were available for 665/694 (95.8%) of patients (Tables S5 and S6, Supplementary Appendix). Among those assigned to the lopinavir-ritonavir, 220/247 (89.1%) received the allocated intervention for 7.0 days (5.0-12.0), among those assigned to hydroxychloroquine 46/49 (93.9%) for 7.0 days (5.0-12.0), among patients assigned to combination therapy 20/24 (83.3) for 11.5 days (5.8-14.0) and among those assigned to control group 360/362 (99.4%) received the assigned interventions (Tables S5 and S6, Supplementary Appendix). Concomitant therapy with corticosteroids, IL-6 receptor antagonists (Tocilizumab and

Sarilumab), and remdesivir across patients randomized concurrently with lopinavir-ritonavir (Table S5, Supplementary Appendix) and across patients randomized concurrently with hydroxychloroquine and combination therapy (Table S6, Supplementary Appendix) were generally balanced.

Primary Outcome

The median (IQR) organ support-free days among patients in lopinavir-ritonavir, hydroxychloroquine, and combination therapy groups were 4 (−1 to 15), 0 (−1 to 9) −1 (−1 to 7), respectively, compared to 6 (−1 to 16) days in the control group (Table 2, Figure 1). Compared with control, the corresponding median adjusted ORs (95% CrI) were 0.73 (0.55-0.99) for lopinavir-ritonavir, 0.57 (0.35-0.83) for hydroxychloroquine and 0.41 (0.24-0.72) for combination therapy, yielding posterior probabilities that reached the criteria for futility (all 99.9% or greater), yielding high posterior probabilities of harm (98.0%, 99.9% and >99.9%, respectively, Table 2). In-hospital mortality among patients in lopinavir-ritonavir, hydroxychloroquine, combination therapy was 88/249 (35.3%), 17/49 (34.7%), 13/26 (50.0%), respectively, compared to 106/353 (30.0%) in the control group (Table 2, Figure 2). In the primary analysis of hospital survival, the three interventions decreased survival compared to control, with the corresponding median adjusted ORs (95% CrI) of 0.65 (0.45-0.95), 0.56 (0.36-0.89), 0.36 (0.17-0.73), respectively, yielding high probabilities of harm (98.5% and 99.4% and 99.8%, respectively, Table 2). Estimates from secondary and sensitivity analyses of the organ support-free days and hospital survival, including analyses restricting to concurrent controls of lopinavir-ritonavir and concurrent controls of hydroxychloroquine/combination therapy groups were consistent with the primary analyses (Figure S1, Tables S7 and S8 in Supplementary appendix).

Secondary Outcomes

Lopinavir-ritonavir, hydroxychloroquine, and combination therapy resulted in a longer time to both ICU and hospital discharge compared with control and reduced survival over 90 days.

All secondary outcome analyses yielded high posterior probabilities of futility and harm (Table 3). The distribution of SARS-CoV-2 RNA clearance among patients randomized to receive lopinavir–ritonavir, hydroxychloroquine, combination therapy, and control was not visually different (Figure S2, Supplementary Appendix). The full model was not performed for this outcome because of limited follow-up reverse transcription-polymerase chain reaction (RT-PCR) data.

Safety Outcomes

Serious adverse events were reported in 13/255 (5.1%) patients randomized to lopinavir-ritonavir, 3/50 (6.0%) to hydroxychloroquine, 1/27 (3.7%) to combination therapy, and 12/362 (3.3%) to control. Serious ventricular arrhythmia or sudden unexpected death were reported in 6/239 (2.5%) patients randomized to lopinavir-ritonavir, 2/49 (4.1%) to hydroxychloroquine, 2/26 (7.7%) to combination therapy, and 10/435 (2.9%) to control (Table 3).

Subgroup analyses and interactions with corticosteroids and IL-6 antagonists:

The effects of lopinavir-ritonavir, hydroxychloroquine and combination therapy on the primary outcome were similar across patients who were mechanically ventilated or not, and patients who were in shock or not, at the time of enrollment (Tables S9 and S10, Supplementary Appendix). There was no meaningful interaction between treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy and the effects of corticosteroids or IL-6 receptor antagonists on organ support-free days or hospital survival. (Table S11, Table S12, and Statistical Analysis Committee Primary Analysis Report, Supplementary Appendix).

Discussion

Among critically ill patients with COVID-19, treatment with lopinavir-ritonavir, hydroxychloroquine or combination therapy did not improve outcomes and demonstrated a

high probability of being harmful. The findings were robust on sensitivity analyses, including analyses restricting to patients randomized concurrently with lopinavir-ritonavir arm or patients randomized concurrently hydroxychloroquine/combination therapy arms, and were consistent across secondary outcomes. Treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy demonstrated similar harm regardless of concomitant therapy with corticosteroids or IL-6 receptor antagonists with no differential effects across assignments to these therapies.

The observed clinical findings are discordant with in vitro data that demonstrate antiviral activity against SARS-CoV-2.[9-11] This may be related to several factors. It is unclear whether standard doses of lopinavir-ritonavir and hydroxychloroquine achieve adequate, safe and sustainable SARS-CoV-2 inhibitory concentrations in the lung and plasma as predicted by pharmacokinetic studies.[12, 31, 32] Both lopinavir-ritonavir and hydroxychloroquine are known for drug interactions and for their effects on prolonging QT prolongation and inducing cardiac arrhythmia. Hydroxychloroquine could worsen acute organ injury in critically ill patients with COVID-19 by inhibiting autophagy.[33] Additionally, ritonavir may increase the blood levels of hydroxychloroquine, further increasing the risk of adverse events with combination therapy.[34] We did not document significantly higher reports of serious ventricular arrhythmia or sudden unexpected death, but this analysis may be limited by the low number of events.

Previous studies have demonstrated a lack of benefit of lopinavir-ritonavir and hydroxychloroquine among hospitalized patients. These trials included predominantly patients admitted to hospital wards.[19, 20] For example, 4% of patients in the RECOVERY trial were receiving invasive mechanical ventilation, and 9% of patients in the Solidarity trial were mechanically ventilated at enrollment. On the other hand, REMAP-CAP which enrolled critically ill patients with COVID-19 receiving respiratory or cardiovascular support demonstrates a high probability of harm with these treatments. The observed harm in the

current trial may reflect the fact that critically ill patients are generally at a higher risk for harm compared to those who are less ill and are hospitalized on the wards.[35] Additionally, treatment at a later time point in the disease course, when the patient becomes critically ill, may correspond to viral replication becoming a less prominent feature in the disease pathogenesis, at which point the harm of antiviral therapy outweighs any potential benefit. The consistent findings from different sensitivity analyses, including the model restricted to patients in the COVID-19 Antiviral Therapy Domain, demonstrated the robustness of the findings.

This study highlights some of the features of the platform adaptive trial design used in REMAP-CAP. The platform adaptive trial design allows efficient enrollment into multiple therapeutic domains simultaneously and studying interactions with several agents; a feature that explains its increasing use in other medical fields including oncology and psychiatry. The design has the flexibility to allow different interventions to be added or removed into the platform, and to allow sites to choose some or all interventions, based on the local drug availability and equipoise. These features, along with the multicenter, multinational pragmatic conduct, contribute to the efficiency of the trial and the generalizability of the results, thus facilitating quick answers to multiple questions; a highly desirable feature during a global pandemic. Our study also illustrates the efficiency that is associated with the REMAP-CAP design; the ongoing recruitment of patients into the platform even after the hydroxychloroquine interventions stopped enrolling provided more information to be included in the analytical model, with appropriate adjustment for time, to inform specific treatment effects.[36, 37] The real-time adaptive analyses, which are based on data from patients with completed outcome information, allow quick decisions about halting interventions upon reaching futility thresholds. In the case of lopinavir-ritonavir, enrollment was halted once the futility threshold was met based on available data at the time of the adaptive analysis. By definition of the statistical triggers, the futility trigger must occur prior to the harm trigger. Because of this ordered relationship, the pre-specified trigger for harm is only evaluated at

the final analysis while the futility trigger is evaluated at adaptive and final analyses. Once outcome data on the remaining patients were completed, the final analysis demonstrated that the intervention was not only futile, but also harmful. This feature of frequent adaptive analyses allows for ongoing assessment for futility, thus reducing the unnecessary exposure of additional patients to non-effective or harmful therapies, compared to standard RCT. The drawback of this study design is that study groups may end up unequal in size, may not be entirely concurrent in time, or balanced in some of the baseline characteristics despite equal randomization at any given point.[38] In our study, this explains the different sizes of the study groups. Additionally, patients were enrolled in the hydroxychloroquine and combination therapy groups at a time when ICUs were under strain and corticosteroid therapy was not the standard of care. To address these recognized issues with the adaptive platform design, the primary model adjusted for time and site and corticosteroid therapy. To further address the possible effect of concurrent control, we conducted additional analysis restricted to the concurrent controls of lopinavir-ritonavir and to the concurrent controls of hydroxychloroquine and combination therapy groups. These analyses demonstrated that baseline characteristics (including invasive mechanical ventilation) and co-interventions (including corticosteroids and remdesivir) were generally balanced between intervention groups and respected concurrent controls, and that the treatment effects are consistent results with the primary analysis. To limit potential sources of bias, we used a centralized randomization with concealed allocation and performed analysis based on the intention-to-treat principle. In addition, all analyses were specified prior to unblinding results. The study has limitations. Enrollment into the hydroxychloroquine and combination therapy study arms was halted before reaching any pre-specified internal trigger but based on external evidence. While the small sample size is a limitation of the current study, the strong signal observed in the small number of patients results in a high probability of harm. Data on the bioavailability of dissolved or crushed lopinavir-ritonavir tablets in critically ill patients are limited. The study used an open-label design, although clinician and patient awareness of study assignment

likely had minimal effect on the organ-support or mortality components of the primary outcome.

In conclusion, among critically ill patients with COVID-19, treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy resulted in worse outcomes compared to no COVID-19 antiviral therapy.

REFERENCES

1. Al-Abaidani IS, Al-Maani AS, Al-Kindi HS, Al-Jardani AK, Abdel-Hady DM, Zayed BE, Al-Harthy KS, Al-Shaqsi KH, Al-Abri SS, (2014) Overview of preparedness and response for Middle East respiratory syndrome coronavirus (MERS-CoV) in Oman. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 29: 309-310

2. Horie S, McNicholas B, Rezoagli E, Pham T, Curley G, McAuley D, O'Kane C, Nichol A, Dos Santos C, Rocco PRM, Bellani G, Laffey JG, (2020) Emerging pharmacological therapies for ARDS: COVID-19 and beyond. Intensive Care Med 46: 2265-2283

3. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, van den Hoogen BG, Neyts J, Snijder EJ, (2014) Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrobial agents and chemotherapy 58: 4875-4884

4. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS, Yuen KY, Group HUSS, (2004) Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 59: 252-256

5. Chan JF, Yao Y, Yeung ML, Deng W, Bao L, Jia L, Li F, Xiao C, Gao H, Yu P, Cai JP, Chu H, Zhou J, Chen H, Qin C, Yuen KY, (2015) Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. The Journal of infectious diseases 212: 1904-1913

6. Arabi YM, Asiri AY, Assiri AM, Balkhy HH, Al Bshabshe A, Al Jeraisy M, Mandourah Y, Azzam MHA, Bin Eshaq AM, Al Johani S, Al Harbi S, Jokhdar HAA, Deeb AM, Memish ZA, Jose J, Ghazal S, Al Faraj S, Al Mekhlafi GA, Sherbeeni NM, Elzein FE, Al-Hameed F, Al Saedi A, Alharbi NK, Fowler RA, Hayden FG, Al-Dawood A, Abdelzaher M, Bajhmom W, AlMutairi BM, Hussein MA, Alothman A, Saudi Critical Care Trials G, (2020) Interferon Beta-1b and Lopinavir-Ritonavir for Middle East Respiratory Syndrome. The New England journal of medicine 383: 1645-1656

7. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF, (2020) Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. Intensive Care Med 46: 579-582

8. Arabi YM, Fowler R, Hayden FG, (2020) Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med 46: 315-328

9. Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY, Chu DKW, Chan MCW, Cheung PP, Huang X, Peiris M, Yen HL, (2020) Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral research 178: 104786

10. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D, (2020) In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 71: 732-739

11. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G, (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research 30: 269-271

12. Arshad U, Pertinez H, Box H, Tatham L, Rajoli RKR, Curley P, Neary M, Sharp J, Liptrott NJ, Valentijn A, David C, Rannard SP, O'Neill PM, Aljayyoussi G, Pennington SH, Ward SA, Hill A, Back DJ, Khoo SH, Bray PG, Biagini GA, Owen A, (2020) Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics. Clin Pharmacol Ther 108: 775-790

13.   Park SJ, Yu KM, Kim YI, Kim SM, Kim EH, Kim SG, Kim EJ, Casel MAB, Rollon R, Jang SG, Lee MH, Chang JH, Song MS, Jeong HW, Choi Y, Chen W, Shin WJ, Jung JU, Choi YK, (2020) Antiviral Efficacies of FDA-Approved Drugs against SARS-CoV-2 Infection in Ferrets. mBio 11

14.   Gonzalez Cortes R, Garcia-Salido A, Roca Pascual D, Slocker Barrio M, de Carlos Vicente JC, Patients SSGoS-C-iCIP, (2020) A multicenter national survey of children with SARS-CoV-2 infection admitted to Spanish Pediatric Intensive Care Units. Intensive Care Med 46: 1774-1776

15.   Wang K, Zhang Z, Yu M, Tao Y, Xie M, (2020) 15-day mortality and associated risk factors for hospitalized patients with COVID-19 in Wuhan, China: an ambispective observational cohort study. Intensive Care Med 46: 1472-1474

16.   Tu WJ, Cao J, Yu L, Hu X, Liu Q, (2020) Clinicolaboratory study of 25 fatal cases of COVID-19 in Wuhan. Intensive Care Med 46: 1117-1120

17.   Dagens A, Sigfrid L, Cai E, Lipworth S, Cheng V, Harris E, Bannister P, Rigby I, Horby P, (2020) Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic: rapid review. Bmj 369: m1936

18.   Food and Drug Administration (FDA). https://www.fda.gov/media/138945/download. Accessed Dec 27-2020

19.   Axfors C, Schmitt AM, Janiaud P, Van't Hooft J, Abd-Elsalam S, Abdo EF, Abella BS, Akram J, Amaravadi RK, Angus DC, Arabi YM, Azhar S, Baden LR, Baker AW, Belkhir L, Benfield T, Berrevoets MAH, Chen CP, Chen TC, Cheng SH, Cheng CY, Chung WS, Cohen YZ, Cowan LN, Dalgard O, de Almeida EVFF, de Lacerda MVG, de Melo GC, Derde L, Dubee V, Elfakir A, Gordon AC, Hernandez-Cardenas CM, Hills T, Hoepelman AIM, Huang YW, Igau B, Jin R, Jurado-Camacho F, Khan KS, Kremsner PG, Kreuels B, Kuo CY, Le T, Lin YC, Lin WP, Lin TH, Lyngbakken MN, McArthur C, McVerry BJ, Meza-Meneses P, Monteiro WM, Morpeth SC, Mourad A, Mulligan MJ, Murthy S, Naggie S, Narayanasamy S, Nichol A, Novack LA, O'Brien SM, Okeke NL, Perez L, Perez-Padilla R, Perrin L, Remigio-Luna A, Rivera-Martinez NE, Rockhold FW, Rodriguez-Llamazares S, Rolfe R, Rosa R, Rosjo H, Sampaio VS, Seto TB, Shehzad M, Soliman S, Stout JE, Thirion-Romero I, Troxel AB, Tseng TY, Turner NA, Ulrich RJ, Walsh SR, Webb SA, Weehuizen JM, Velinova M, Wong HL, Wrenn R, Zampieri FG, Zhong W, Moher D, Goodman SN, Ioannidis JPA, Hemkens LG, (2021) Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nature communications 12: 2349

20.   Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, Pardo-Hernandez H, Rochwerg B, Lamontagne F, Han MA, Liu Q, Agarwal A, Agoritsas T, Chu DK, Couban R, Darzi A, Devji T, Fang B, Fang C, Flottorp SA, Foroutan F, Ghadimi M, Heels-Ansdell D, Honarmand K, Hou L, Hou X, Ibrahim Q, Khamis A, Lam B, Loeb M, Marcucci M, McLeod SL, Motaghi S, Murthy S, Mustafa RA, Neary JD, Qasim A, Rada G, Riaz IB, Sadeghirad B, Sekercioglu N, Sheng L, Sreekanta A, Switzer C, Tendal B, Thabane L, Tomlinson G, Turner T, Vandvik PO, Vernooij RW, Viteri-Garcia A, Wang Y, Yao L, Ye Z, Guyatt GH, Brignardello-Petersen R, (2020) Drug treatments for covid-19: living systematic review and network meta-analysis. Bmj 370: m2980

21.   Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S, (2021) Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. The New England journal of medicine 384: 497-511

22. RECOVERY Collaborative Group RC, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ, (2020) Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. The New England journal of medicine 383: 2030-2040

23. RECOVERY Collaborative Group RC, (2020) Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet

24. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, Bhimani Z, Bonten M, Broglio K, Brunkhorst F, Cheng AC, Chiche JD, De Jong M, Detry M, Goossens H, Gordon A, Green C, Higgins AM, Hullegie SJ, Kruger P, Lamontagne F, Litton E, Marshall J, McGlothlin A, McGuinness S, Mouncey P, Murthy S, Nichol A, O'Neill GK, Parke R, Parker J, Rohde G, Rowan K, Turner A, Young P, Derde L, McArthur C, Webb SA, (2020) The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Ann Am Thorac Soc 17: 879-891

25. Best BM, Capparelli EV, Diep H, Rossi SS, Farrell MJ, Williams E, Lee G, van den Anker JN, Rakhmanina N, (2011) Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. Journal of acquired immune deficiency syndromes 58: 385-391

26. Staff PM, (2020) Correction: COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLoS Med 17: e1003445

27. Laterre PF, Berry SM, Blemings A, Carlsen JE, Francois B, Graves T, Jacobsen K, Lewis RJ, Opal SM, Perner A, Pickkers P, Russell JA, Windelov NA, Yealy DM, Asfar P, Bestle MH, Muller G, Bruel C, Brule N, Decruyenaere J, Dive AM, Dugernier T, Krell K, Lefrant JY, Megarbane B, Mercier E, Mira JP, Quenot JP, Rasmussen BS, Thorsen-Meyer HC, Vander Laenen M, Vang ML, Vignon P, Vinatier I, Wichmann S, Wittebole X, Kjolbye AL, Angus DC, Investigators S-A, (2019) Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. Jama 322: 1476-1485

28. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infectionCharacterisation WHOWGotC, Management of C-i, (2020) A minimal common outcome measure set for COVID-19 clinical research. The Lancet Infectious diseases 20: e192-e197

29. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, Bradbury C, Brunkhorst F, Buxton M, Buzgau A, Cheng AC, de Jong M, Detry M, Estcourt L, Fitzgerald M, Goossens H, Green C, Haniffa R, Higgins AM, Horvat C, Hullegie SJ, Kruger P, Lamontagne F, Lawler PR, Linstrum K, Litton E, Lorenzi E, Marshall J, McAuley D, McGlothin A, McGuinness S, McVerry B, Montgomery S, Mouncey P, Murthy S, Nichol A, Parke R, Parker J, Rowan K, Sanil A, Santos M, Saunders C, Seymour C, Turner A, van de Veerdonk F, Venkatesh B, Zarychanski R, Berry S, Lewis RJ, McArthur C, Webb SA, Gordon AC, Writing Committee for the R-CAPI, Al-Beidh F, Angus D, Annane D, Arabi Y, van Bentum-Puijk W, Berry S, Beane A, Bhimani Z, Bonten M, Bradbury C, Brunkhorst F, Buxton M, Cheng A, De Jong M, Derde L, Estcourt L, Goossens H, Gordon A, Green C, Haniffa R, Lamontagne F, Lawler P, Litton E, Marshall J, McArthur C, McAuley D, McGuinness S, McVerry B, Montgomery S, Mouncey P, Murthy S, Nichol A, Parke R, Rowan K, Seymour C, Turner A, van de Veerdonk F, Webb S, Zarychanski R, Campbell L, Forbes A, Gattas D, Heritier S, Higgins L, Kruger P, Peake S, Presneill J, Seppelt I, Trapani T, Young P, Bagshaw S, Daneman N, Ferguson N, Misak C, Santos M, Hullegie S, Pletz M, Rohde G, Rowan K, Alexander B, Basile K, Girard T, Horvat C, Huang D, Linstrum K, Vates J, Beasley R, Fowler R, McGloughlin S, Morpeth S, Paterson D, Venkatesh B, Uyeki T, Baillie K, Duffy E, Fowler R, Hills T, Orr K, Patanwala A, Tong S, Netea M, Bihari S, Carrier M, Fergusson D, Goligher E, Haidar G, Hunt B, Kumar A, Laffan M, Lawless P, Lother S, McCallum P, Middeldopr S, McQuilten Z, Neal M, Pasi J, Schutgens R, Stanworth S, Turgeon A, Weissman A, Adhikari N, Anstey M, Brant E, de Man A, Lamonagne F, Masse MH, Udy A, Arnold D, Begin P, Charlewood R, Chasse M, Coyne M, Cooper J, Daly J,

Gosbell I, Harvala-Simmonds H, Hills T, MacLennan S, Menon D, McDyer J, Pridee N, Roberts D, Shankar-Hari M, Thomas H, Tinmouth A, Triulzi D, Walsh T, Wood E, Calfee C, O'Kane C, Shyamsundar M, Sinha P, Thompson T, Young I, Bihari S, Hodgson C, Laffey J, McAuley D, Orford N, Neto A, Detry M, Fitzgerald M, Lewis R, McGlothlin A, Sanil A, Saunders C, Berry L, Lorenzi E, Miller E, Singh V, Zammit C, van Bentum Puijk W, Bouwman W, Mangindaan Y, Parker L, Peters S, Rietveld I, Raymakers K, Ganpat R, Brillinger N, Markgraf R, Ainscough K, Brickell K, Anjum A, Lane JB, Richards-Belle A, Saull M, Wiley D, Bion J, Connor J, Gates S, Manax V, van der Poll T, Reynolds J, van Beurden M, Effelaar E, Schotsman J, Boyd C, Harland C, Shearer A, Wren J, Clermont G, Garrard W, Kalchthaler K, King A, Ricketts D, Malakoutis S, Marroquin O, Music E, Quinn K, Cate H, Pearson K, Collins J, Hanson J, Williams P, Jackson S, Asghar A, Dyas S, Sutu M, Murphy S, Williamson D, Mguni N, Potter A, Porter D, Goodwin J, Rook C, Harrison S, Williams H, Campbell H, Lomme K, Williamson J, Sheffield J, van't Hoff W, McCracken P, Young M, Board J, Mart E, Knott C, Smith J, Boschert C, Affleck J, Ramanan M, D'Souza R, Pateman K, Shakih A, Cheung W, Kol M, Wong H, Shah A, Wagh A, Simpson J, Duke G, Chan P, Cartner B, Hunter S, Laver R, Shrestha T, Regli A, Pellicano A, McCullough J, Tallott M, Kumar N, Panwar R, Brinkerhoff G, Koppen C, Cazzola F, Brain M, Mineall S, Fischer R, Biradar V, Soar N, White H, Estensen K, Morrison L, Smith J, Cooper M, Health M, Shehabi Y, Al-Bassam W, Hulley A, Whitehead C, Lowrey J, Gresha R, Walsham J, Meyer J, Harward M, Venz E, Williams P, Kurenda C, Smith K, Smith M, Garcia R, Barge D, Byrne D, Byrne K, Driscoll A, Fortune L, Janin P, Yarad E, Hammond N, Bass F, Ashelford A, Waterson S, Wedd S, McNamara R, Buhr H, Coles J, Schweikert S, Wibrow B, Rauniyar R, Myers E, Fysh E, Dawda A, Mevavala B, Litton E, Ferrier J, Nair P, Buscher H, Reynolds C, Santamaria J, Barbazza L, Homes J, Smith R, Murray L, Brailsford J, Forbes L, Maguire T, Mariappa V, Smith J, Simpson S, Maiden M, Bone A, Horton M, Salerno T, Sterba M, Geng W, Depuydt P, De Waele J, De Bus L, Fierens J, Bracke S, Reeve B, Dechert W, Chasse M, Carrier FM, Boumahni D, Benettaib F, Ghamraoui A, Bellemare D, Cloutier E, Francoeur C, Lamontagne F, D'Aragon F, Carbonneau E, Leblond J, Vazquez-Grande G, Marten N, Wilson M, Albert M, Serri K, Cavayas A, Duplaix M, Williams V, Rochwerg B, Karachi T, Oczkowski S, Centofanti J, Millen T, Duan E, Tsang J, Patterson L, English S, Watpool I, Porteous R, Miezitis S, McIntyre L, Brochard L, Burns K, Sandhu G, Khalid I, Binnie A, Powell E, McMillan A, Luk T, Aref N, Andric Z, Cviljevic S, Dimoti R, Zapalac M, Mirkovic G, Barsic B, Kutlesa M, Kotarski V, Vujaklija Brajkovic A, Babel J, Sever H, Dragija L, Kusan I, Vaara S, Pettila L, Heinonen J, Kuitunen A, Karlsson S, Vahtera A, Kiiski H, Ristimaki S, Azaiz A, Charron C, Godement M, Geri G, Vieillard-Baron A, Pourcine F, Monchi M, Luis D, Mercier R, Sagnier A, Verrier N, Caplin C, Siami S, Aparicio C, Vautier S, Jeblaoui A, Fartoukh M, Courtin L, Labbe V, Leparco C, Muller G, Nay MA, Kamel T, Benzekri D, Jacquier S, Mercier E, Chartier D, Salmon C, Dequin P, Schneider F, Morel G, L'Hotellier S, Badie J, Berdaguer FD, Malfroy S, Mezher C, Bourgoin C, Megarbane B, Voicu S, Deye N, Malissin I, Sutterlin L, Guitton C, Darreau C, Landais M, Chudeau N, Robert A, Moine P, Heming N, Maxime V, Bossard I, Nicholier TB, Colin G, Zinzoni V, Maquigneau N, Finn A, Kress G, Hoff U, Friedrich Hinrichs C, Nee J, Pletz M, Hagel S, Ankert J, Kolanos S, Bloos F, Petros S, Pasieka B, Kunz K, Appelt P, Schutze B, Kluge S, Nierhaus A, Jarczak D, Roedl K, Weismann D, Frey A, Klinikum Neukolln V, Reill L, Distler M, Maselli A, Belteczki J, Magyar I, Fazekas A, Kovacs S, Szoke V, Szigligeti G, Leszkoven J, Collins D, Breen P, Frohlich S, Whelan R, McNicholas B, Scully M, Casey S, Kernan M, Doran P, O'Dywer M, Smyth M, Hayes L, Hoiting O, Peters M, Rengers E, Evers M, Prinssen A, Bosch Ziekenhuis J, Simons K, Rozendaal W, Polderman F, de Jager P, Moviat M, Paling A, Salet A, Rademaker E, Peters AL, de Jonge E, Wigbers J, Guilder E, Butler M, Cowdrey KA, Newby L, Chen Y, Simmonds C, McConnochie R, Ritzema Carter J, Henderson S, Van Der Heyden K, Mehrtens J, Williams T, Kazemi A, Song R, Lai V, Girijadevi D, Everitt R, Russell R, Hacking D, Buehner U, Williams E, Browne T, Grimwade K, Goodson J, Keet O, Callender O, Martynoga R, Trask K, Butler A, Schischka L, Young C, Lesona E, Olatunji S, Robertson Y, Jose N, Amaro dos Santos Catorze T, de Lima Pereira TNA, Neves Pessoa LM, Castro Ferreira RM, Pereira Sousa Bastos JM, Aysel Florescu S, Stanciu D, Zaharia MF, Kosa

AG, Codreanu D, Marabi Y, Al Qasim E, Moneer Hagazy M, Al Swaidan L, Arishi H, Munoz-Bermudez R, Marin-Corral J, Salazar Degracia A, Parrilla Gomez F, Mateo Lopez MI, Rodriguez Fernandez J, Carcel Fernandez S, Carmona Flores R, Leon Lopez R, de la Fuente Martos C, Allan A, Polgarova P, Farahi N, McWilliam S, Hawcutt D, Rad L, O'Malley L, Whitbread J, Kelsall O, Wild L, Thrush J, Wood H, Austin K, Donnelly A, Kelly M, O'Kane S, McClintock D, Warnock M, Johnston P, Gallagher LJ, Mc Goldrick C, Mc Master M, Strzelecka A, Jha R, Kalogirou M, Ellis C, Krishnamurthy V, Deelchand V, Silversides J, McGuigan P, Ward K, O'Neill A, Finn S, Phillips B, Mullan D, Oritz-Ruiz de Gordoa L, Thomas M, Sweet K, Grimmer L, Johnson R, Pinnell J, Robinson M, Gledhill L, Wood T, Morgan M, Cole J, Hill H, Davies M, Antcliffe D, Templeton M, Rojo R, Coghlan P, Smee J, Mackay E, Cort J, Whileman A, Spencer T, Spittle N, Kasipandian V, Patel A, Allibone S, Genetu RM, Ramali M, Ghosh A, Bamford P, London E, Cawley K, Faulkner M, Jeffrey H, Smith T, Brewer C, Gregory J, Limb J, Cowton A, O'Brien J, Nikitas N, Wells C, Lankester L, Pulletz M, Williams P, Birch J, Wiseman S, Horton S, Alegria A, Turki S, Elsefi T, Crisp N, Allen L, McCullagh I, Robinson P, Hays C, Babio-Galan M, Stevenson H, Khare D, Pinder M, Selvamoni S, Gopinath A, Pugh R, Menzies D, Mackay C, Allan E, Davies G, Puxty K, McCue C, Cathcart S, Hickey N, Ireland J, Yusuff H, Isgro G, Brightling C, Bourne M, Craner M, Watters M, Prout R, Davies L, Pegler S, Kyeremeh L, Arbane G, Wilson K, Gomm L, Francia F, Brett S, Sousa Arias S, Elin Hall R, Budd J, Small C, Birch J, Collins E, Henning J, Bonner S, Hugill K, Cirstea E, Wilkinson D, Karlikowski M, Sutherland H, Wilhelmsen E, Woods J, North J, Sundaran D, Hollos L, Coburn S, Walsh J, Turns M, Hopkins P, Smith J, Noble H, Depante MT, Clarey E, Laha S, Verlander M, Williams A, Huckle A, Hall A, Cooke J, Gardiner-Hill C, Maloney C, Qureshi H, Flint N, Nicholson S, Southin S, Nicholson A, Borgatta B, Turner-Bone I, Reddy A, Wilding L, Chamara Warnapura L, Agno Sathianathan R, Golden D, Hart C, Jones J, Bannard-Smith J, Henry J, Birchall K, Pomeroy F, Quayle R, Makowski A, Misztal B, Ahmed I, KyereDiabour T, Naiker K, Stewart R, Mwaura E, Mew L, Wren L, Willams F, Innes R, Doble P, Hutter J, Shovelton C, Plumb B, Szakmany T, Hamlyn V, Hawkins N, Lewis S, Dell A, Gopal S, Ganguly S, Smallwood A, Harris N, Metherell S, Lazaro JM, Newman T, Fletcher S, Nortje J, Fottrell-Gould D, Randell G, Zaman M, Elmahi E, Jones A, Hall K, Mills G, Ryalls K, Bowler H, Sall J, Bourne R, Borrill Z, Duncan T, Lamb T, Shaw J, Fox C, Moreno Cuesta J, Xavier K, Purohit D, Elhassan M, Bakthavatsalam D, Rowland M, Hutton P, Bashyal A, Davidson N, Hird C, Chhablani M, Phalod G, Kirkby A, Archer S, Netherton K, Reschreiter H, Camsooksai J, Patch S, Jenkins S, Pogson D, Rose S, Daly Z, Brimfield L, Claridge H, Parekh D, Bergin C, Bates M, Dasgin J, McGhee C, Sim M, Hay SK, Henderson S, Phull MK, Zaidi A, Pogreban T, Rosaroso LP, Harvey D, Lowe B, Meredith M, Ryan L, Hormis A, Walker R, Collier D, Kimpton S, Oakley S, Rooney K, Rodden N, Hughes E, Thomson N, McGlynn D, Walden A, Jacques N, Coles H, Tilney E, Vowell E, Schuster-Bruce M, Pitts S, Miln R, Purandare L, Vamplew L, Spivey M, Bean S, Burt K, Moore L, Day C, Gibson C, Gordon E, Zitter L, Keenan S, Baker E, Cherian S, Cutler S, Roynon-Reed A, Harrington K, Raithatha A, Bauchmuller K, Ahmad N, Grecu I, Trodd D, Martin J, Wrey Brown C, Arias AM, Craven T, Hope D, Singleton J, Clark S, Rae N, Welters I, Hamilton DO, Williams K, Waugh V, Shaw D, Puthucheary Z, Martin T, Santos F, Uddin R, Somerville A, Tatham KC, Jhanji S, Black E, Dela Rosa A, Howle R, Tully R, Drummond A, Dearden J, Philbin J, Munt S, Vuylsteke A, Chan C, Victor S, Matsa R, Gellamucho M, Creagh-Brown B, Tooley J, Montague L, De Beaux F, Bullman L, Kersiake I, Demetriou C, Mitchard S, Ramos L, White K, Donnison P, Johns M, Casey R, Mattocks L, Salisbury S, Dark P, Claxton A, McLachlan D, Slevin K, Lee S, Hulme J, Joseph S, Kinney F, Senya HJ, Oborska A, Kayani A, Hadebe B, Orath Prabakaran R, Nichols L, Thomas M, Worner R, Faulkner B, Gendall E, Hayes K, Hamilton-Davies C, Chan C, Mfuko C, Abbass H, Mandadapu V, Leaver S, Forton D, Patel K, Paramasivam E, Powell M, Gould R, Wilby E, Howcroft C, Banach D, Fernandez de Pinedo Artaraz Z, Cabreros L, White I, Croft M, Holland N, Pereira R, Zaki A, Johnson D, Jackson M, Garrard H, Juhaz V, Roy A, Rostron A, Woods L, Cornell S, Pillai S, Harford R, Rees T, Ivatt H, Sundara Raman A, Davey M, Lee K, Barber R, Chablani M, Brohi F, Jagannathan V, Clark M, Purvis S, Wetherill B, Dushianthan A, Cusack R, de Courcy-Golder K, Smith S, Jackson S, Attwood B,

Parsons P, Page V, Zhao XB, Oza D, Rhodes J, Anderson T, Morris S, Xia Le Tai C, Thomas A, Keen A, Digby S, Cowley N, Wild L, Southern D, Reddy H, Campbell A, Watkins C, Smuts S, Touma O, Barnes N, Alexander P, Felton T, Ferguson S, Sellers K, Bradley-Potts J, Yates D, Birkinshaw I, Kell K, Marshall N, Carr-Knott L, Summers C, (2020) Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. Jama 324: 1317-1329

30.   REMAP-CAP Investigators R C, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettila V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG, (2021) Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. The New England journal of medicine 384: 1491-1502

31.   Painvin B, Guillot P, Verdier MC, Gacouin A, Maamar A, (2020) Hydroxychloroquine pharmacokinetic in COVID-19 critically ill patients: an observational cohort study. Intensive Care Med 46: 1772-1773

32.   Marzolini C, Stader F, Stoeckle M, Franzeck F, Egli A, Bassetti S, Hollinger A, Osthoff M, Weisser M, Gebhard CE, Baettig V, Geenen J, Khanna N, Tschudin-Sutter S, Mueller D, Hirsch HH, Battegay M, Sendi P, (2020) Effect of Systemic Inflammatory Response to SARS-CoV-2 on Lopinavir and Hydroxychloroquine Plasma Concentrations. Antimicrobial agents and chemotherapy 64

33.   Edelstein CL, Venkatachalam MA, Dong Z, (2020) Autophagy inhibition by chloroquine and hydroxychloroquine could adversely affect acute kidney injury and other organ injury in critically ill patients with COVID-19. Kidney international 98: 234-235

34.   Pastick KA, Okafor EC, Wang F, Lofgren SM, Skipper CP, Nicol MR, Pullen MF, Rajasingham R, McDonald EG, Lee TC, Schwartz IS, Kelly LE, Lother SA, Mitja O, Letang E, Abassi M, Boulware DR, (2020) Review: Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19). Open Forum Infect Dis 7: ofaa130

35.   Perner A, Tirupakuzhi Vijayaraghavan BK, Venkatesh B, (2020) How likely are COVID-19 interventions to benefit the sickest patients? Intensive Care Med 46: 1441-1444

36.   Bittl John A, He Y, (2017) Bayesian Analysis: A Practical Approach to Interpret Clinical Trials and Create Clinical Practice Guidelines. Circulation: Cardiovascular Quality and Outcomes 10: e003563

37.   Quintana M, Viele K, Lewis RJ, (2017) Bayesian Analysis: Using Prior Information to Interpret the Results of Clinical Trials. JAMA 318: 1605-1606

38.   Dodd LE, Freidlin B, Korn EL, (2021) Platform Trials - Beware the Noncomparable Control Group. The New England journal of medicine 384: 1572-1573

Figure 1: Screening, randomization, and follow-up of patients in the REMAP-CAP COVID-19 Antiviral Therapy Domain randomized controlled trial.

---

[a] Patients could meet more than 1 ineligibility criterion (Table S2, Supplementary Appendix).

[b] Details of platform exclusions are provided in the Supplementary Results (Supplementary Appendix).

[c] The primary analysis of organ support-free days (OSFD) and hospital survival were conducted on the REMAP-CAP intention-to-treat cohort which included all patients enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least one domain, adjusting for patient factors and for assignment to interventions in other domains (Table S3, Supplementary Appendix).

^ Contraindications include hypersensitivity, receiving the study drug as usual medication prior to hospitalization, human immune deficiency (HIV) infection (contraindication of lopinavir-ritonavir), severe liver failure (contraindication of lopinavir-ritonavir), receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to assessment (contraindication of lopinavir-ritonavir) and high clinical risk of sustained ventricular dysrhythmia (contraindication of hydroxychloroquine) (Table S2, Supplementary Appendix).

Figure 2: Organ support-free days and mortality.

A. Organ support-free days in patients allocated to lopinavir-ritonavir, hydroxychloroquine, combination therapy and control among critically ill patients in the COVID-19 Antiviral Therapy Domain of the REMAP-CAP trial. Distributions of organ support-free days are displayed as the cumulative proportion (y axis) for each study group by day (x axis). Curves that rise more slowly are more favorable. The height of each curve at "−1" indicates the in-hospital mortality for each intervention. The height of each curve at any time point indicates the proportion of patients who had that number of organ support-free days or fewer. The difference in the height of the curves at any point represents the difference in the percentile in the distribution of organ support-free days associated with that number of days alive and free of organ support.

B. Organ support-free days are displayed as horizontally stacked proportions by study group. Red represents worse values and blue represents better values. On primary analysis of organ support-free days, the three interventions decreased organ support-free days compared to control, with corresponding median adjusted ORs and 95% credible intervals of 0.73 (0.55-0.99), 0.57 (0.35-0.83) and 0.41 (0.24-0.72), respectively, yielding high posterior probabilities of futility (99.0% or greater) and high posterior probabilities of harm compared to control (98.0%, 98.8% and 99.2%, respectively).

C. Empirical distribution of survival for lopinavir−ritonavir, hydroxychloroquine, combination therapy and control. Lopinavir-ritonavir, hydroxychloroquine and combination therapy resulted in reduced survival over 90 days compared to control, with adjusted median hazard ratios (95% CrI) of 0.83 (0.65, 1.07), 0.71 (0.45, 0.97), 0.58 (0.36, 0.92), yielding high probabilities of harm compared with control of 92.0% and 98.4% and 98.7%, respectively,