SISTEMA SANITARIO REGIONALE
IRCCS
LAZZARO SPALLANZANI

Istituto Nazionale per le Malattie Infettive
"Lazzaro Spallanzani"
Istituto di Ricovero e Cura a Carattere Scientifico

REGIONE LAZIO

L'intervento terapeutico nelle varie fasi di malattia: la evidenza scientifica

ovvero clinical management of patients with COVID-19
ovvero no one is safe until we are all safe

Emanuele Nicastri

UOC Malattie Infettive ad Alta Intensità di Cure

BM MI Regione Lazio

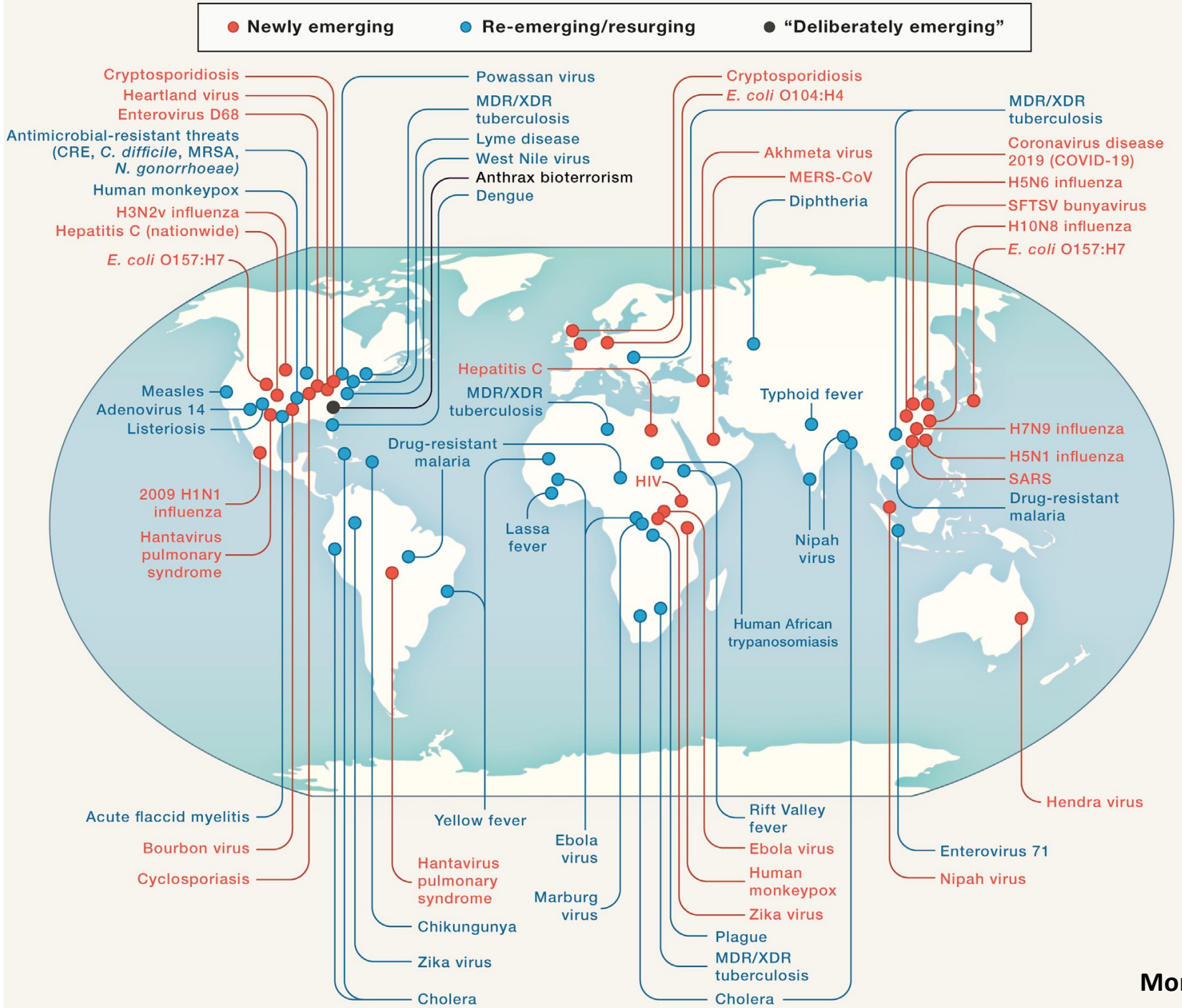
INMI «*L. Spallanzani*» IRCCS

WHO Collaborating Center for clinical care, diagnosis, response and training on Highly Infectious Diseases

In 1918, barriers were erected around soldiers' beds at a naval station in San Francisco to slow the spread of flu. U.S. NAVAL HISTORY AND HERITAGE COMMAND PHOTOGRAPH

Epidemics are a natural part of life, predictable in occurrence.
The sequential arrival of HIV, SARS, H1N1 influenza, MERS, and now Covid-19 highlights the ineluctable march of zoonoses since the 1980s. Although some may label the latest as a "Black Swan," a totally unpredictable occurrence with threatening consequences], **the only uncertainties about epidemics are when and how severe**.

RP Wenzel CID 2020



Morens & Fauci Cell 11.2020

The New York Times

© 2021 The New York Times Company NEW YORK, TUESDAY, SEPTEMBER 28, 2021

Covid Politics Are Walloping Red America

Concentration of Cases in Right-Leaning Areas

DAVID LEONHARDT
THE MORNING

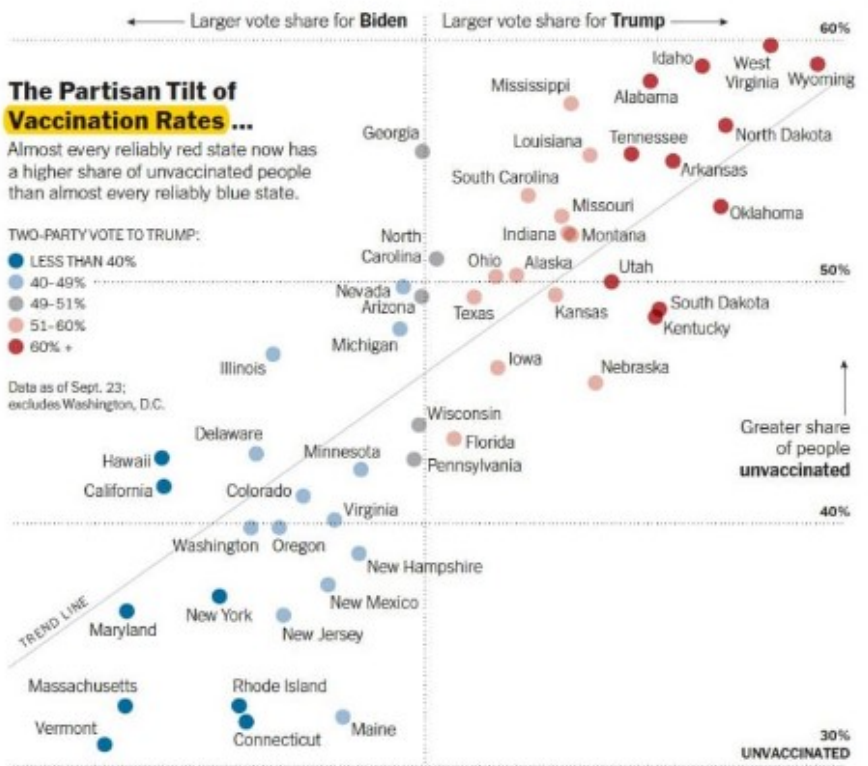
During the early months of Covid-19 vaccinations, several major demographic groups lagged in receiving shots, including Black Americans, Latino Americans and Republican voters.

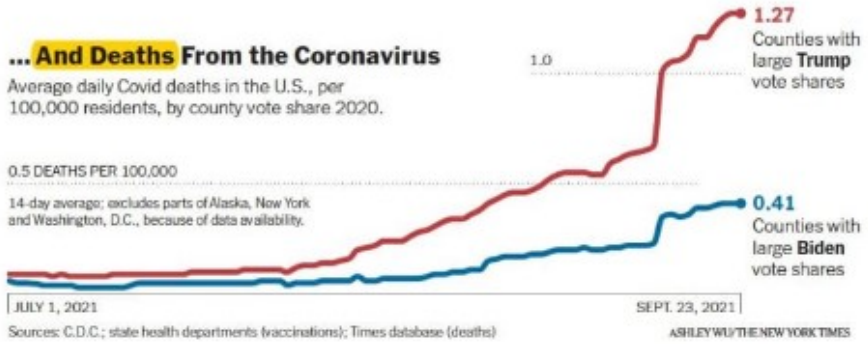
More recently, the racial gaps — while still existing — have narrowed. The partisan gap, however, continues to be enormous. A Pew Research Center poll last month found that 86 percent of Democratic voters had received at least one shot, compared with 60 percent of Republican voters.

The political divide over vaccinations is so large that almost every reliably blue state now has a higher vaccination rate than almost every reliably red state.

Because the vaccines are so effective at preventing serious illness, Covid deaths are also showing a partisan pattern. Covid is still a national crisis, but the worst forms of it are increasingly concentrated in red America.

As is often the case, state-by-state numbers can understate the true pattern, because every state has both liberal and conservative areas. When you look at the county level, the gap can look even starker.

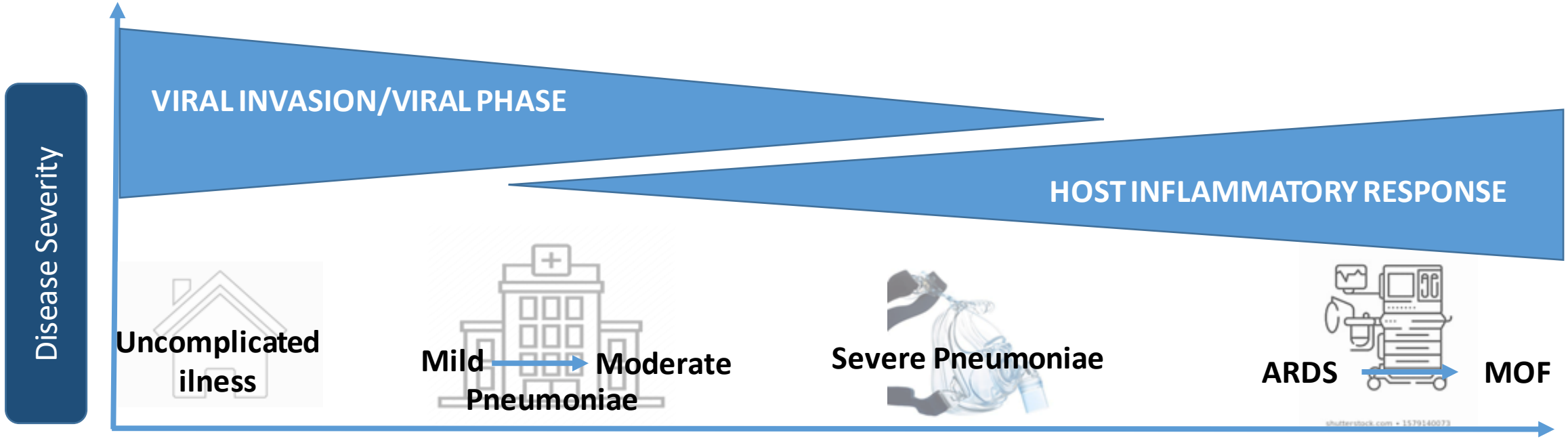




The New York Times del 28 settembre 2021

1. Andamento della copertura vaccinale per SARS-CoV-2 negli stati USA a seconda dei voti repubblicani nella ultima elezioen presidenziali da <40% in blue a >60% in rosso

2. Incidenza giornaliera di decessi per COVID per 1000 residenti per gli stati USA elettori di Trump, in blue, vs stati elettori di Biden in rosso



Days from 1°symptoms	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
VIRAL SHEDDING (RT- REAL TIME PCR SARS-COV-2 RNA)																							
Respiratory swab	+	+	+	+	NA	NA	+	+	+	NA	NA	NA	+	+	+	+	+	-	-	-	-	-	
	+	+	+	+	NA	+	NA	+	+	NA	NA	NA	-	-	-	-	-	-	-	-	-	-	

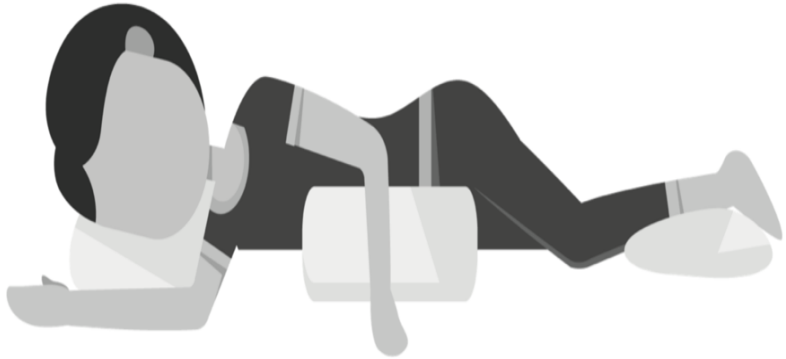
Features	fever, general malaise, anosmia, headache, diarrhea	PaO2/Fi02 ratio >300, increase D-Dimer, LDH, Ferritin, Lymphopenia	PaO2/Fi02 ratio 300-200 mmHg	PaO2/Fi02 ratio 200-100 mmHg	PaO2/Fi02 ratio <100 mmHg
Drugs	Mono Ab	Steroids only if Oxygen support needed, Mono Ab, proph/therap heparin, remdesevir, immune modulant	Remdesevir (?), systemic steroids, and proph/therap heparin, immune modulant	systemic steroids, immune modulant (anti Il6, anti JAK), and proph/therap heparin	
O2 Therapy and other	Pronation	Pronation & Venturi Mask to achieve Sat>95%	Pronation & NIV or CPAP to achieve Sat>95%	Pronation & mechanical ventilation	

	Symptoms	Epi and clinical check	Treatment	Isolation	Setting/surveillance
Pauci / asymptomatic with no evidence of pneumonia	Fever cough Anosmya Congiuntivitis Cefalea Astenya Mild dhyarrea	Anamnesis Vital parameters: PA/FC ≥95% basal O2 level and negative 6 minute Walking Test (6MWT)	Paracetamol/FANS Pronation, Monoclonal Ab if at risk, intranasal or areosol CS	Home Isolation residence	Strict daily phone monitoring with O2 check by saturimetry& 6MWT Home check with thorax US Home hemo assay(?)

	Symptoms	Epi and clinical check	Treatment	Isolation	Setting/surveillance
Symptomatic with pneumonia evidence	> 70 yo Fever > 37,5° Prolonged cough Respiratory sympt Comorbidities	Anamnesis, Vital parameters: MEWS basal O2 level & 6MWT If at ER Arterial Blood gas (ABG): P/F ratio > 300 Inflammatory index (CRP, d-Dimer, ferritin, Hb, WBC, Lympho, plt) Chest XR, US, CT Scan	Oxygen Venturi Mask (?) Paracetamol/FANS Systemic Steroids Pronation baricitinib/anakinra/Ab Il6 Monoclonal Ab if S seronegative LMWP if low mobility	≥95% basal O2 & negative 6MWT & ABG, MEWS ≤1: discharge at home or residence	Strict daily phone monitoring with O2 check by saturimetry& 6MWT Home check with thorax US Home hemo assay(?)
				≤95% basal O2 or positive 6MWT or ABG, MEWS ≥1: Admission	Basal O2, 6MWT & ABG Imaging Hemo assay

	Symptoms	Epi and clinical check	Treatment	Isolation	Setting/surveillance
ARDS	> 70 yo Fever > 38° Dyspnea Sepsis Comorbidities	Anamnesis ABG: P/F ratio < 300 Inflammatory index (CRP, d-Dimer, ferritin, Hb, WBC, Lympho, plt) Chest XR, US, CT Scan Non Invasive monitoring	HFOT/cPap/ NIV with pronation; Remdesivi; Steroids, LMWH on prophyl/treament Ivermectin 200µ/kg/dayx2d if suspect Strongylo	COVID acute care, Semi ICU	Acute care setting with multidisciplinary HCWs Strict daily monitoring ABG Imaging Hemo assay
Clinically instable	Plus MODS Septic shock	Plus Invasive monitoring	VM with pronation Steroids LMWH terapeutics Plasma if RCT Ivermectin as above	Semi ICU ICU	

POSIZIONE PRONA DA SVEGLI



Less Time
Like This

- COME SAPRA', I SUOI LIVELLI DI OSSIGENO SONO BASSI A CAUSA DELLE SUE ATTUALI CONDIZIONI CLINICHE
- MENTRE IL SUO TEAM DI MEDICI ED INFERMIERI STA LAVORANDO PER TRATTARE IL PROBLEMA, PUO' AIUTARE A MIGLIORARE I SUOI LIVELLI DI OSSIGENO CON DETERMINATI CAMBIAMENTI DI POSIZIONE
- SE POSSIBILE, CERCHI DI NON PASSARE MOLTO TEMPO SDRAIATO SULLA SCHIENA
- CERCHI DI SDRAIARSI A PANCIA IN GIÙ 2-3 VOLTE AL GIORNO (DA 30 MIN A QUALCHE ORA ALLA VOLTA SE POSSIBILE)
- STARE A PANCIA IN GIÙ (POSIZIONE PRONA) LA AIUTERÀ A FAR ENTRARE PIÙ ARIA NEI SUOI POLMONI E MIGLIORERA' I LIVELLI DI OSSIGENO
- SE NON L'HAI MAI PROVATO PRIMA, ALL'INIZIO LE POTREBBE SEMBRARE UN PO' SCOMODO. IL PERSONALE SANITARIO LA AIUTERA' A METTERSI IN UNA POSIZIONE COMODA
- ANCHE STARE SEDUTI È MEGLIO CHE SDRAIARSI SULLA SCHIENA (POSIZIONE SUPINA)
- SE NON RIESCE A METTERSI IN QUELLA POSIZIONE, VA BENE LO STESSO. IL SUO TEAM DI MEDICI ED INFERMIERI FARA' COMUNQUE IL POSSIBILE PER MIGLIORARE LA SUA CONDIZIONE.

AWAKE PRONE POSITIONING (APP)

- *AS YOU ARE AWARE, YOUR OXYGEN LEVELS ARE LOW BECAUSE OF YOUR CURRENT MEDICAL CONDITION*
- *WHILE YOUR MEDICAL TEAM IS WORKING ON TREATING THE PROBLEM, YOU CAN HELP IMPROVE YOUR OXYGEN LEVELS WITH CERTAIN POSITION CHANGES*
- *IF POSSIBLE, TRY TO NOT SPEND A LOT OF TIME LYING FLAT ON YOUR BACK*
- *TRY TO LIE ON YOUR STOMACH 2-3 TIMES PER DAY (30 MIN-FEW HOURS AT A TIME IF POSSIBLE)*
- *LAYING ON YOUR STOMACH (PRONE POSITION) WILL HELP TO GET MORE AIR INTO YOUR LUNGS, AND IMPROVE YOUR OXYGEN LEVELS*
- *IT MAY FEEL A BIT UNCOMFORTABLE AT FIRST, IF YOU HAVE NOT TRIED IT BEFORE. ASK YOUR NURSE FOR ASSISTANCE IF NEEDED, TO HELP YOU GET INTO A COMFORTABLE POSITION.*
- *EVEN SITTING UP IS BETTER THAN LAYING ON YOUR BACK (SUPINE POSITION)*
- *IF YOU ARE UNABLE TO GET INTO THAT POSITION, IT'S ALRIGHT. YOUR MEDICAL TEAM WILL KEEP WORKING ON OTHER STRATEGIES TO IMPROVE YOUR CONDITION.*

Prolonged prone position ventilation for SARS-CoV-2 patients is feasible and effective

Carsetti *et al. Critical Care* (2020) 24:225
https://doi.org/10.1186/s13054-020-02956-w

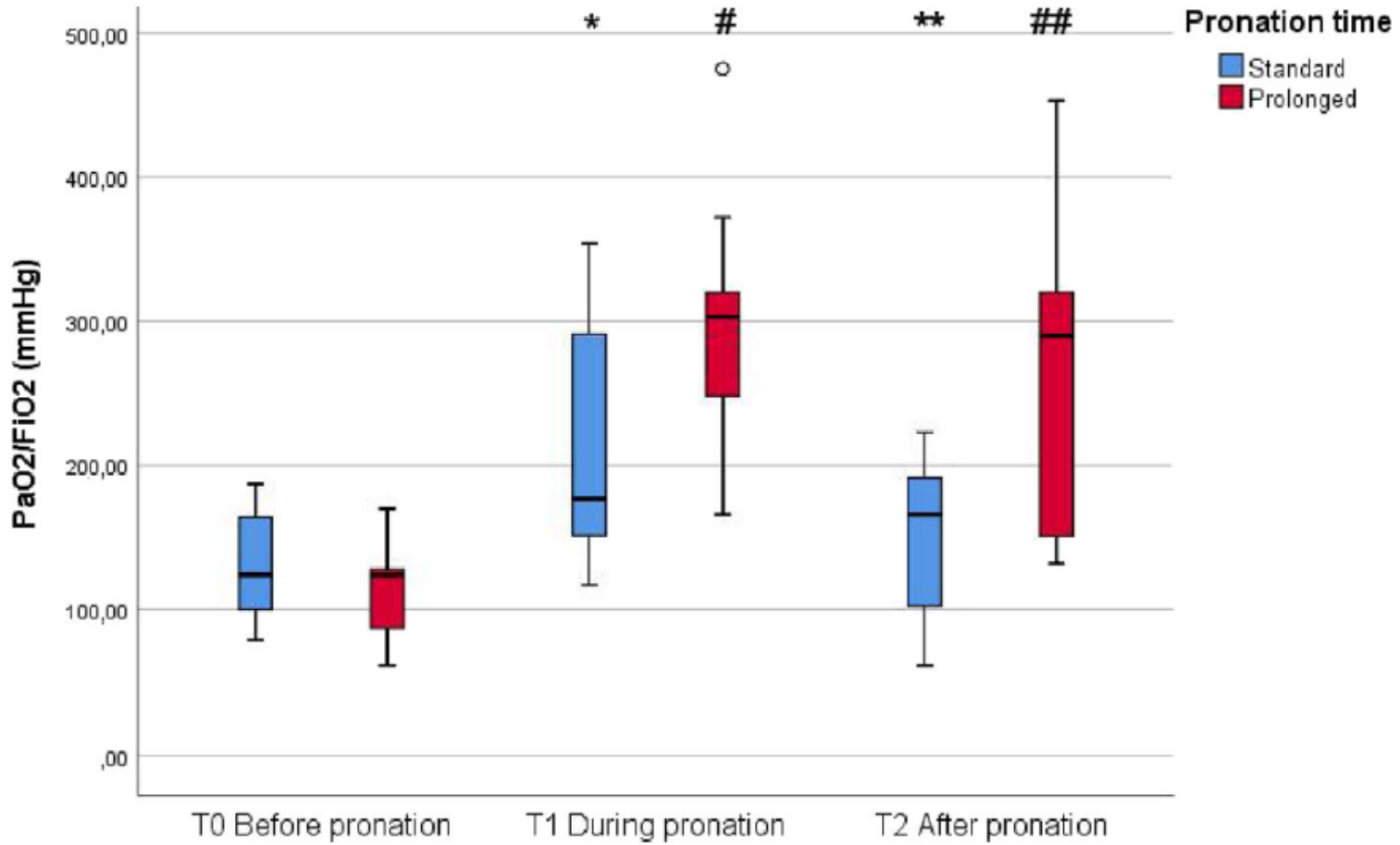
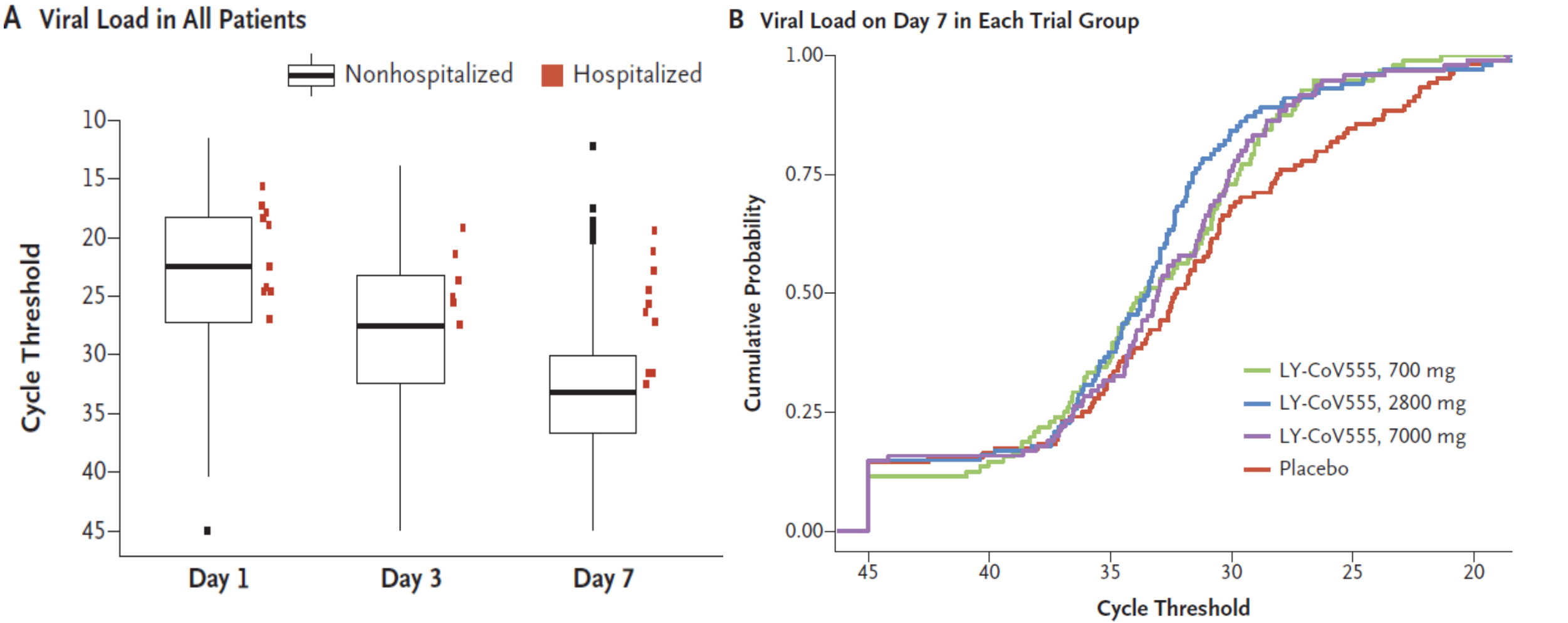


Fig. 1 PaO_2/FiO_2 comparison between standard and prolonged prone position ventilation. *Standard pronation: T1 vs. T0, $p = 0.01$; **standard pronation: T2 vs. T1, $p = 0.016$; #prolonged pronation: T1 vs. T0, $p < 0.001$; ##prolonged pronation: T2 vs. T0, $p = 0.034$

Home based treatment

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19



SARS-CoV-2 Viral Load in All Patients and According to Trial Group on Day 7.

This article was published on October 28, 2020, at NEJM.org.

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

Table 2. Change from Baseline in Viral Load.

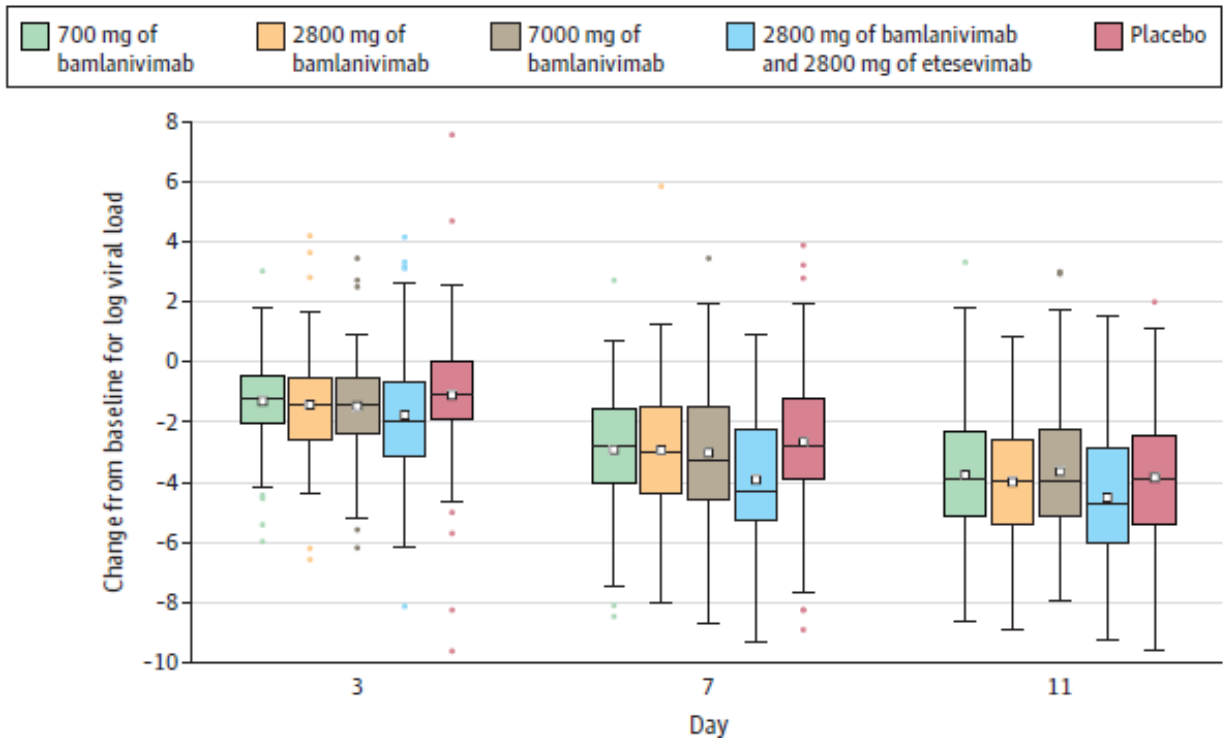
Variable	LY-CoV555 (N=309)	Placebo (N=143)	Difference (95% CI)
Primary outcome			
Mean change from baseline in viral load at day 11		−3.47	
	700 mg, −3.67		−0.20 (−0.66 to 0.25)
	2800 mg, −4.00		−0.53 (−0.98 to −0.08)
	7000 mg, −3.38		0.09 (−0.37 to 0.55)
	Pooled doses, −3.70		−0.22 (−0.60 to 0.15)
Secondary outcomes*			
Mean change from baseline in viral load at day 3		−0.85	
	700 mg, −1.27		−0.42 (−0.89 to 0.06)
	2800 mg, −1.50		−0.64 (−1.11 to −0.17)
	7000 mg, −1.27		−0.42 (−0.90 to 0.06)
	Pooled doses, −1.35		−0.49 (−0.87 to −0.11)
Mean change from baseline in viral load at day 7		−2.56	
	700 mg, −2.82		−0.25 (−0.73 to 0.23)
	2800 mg, −3.01		−0.45 (−0.92 to 0.03)
	7000 mg, −2.85		−0.28 (−0.77 to 0.20)
	Pooled doses, −2.90		−0.33 (−0.72 to 0.06)

This article was published on October 28, 2020, at NEJM.org.

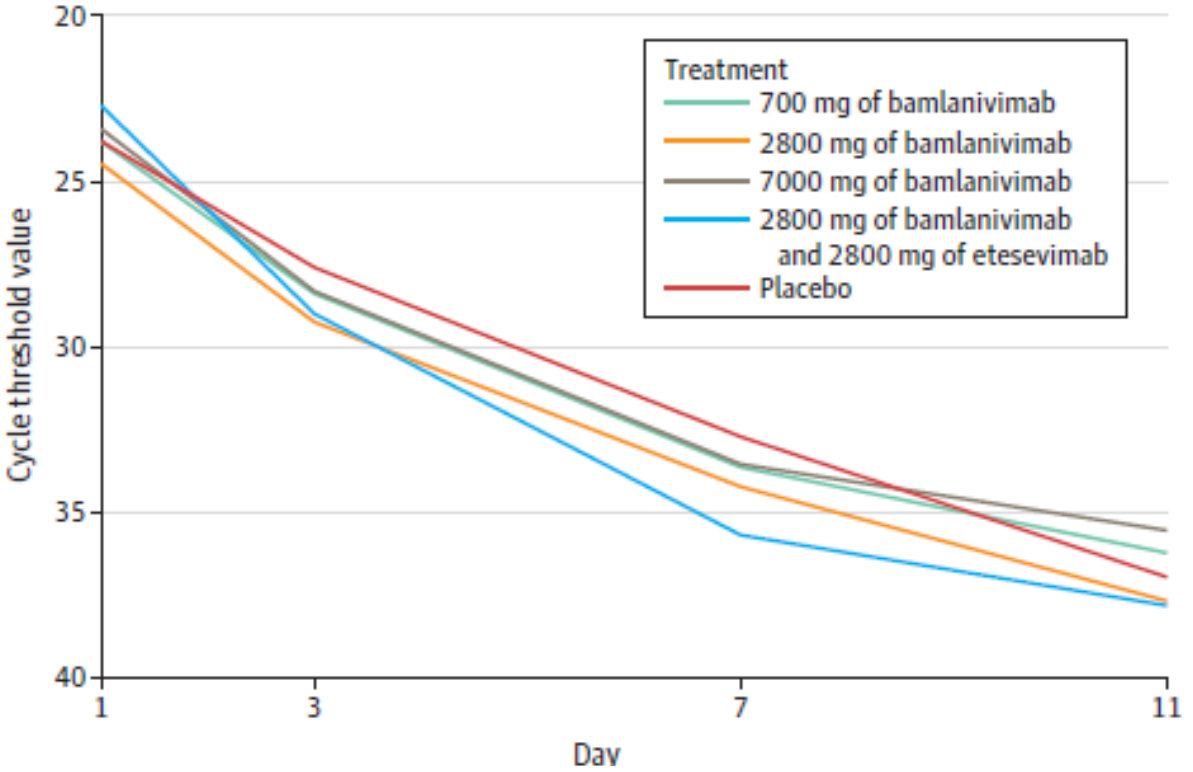
Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19

A Randomized Clinical Trial

Change in Log Viral Load and in Viral Load Cycle Threshold Over Time With Bamlanivimab Monotherapy and Bamlanivimab and Etesevimab Combination Therapy



Box plot for change from baseline to log viral load



Mean SARS-CoV-2 viral load cycle threshold value

JAMA. doi:10.1001/jama.2021.0202
Published online January 21, 2021.

Pause in the Distribution of bamlanivimab/etesevimab

June 25, 2021

The Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services are committed to ensuring timely and transparent communication regarding the COVID-19 monoclonal antibody treatments currently authorized for emergency use in certain patients with COVID-19.

Today, we are informing you that ASPR is immediately pausing all distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA 094) on a national basis until further notice. In addition, FDA recommends that health care providers nationwide use alternative authorized monoclonal antibody therapies, as described below, and not use bamlanivimab and etesevimab administered together at this time.

The Centers for Disease Control and Prevention (CDC) has identified that the combined frequencies of the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and the B.1.351/Beta variant (first identified in South Africa) throughout the United States now exceed 11% and are trending upward (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Results from in vitro assays that are used to assess the susceptibility of viral variants to particular monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P.1 or B.1.351 variants. These assays use "pseudotyped virus-like particles" that help determine likely susceptibility of the live SARS-CoV-2 variant viruses.

Related Resources

- Casirivimab/imdevimab
- Bamlanivimab/etesevimab
- SPEED: Special Projects for Equitable and Efficient Distribution of COVID-19 Outpatient Therapeutics
- Locating Sites for COVID-19 Antibody Treatments

FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB

(September 2, updated September 16, 2021)

Limitations of Authorized Use

Combined Frequency of Variants Resistant to Bamlanivimab and Etesevimab

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.[1]
  - A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: https://www.fda.gov/media/151719/download

(On October 9 only Hawai are not authorized

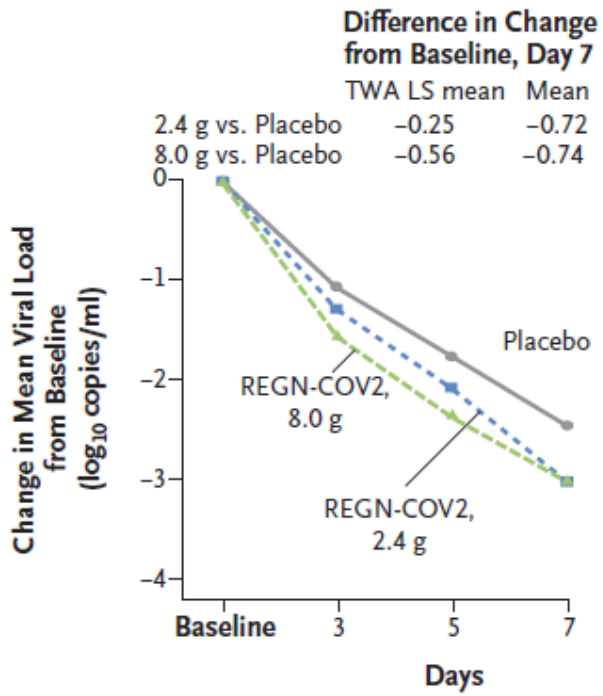
POST-EXPOSURE PROPHYLAXIS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[1] or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[2]) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[3] **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) *[see*

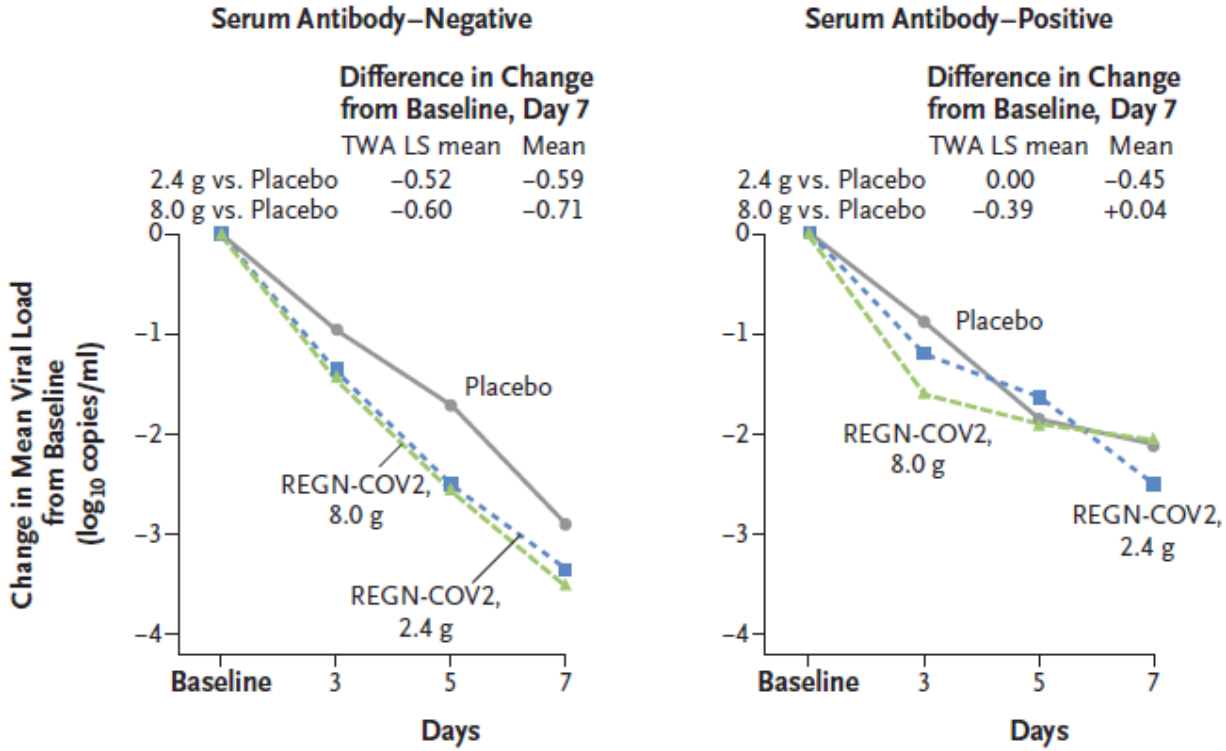
REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

A Viral Load over Time in the Overall Population



No. at Risk				
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

B Viral Load over Time According to Baseline Antibody Status

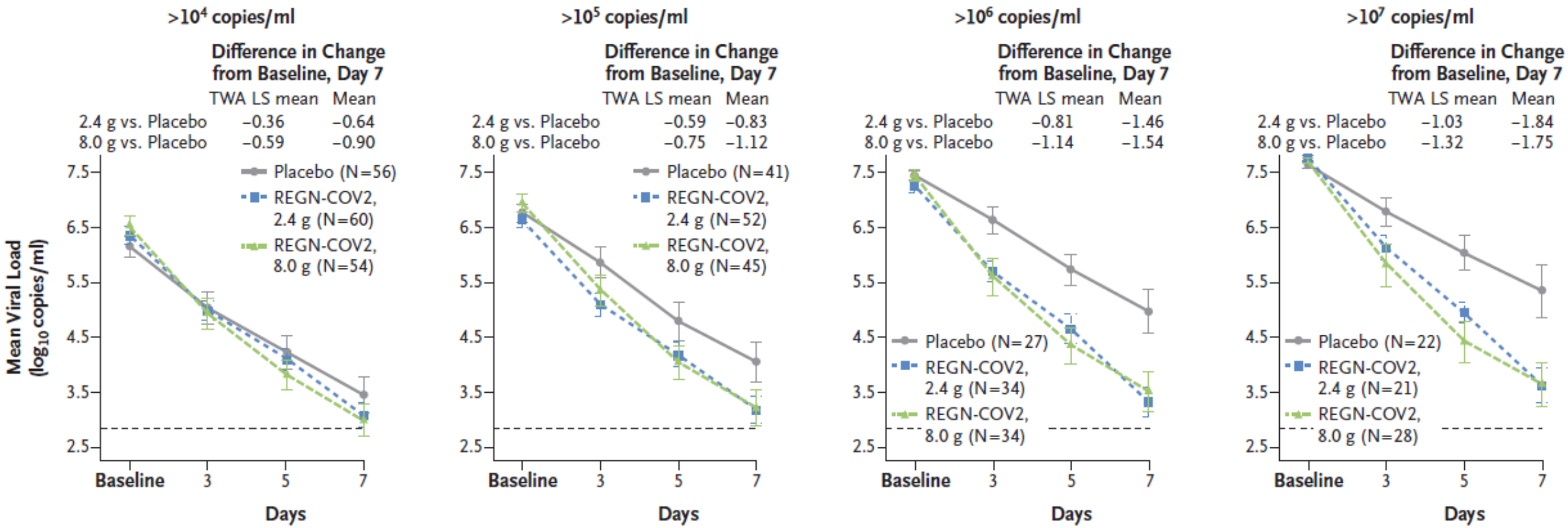


No. at Risk								
Placebo	30	23	28	28	38	35	37	37
REGN-COV2, 2.4 g	35	32	34	34	27	26	27	27
REGN-COV2, 8.0 g	36	34	35	35	29	38	29	29

This article was published on December 17, 2020, and updated on December 18, 2020, at NEJM.org.

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

C Viral Load over Time According to Baseline Viral Load Category



This article was published on December 17, 2020, and updated on December 18, 2020, at NEJM.org.

REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19

This article was published on September 29, 2021, at NEJM.org.

Patient population:

- Adult, *non-hospitalized* patients with Covid-19
- Symptom onset ≤7 days from randomization
- SARS-CoV-2 confirmed by molecular testing ≤72 hours from randomization
- Not on any putative Covid-19 therapies

Original phase 3 portion comparing 8000 mg and 2400 mg versus placebo

R 1:1:1

- REGEN-COV 8000 mg IV
- REGEN-COV 2400 mg IV
- Placebo IV

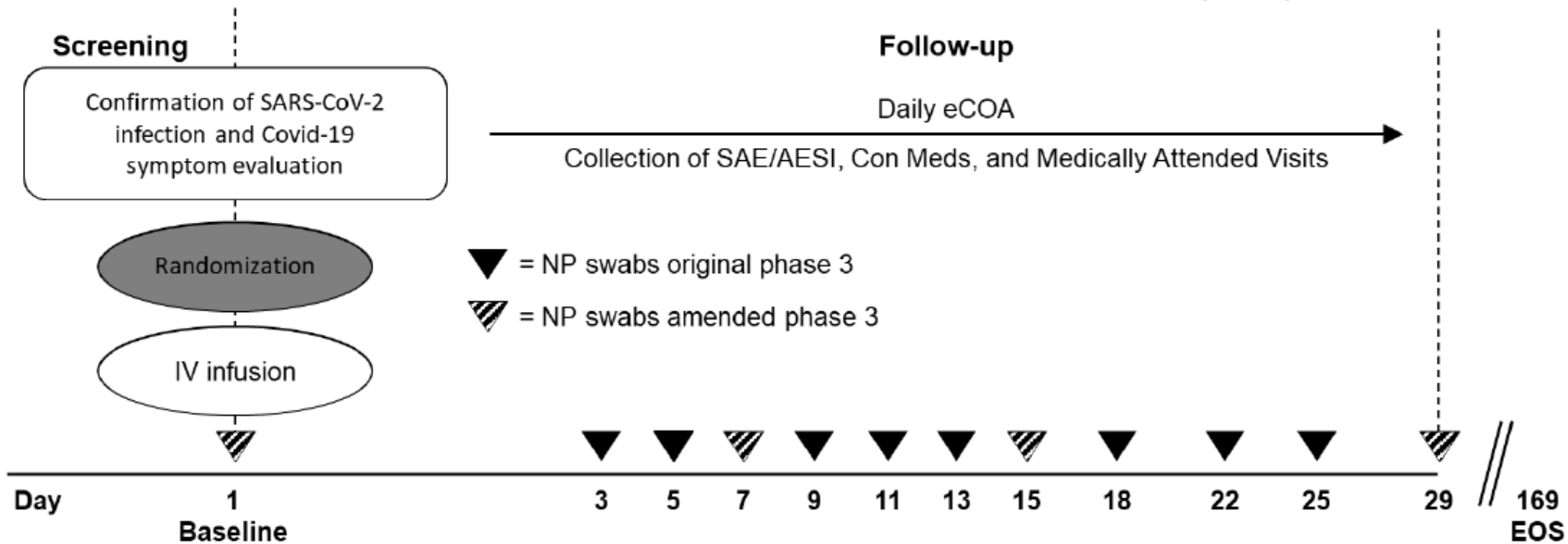
Stratified by no risk factors vs ≥1 risk factor for severe Covid-19*

Amended phase 3 portion comparing 2400 mg and 1200 mg versus placebo

R 1:1:1

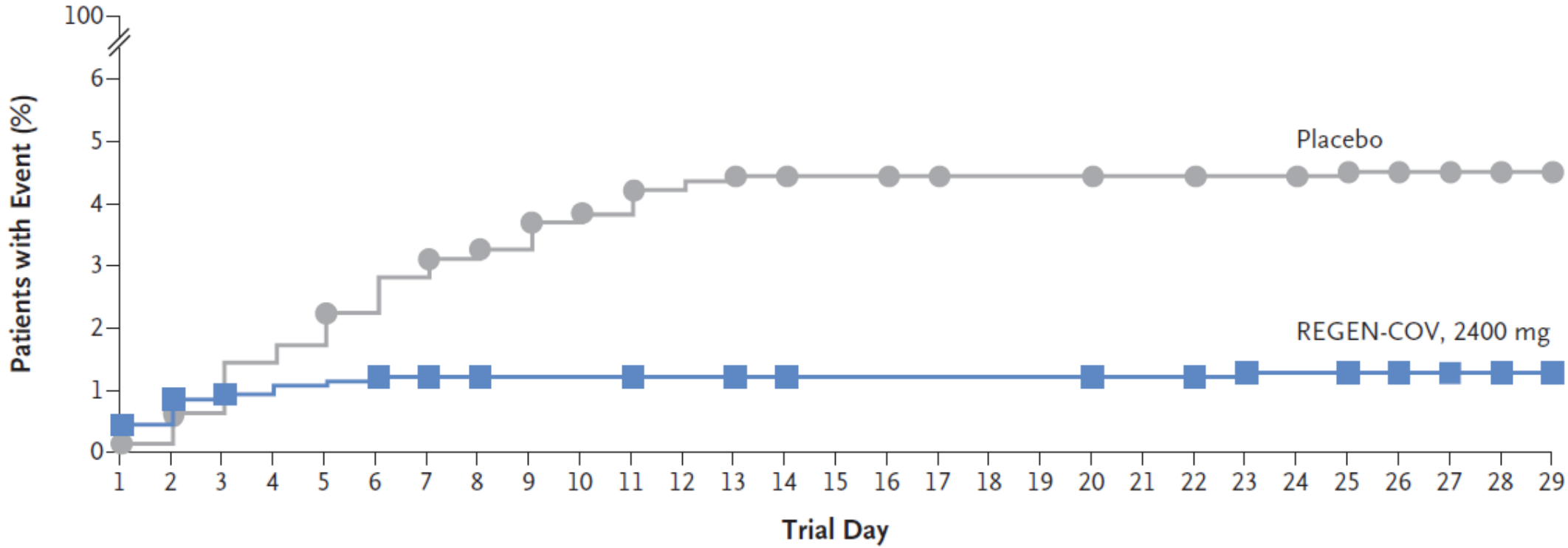
- REGEN-COV 2400 mg IV
- REGEN-COV 1200 mg IV
- Placebo IV

All patients required to have ≥1 risk factor for severe Covid-19*



REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19

B **Covid-19–Related Hospitalization or Death from Any Cause — Combined Phase 3 Trial**



No. at Risk

Placebo	1341	1330	1315	1298	1287	1275	1265	1260	1259	1258	1257	1242	1241	1211	1052
REGEN-COV, 2400 mg	1355	1339	1335	1332	1329	1329	1327	1324	1324	1324	1323	1316	1314	1292	1113

This article was published on September 29, 2021, at NEJM.org.

REGENERON®

November 8, 2021 at 7:00 AM EST

« Back

NEW PHASE 3 ANALYSES SHOW THAT A SINGLE DOSE OF REGEN-COV® (CASIRIVIMAB AND IMDEVIMAB) PROVIDES LONG-TERM PROTECTION AGAINST COVID-19

TARRYTOWN, N.Y., Nov. 8, 2021 /PRNewswire/ --

Single dose of REGEN-COV (1,200 mg subcutaneous) reduced the risk of COVID-19 by 81.6% during the pre-specified follow-up period (months 2-8), maintaining the 81.4% risk reduction previously reported during month 1

During the 8-month assessment period there were 0 hospitalizations for COVID-19 in the REGEN-COV group and 6 in the placebo group

The fully human antibodies in REGEN-COV were developed to provide long-lasting protective effects without any artificial mutations or sequences

Treatment

The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Table 1). See sections 4.4 and 5.1.
Casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19.

Prevention

Post-exposure prophylaxis
The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 2).
Casirivimab with imdevimab should be given as soon as possible after contact with a case of COVID-19.

Pre-exposure prophylaxis
The initial dose in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 2). Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection may be given every 4 weeks until prophylaxis is no longer required. There are no data on repeat dosing beyond 24 weeks (6 doses).

Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab

Table 2. Efficacy Outcomes through Day 29 (Intention-to-Treat Population).*

Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†
Alive and not hospitalized — no. (%)	284 (98)	270 (92)
Data missing — no. (%)		
All patients with missing data	4 (1)	1 (<1)
Patients with missing data because of withdrawal of consent before receipt of sotrovimab or placebo	3 (1)	1 (<1)
Relative risk reduction (97.24% CI)	85 (44–96)	—
P value	0.002	—

COMET-ICE published on October 27, 2021, at NEJM.org.

AZD7442 PROVENT Phase III prophylaxis trial met primary endpoint in preventing COVID-19

Article
Potently neutralizing and protective human antibodies against SARS-CoV-2
Nature | Vol 584 | 20 August 2020 | 447

- PROVENT is a Phase III RCT assessing safety and efficacy of 300mg AZD7442 (combination of 2 long-acting antibodies, tixagevimab and cilgavimab, discovered by Vanderbilt UMC, Nashville and licensed to AZ in 06/20) compared to placebo for the prevention of COVID-19.
- The trial was conducted in US, UK, Spain, France and Belgium. 5,197 participants were randomised in a 2:1 ratio to receive AZD7442 (3460) or placebo (1,737), administered in two IM injections.
- The primary efficacy endpoint was the first COVID case occurring post dose prior to day 183. Participants were adults who would benefit as having increased risk for inadequate response to active immunisation or having increased risk for SARS-CoV-2 infection
- **August 20, 2021**, press media release: AZD7442 reduced the risk of developing symptomatic COVID-19 by 77%. No severe COVID-19 or COVID-19-deaths in AZD7442 treated. In placebo arm, 3 severe COVID-19 cases, including 2 deaths.
- **October 5, 2021** AZ submitted a FDA request for EUA for AZD7442 for prophylaxis of symptomatic COVID-19

Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial

> 4000 patients were randomly assigned to receive oral colchicine (0·5 mg twice per day for 3 days and then once per day for 27 days) or placebo

	Colchicine (n=2075)	Placebo (n=2084)	Odds ratio (95% CI)	p value
Primary composite endpoint	96 (4·6%)	126 (6·0%)	0·75 (0·57–0·99)	0·042
Components of primary endpoint				
Death	5 (0·2%)	9 (0·4%)	0·56 (0·19–1·66)	..
Hospitalisation for COVID-19	93 (4·5%)	123 (5·9%)	0·75 (0·57–0·99)	..
Secondary endpoint mechanical ventilation	10 (0·5%)	20 (1·0%)	0·50 (0·23–1·07)	..

Data are n (%). Evaluation of the primary endpoint in the subgroup of patients with PCR-confirmed COVID-19 was prespecified and that of components of the primary endpoint and the secondary endpoints were done as post-hoc analyses.

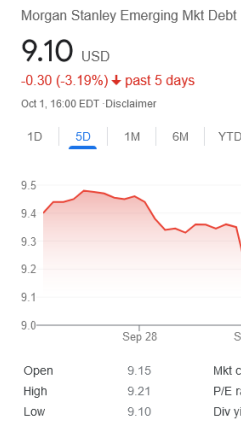
***Table 3*: Rates and odds ratios for major clinical outcomes in the subgroup of patients with PCR-confirmed COVID-19 in the intent-to-treat population**

Lancet resp med 05.21

Molnupiravir: coding for catastrophe

- Molnupiravir was invented at Drug Innovations at Emory (DRIVE), LLC, a not-for-profit biotechnology company owned by Emory University, and is being developed by Merck & Co., Inc. with Ridgeback Biotherapeutics

- Molnupiravir (MK-4482, EIDD-2801) is a candidate antiviral that targets the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), inhibits viral propagation through *lethal mutagenesis* by introducing errors in the viral genome, has a pan-coronaviral inhibitory profile, fails to induce viral-resistance mutations.



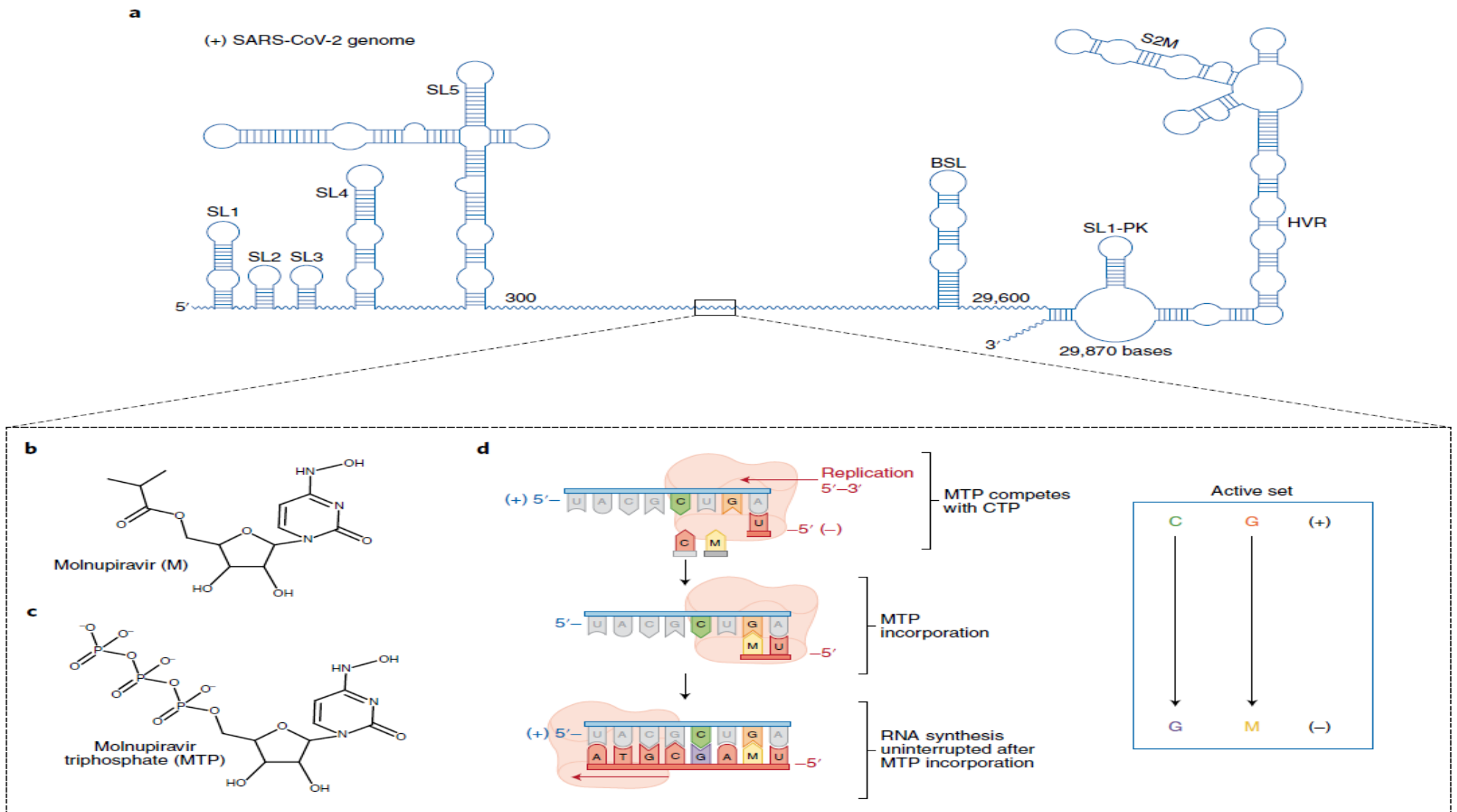
- Molnupiravir-induced lethal mutagenesis is minimally a two-step mechanism characterized by a relatively high selectivity of MTP for incorporation as a CTP analog and the indiscriminate incorporation of either ATP (mutagenesis) or GTP when MNP is localized in the templating strand.

- The erroneously incorporated AMP can subsequently template UTP incorporation, generating downstream C-to-U mutations. The accumulation of mutations pushes viral replication over the ‘error threshold’ that demarcates the replication fidelity required for viability.

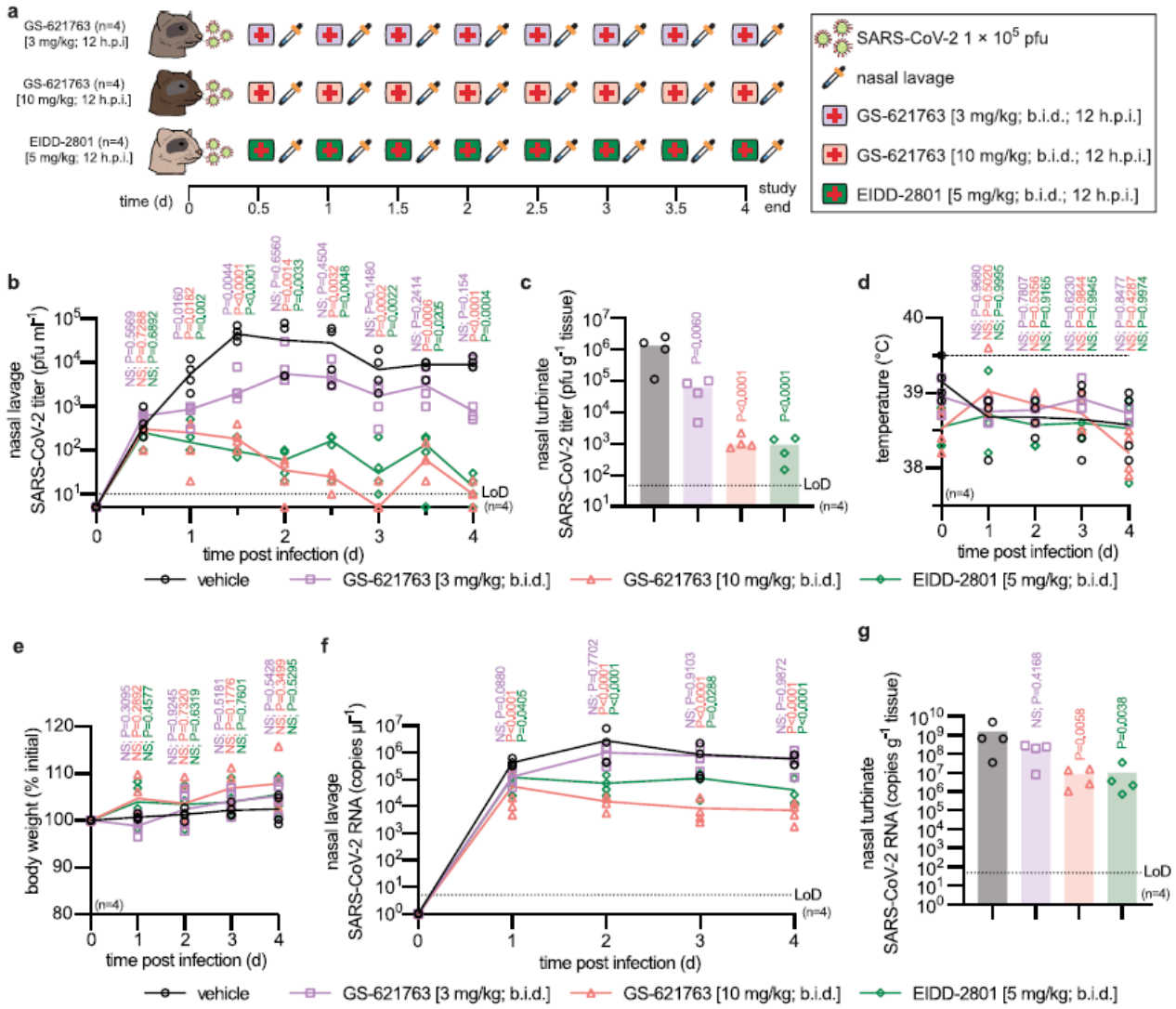
- This mechanism distinguishes molnupiravir from remdesivir, which impedes the progression of viral RdRp, and provides insights into alternative mechanisms of RdRp inhibition. Finally, molnupiravir possesses excellent pharmacokinetic properties, which include oral administration

Molnupiravir: coding for catastrophe

)-19,



Oral prodrug of remdesivir parent GS-441524 is efficacious against SARS-CoV-2 in ferrets



Oral GS-621763 is efficiently converted to plasma metabolite GS-441524, and in lungs to the triphosphate metabolite identical to that generated by remdesivir, demonstrating a consistent mechanism of activity.

Twice-daily oral administration of 10 mg/kg GS-621763 reduces SARS-CoV-2 burden to near-undetectable levels in ferrets.

When dosed therapeutically against VOC P.1 gamma γ, oral GS-621763 blocks virus replication and prevents transmission to untreated contact animals.

Cox Nat Com Nov 8, 2021

PFIZER'S NOVEL COVID-19 ORAL ANTIVIRAL TREATMENT CANDIDATE REDUCED RISK OF HOSPITALIZATION OR DEATH BY 89% IN INTERIM ANALYSIS OF PHASE 2/3 EPIC-HR STUDY

Friday, November 05, 2021 - 06:45am

- Interim analysis of the Phase 2/3 EPIC-HR (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients) randomized, double-blind study of 1219 non-hospitalized adults with COVID-19, at high risk of clinical progression treated with PAXLOVID (PF-07321332 plus ritonavir), an oral SARS-CoV-2-3CL protease inhibitor
- The scheduled interim analysis showed an 89% reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint); 0.8% of patients who received PAXLOVID were hospitalized through day 28 following randomization (3/389 hospitalized with no deaths), compared to 7.0% of patients who received placebo and were hospitalized or died (27/385 hospitalized with 7 subsequent deaths) ($p<0.0001$).
- Similar reductions in patients treated within five days of symptom onset; 1.0% of patients under PAXLOVID were hospitalized through day 28 (6/607 hospitalized, with no deaths), compared to 6.7% of patients who received a placebo (41/612 hospitalized with 10 subsequent deaths)($p<0.0001$).
- In the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID™ as compared to 10 (1.6%) deaths in patients who received placebo..

JAMA | Original Investigation

Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19

The ACTIV-4B Randomized Clinical Trial

Connors et al, JAMA online October 11, 2021

Table 2. Suspected and Adjudicated Efficacy Outcomes and Hemorrhagic Events Within 45 Days of Drug Initiation Among Those Who Initiated Trial Therapy, Stratified by Assigned Treatment

	No. (%)			
	Aspirin (81 mg once daily) (n = 144)	Apixaban (2.5 mg twice daily) (n = 135)	Apixaban (5 mg twice daily) (n = 143)[a]	Placebo (n = 136)[a]
Adjudicated outcomes[d]				
Composite primary end point	0	1 (0.7)	2 (1.4)	0
Risk difference (in percentage points) vs placebo (95% CI)	0	0.7 (-2.1 to 4.1)	1.4 (-1.5 to 5.0)	
Components of primary end point				
Cardiopulmonary hospitalizations	0	1 (0.7)	2 (1.4)	0
Deep vein thrombosis or pulmonary embolism	0	0	0	0
Myocardial infarction, stroke or other arterial embolism	0	0	0	0
Death	0	0	0	0

A Cumulative incidence of adjudicated primary end point

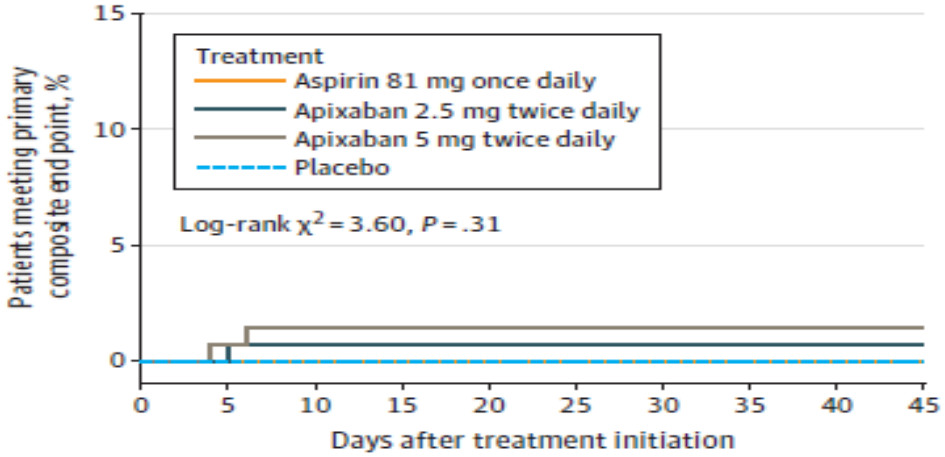
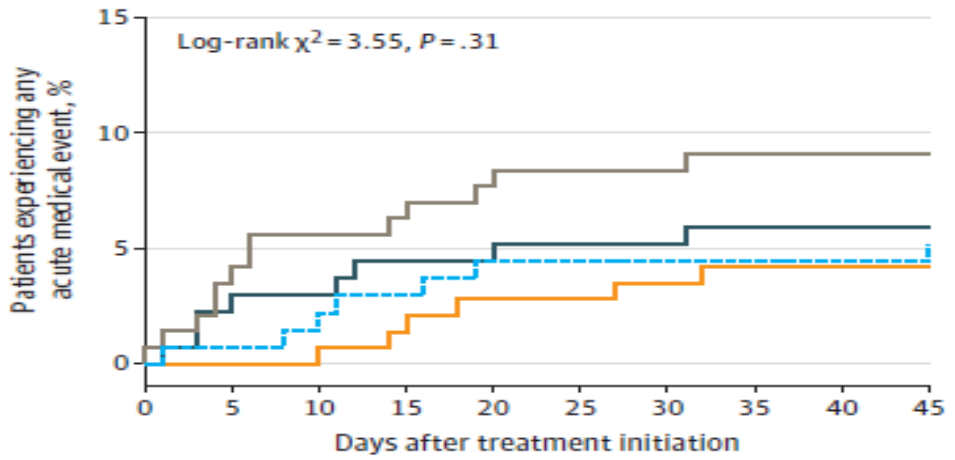


Table 2. Suspected and Adjudicated Efficacy Outcomes and Hemorrhagic Events Within 45 Days of Drug Initiation Among Those Who Initiated Trial Therapy, Stratified by Assigned Treatment

	No. (%)			
	Aspirin (81 mg once daily) (n = 144)	Apixaban (2.5 mg twice daily) (n = 135)	Apixaban (5 mg twice daily) (n = 143)[a]	Placebo (n = 136)[a]
Suspected hemorrhagic events				
Any bleeding event[e]	6 (4.2)	9 (6.7)	13 (9.1)	3 (2.2)
Risk difference (in percentage points) vs placebo (95% CI)	2.0 (-2.7 to 6.8)	4.5 (-0.7 to 10.2)	6.9 (1.4 to 12.9)	
Type of bleeding event				
Major bleeding	0	0	0	0
Clinically relevant nonmajor bleeding	2 (1.4)	4 (3.0)	2 (1.4)	0
Minor bleeding	4 (2.8)	5 (3.7)	11 (7.7)	3 (2.2)
Adjudicated hemorrhagic events[f]				
Major bleeding	0	0	0	0
Clinically relevant nonmajor bleeding	0	1 (0.7)	1 (0.7)	0

B Cumulative incidence of any acute medical event



In-hospital treatment

Monoclonal Antibodies

REGENERON

September 14, 2020 at 7:00 AM EDT

RECOVERY COVID-19 PHASE 3 TRIAL TO EVALUATE REGENERON'S REGN-COV2 INVESTIGATIONAL ANTIBODY COCKTAIL IN THE UK

RECOVERY
Randomised Evaluation of COVID-19 Therapy

RECOVERY COVID-19 phase 3 trial to evaluate Regeneron's REGN-COV2 investigational antibody cocktail in the UK

14 September 2020

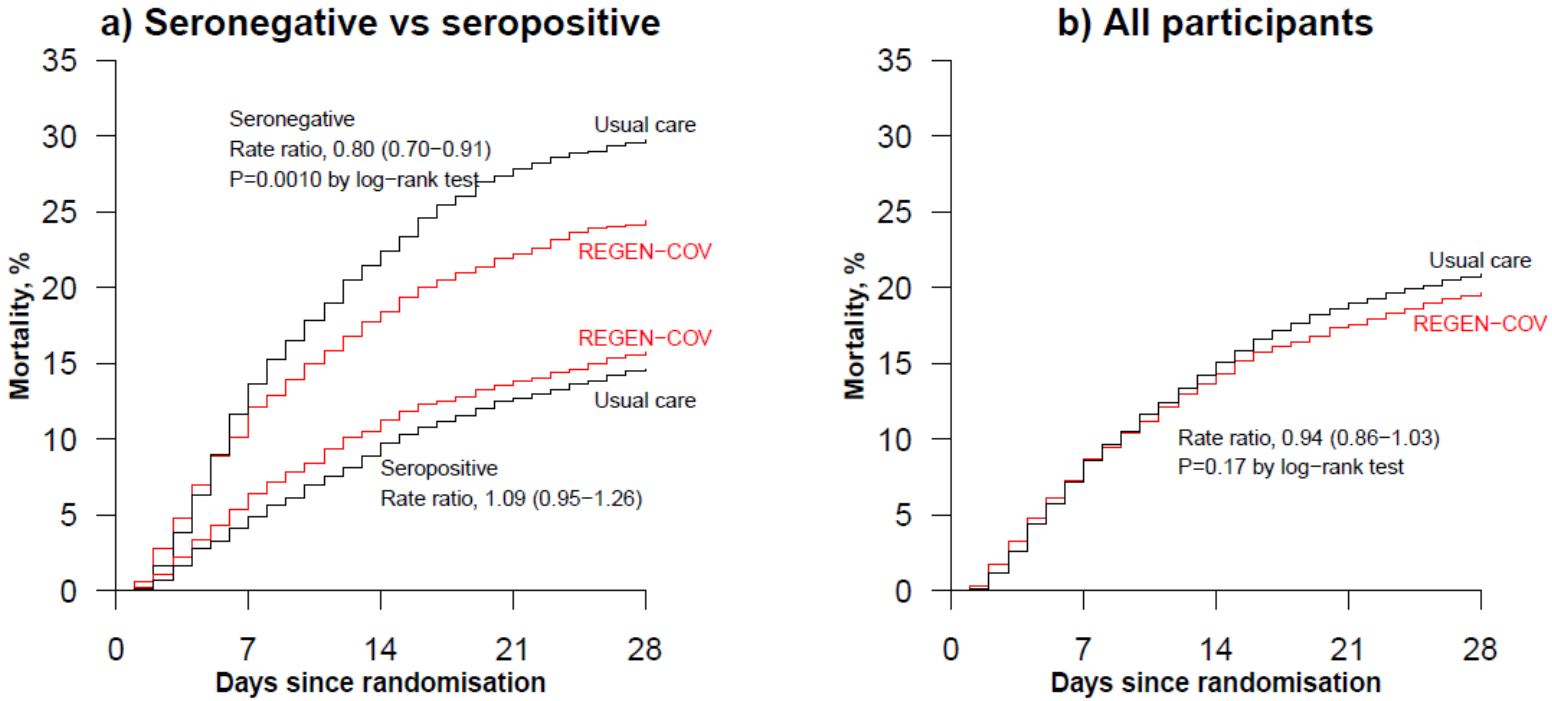
One of the world's largest efforts to find effective COVID-19 treatments will evaluate the impact of REGN-COV2 on mortality, hospital stays, and the need for ventilation.

The open-label RECOVERY trial will assess the impact of adding REGN-COV2 to the usual standard-of-care on all-cause mortality 28 days after randomization. Other endpoints include the impact on hospital stay and the need for ventilation. It is anticipated that at least 2,000 patients will be randomly allocated to receive REGN-COV2 plus usual standard-of-care, and results will be compared with at least 2,000 patients who receive standard-of-care on its own. Usual standard-of-care varies by local hospital.

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised,

Figure 2: Effect of allocation to REGEN−COV on 28−day mortality in: a) seronegative vs seropositive participants; and b) all participants

UNDER EMBARGO UNTIL 16 June 2021



No. at risk, Seronegative

REGEN−COV	1633	1429	1325	1260	1224
Usual Care	1520	1308	1173	1088	1059

No. at risk, Seropositive

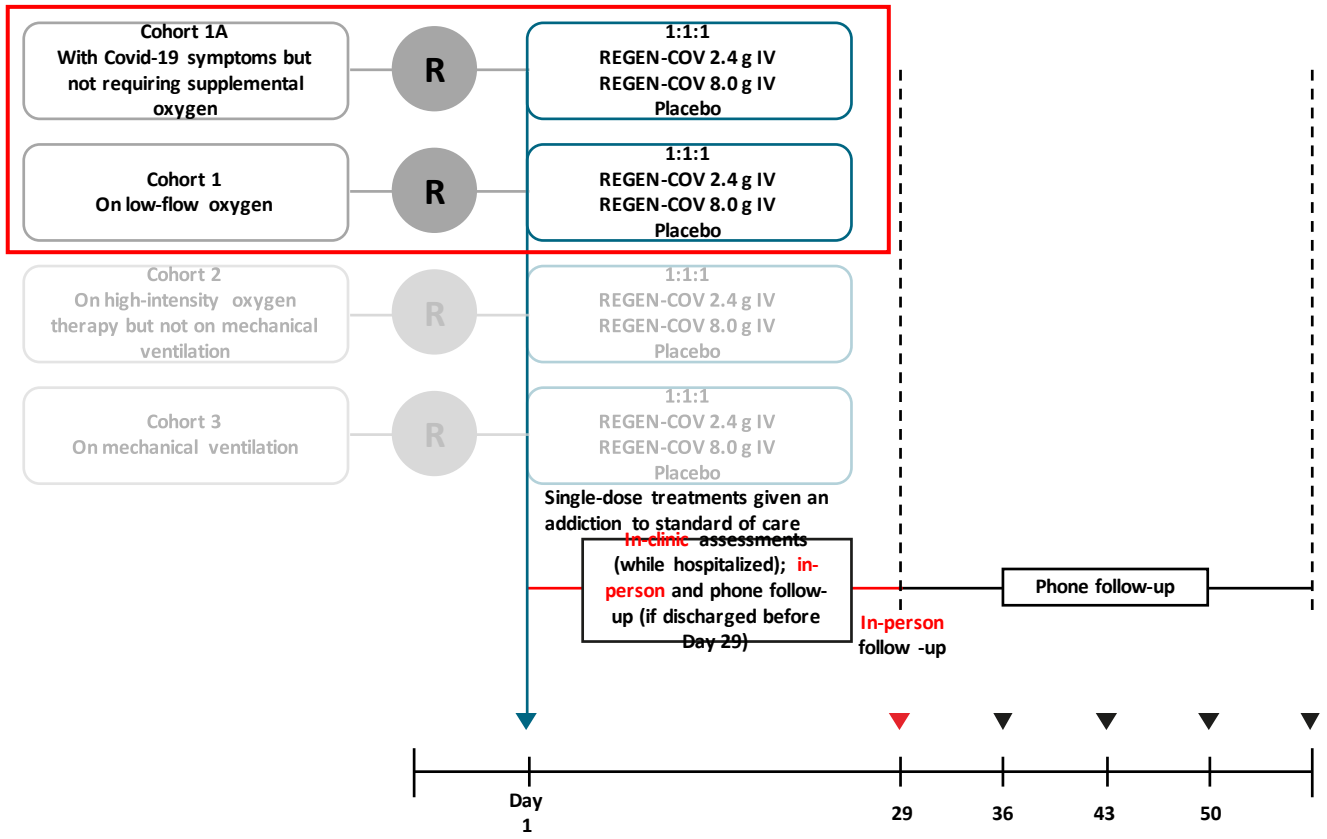
REGEN−COV	2636	2452	2322	2252	2201
Usual Care	2636	2503	2375	2292	2243

No. at risk

REGEN−COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3888

/2021.06.15.21258542;

Study assessing viral load reduction and prevention of death or need for mechanical ventilation



Virology samples collected: Baseline (Day 1), Days 3, 5, 7, 9, 11, 13, 15, 22, and 29.

Patient population

- Hospitalized adult COVID-19 patients (N=1197)
- Symptom onset ≤10 days from randomization
- SARS-CoV-2 confirmed by antigen or molecular testing ≤72 hours from randomization (retest allowed)
- Hospitalized for ≤72 hours

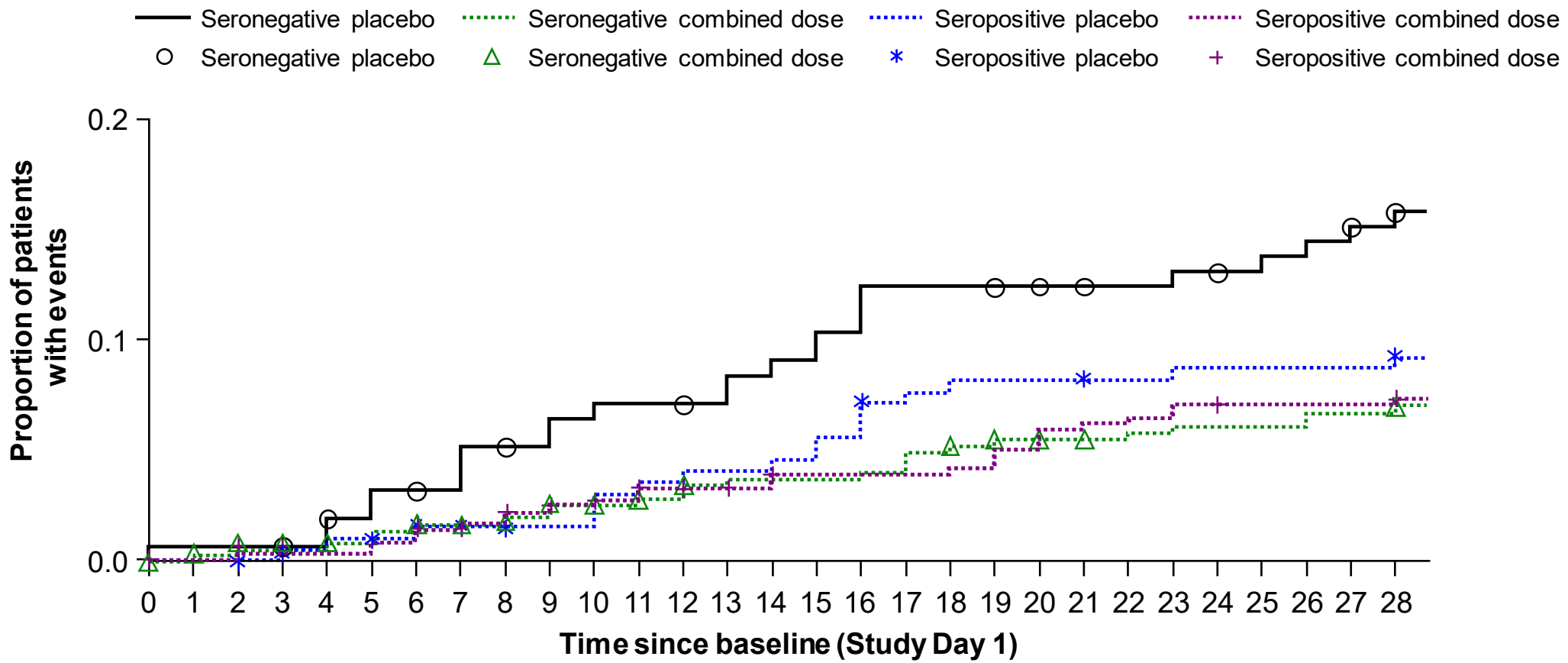
Stratified

- Antiviral only (e.g. remdesivir) at baseline or not on any other COVID-19 treatments or on anti-viral agents (e.g. corticosteroids) or on combination agents (e.g. remdesivir plus corticosteroids)
- Country

EOS, end of study; IV, intravenous; R, randomized.

Mylonakis ID Week 10..21

All cause mortality in treated patients versus placebo

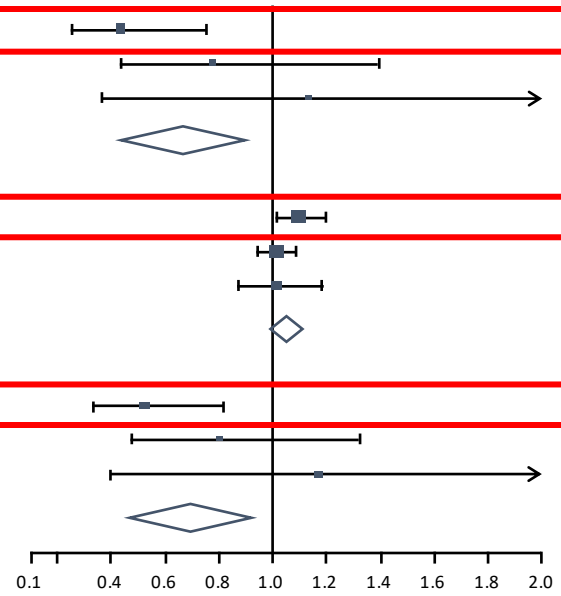


Number of subjects at risk

Seronegative placebo	160	159	159	158	157	153	151	150	147	146	144	143	143	140	138	137	135	132	132	132	131	129	127	127	126	125	124	123	121
Seronegative combined dose	360	358	356	353	352	348	346	343	341	338	333	331	329	325	324	324	324	323	320	316	314	313	312	311	310	310	310	308	308
Seropositive placebo	201	201	201	199	197	196	195	193	192	191	191	188	187	186	186	185	183	179	178	177	177	177	175	175	174	174	174	174	174
Seropositive combined dose	369	367	367	364	364	364	362	357	353	349	347	345	342	340	339	336	336	336	336	335	332	329	328	327	325	324	324	324	324

Casirivimab and imdevimab treatment numerically improved
mortality and death or mechanical ventilation by Day 29†

	Casirivimab and imdevimab combined doses‡	Placebo	Relative risk (95% CI)	Relative risk reduction (95% CI)	*P*-value (nominal)
Death within 28 days					
Seronegative	24/360 (6.7%)	24/160 (15.0%)		55.6% (24.2%, 74%)	0.0032
Seropositive	26/369 (7.0%)	18/201 (9.0%)		21.3% (–40.0%, 55.8%)	0.3153
Sero-undetermined§	9/75 (12.0%)	3/32 (9.4%)		–28.0% (NA, 62.9%)	1.0000
mFAS	**59/840 (7.3%)**	**45/393 (11.5%)**		**35.9% (7.3%, 55.7%)**	**0.0178**
Discharge alive from hospital					
Seronegative	324/360 (90.0%)	130/160 (81.2%)		–10.8% (–20.2%, –2%)	0.0072
Seropositive	323/369 (87.5%)	170/201 (85.6%)		–2.3% (–9.6%, 4.5%)	0.3639
Sero-undetermined§	67/75 (89.3%)	28/32 (87.5%)		–2.1 (–18.9%, 12.3%)	0.7487
mFAS	**712/804 (88.8%)**	**330/393 (84.0%)**		**–5.8% (–11.1%, –0.6%)**	**0.0184**
Death or mechanical ventilation					
Seronegative	37/360 (10.3%)	31/160 (19.4%)		47.0% (17.7%, 65.8%)	0.0061
Seropositive	34/369 (9.2%)	23/201 (11.4%)		19.5% (–32.8%, 51.2%)	0.3010
Sero-undetermined§	11/75 (14.7%)	4/32 (12.5%)		–17.3% (NA, 59.6%)	1.0000
mFAS	**82/804 (10.2%)**	**58/393 (14.8%)**		**30.9% (5.4%, 49.5%)**	**0.0212**



In seronegative patients, there was a 55.6% RRR of mortality by Day 29 and a 47.0% RRR in the proportion of patients who died or went on mechanical ventilation

†Pooled cohorts (low flow or no supplemental oxygen), Day 1 through Day 29.
§Sero-undetermined indicates missing or inconclusive serology results.RRR, relative risk reduction.

‡2.4 g IV and 8.0 g IV.

Treatment

The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Table 1). See sections 4.4 and 5.1.
Casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19.

Prevention

Post-exposure prophylaxis
The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 2).
Casirivimab with imdevimab should be given as soon as possible after contact with a case of COVID-19.

Pre-exposure prophylaxis
The initial dose in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 2). Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection may be given every 4 weeks until prophylaxis is no longer required. There are no data on repeat dosing beyond 24 weeks (6 doses).

Remdesevir for Covid 19

ORIGINAL ARTICLE

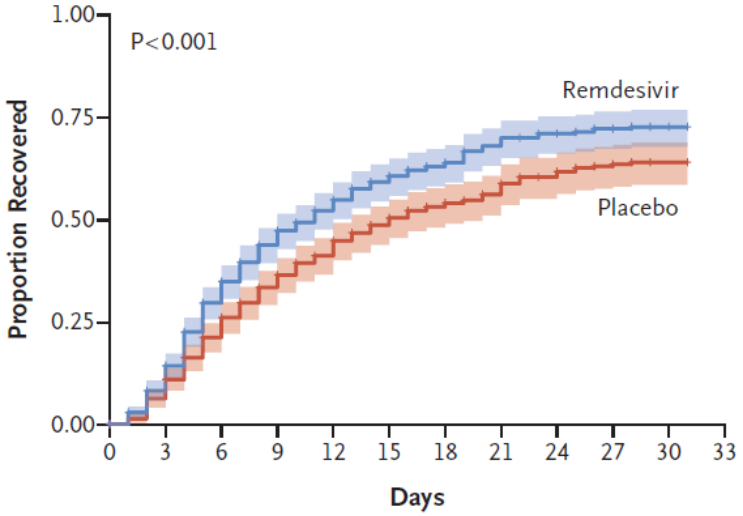
National Institutes of Health
Turning Discovery Into Health

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,

- Preliminary RCT data on 1062 patients began on February 21, the Adaptive COVID-19 Treatment Trial - ACTT, sponsored by NIH.
- Remdesivir was better than placebo, primary endpoint: time to recovery.
- Patients on remdesivir had a 29% faster time to recovery than those who received placebo ($p<0.001$). Specifically, the median time to recovery was 10 days for patients treated with remdesivir compared with 15 days for those who received placebo.
- Results also suggested a survival benefit, with a mortality rate of 6.7% for the group receiving remdesivir versus 11.9% for the placebo group on day 15 and 11.4% versus 15.2 on day 29 (HR 0.73, CI 0.52-1.03).

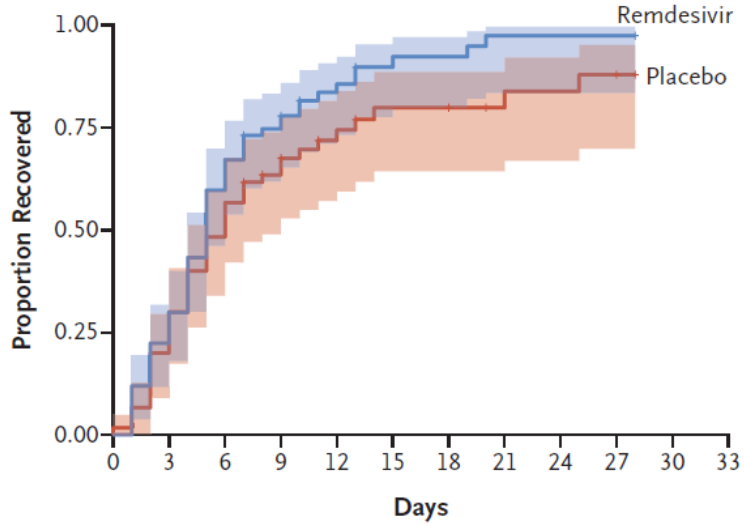
A Overall



No. at Risk

Remdesivir	538	481	363	274	183	142	121	98	78	65	3	0
Placebo	521	481	392	307	224	180	149	115	91	78	2	0

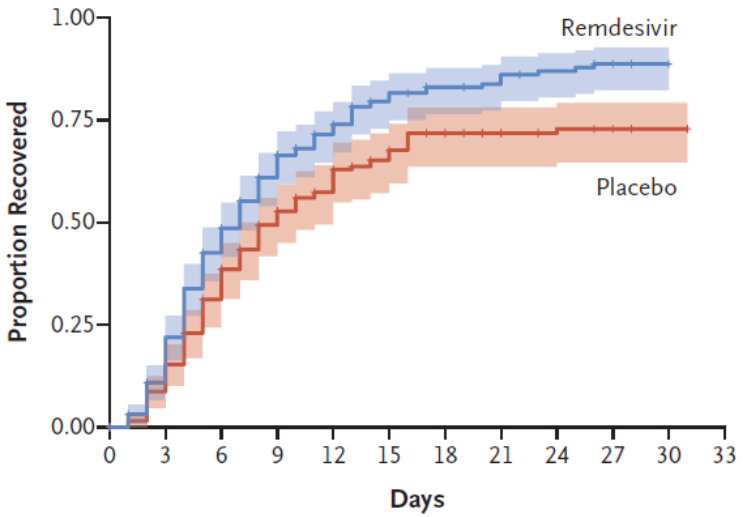
B Patients Not Receiving Oxygen



No. at Risk

Remdesivir	67	52	27	16	8	4	3	1	1	1	0	0
Placebo	60	48	31	18	11	7	7	5	4	3	0	0

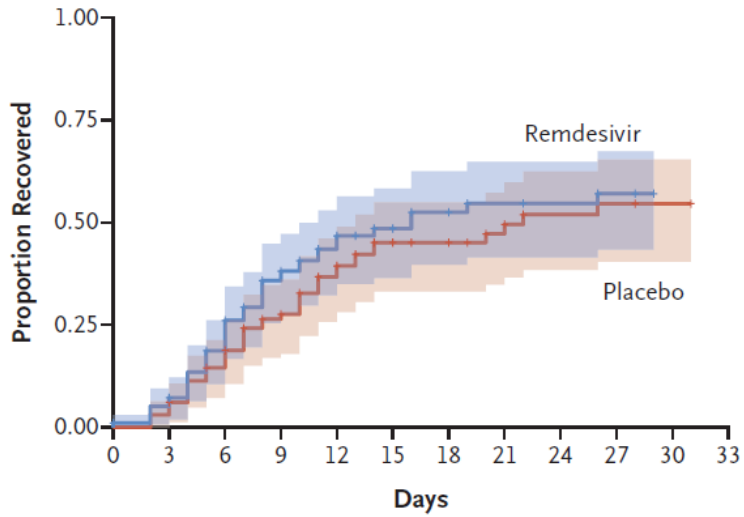
C Patients Receiving Oxygen



No. at Risk

Remdesivir	222	194	124	79	47	30	23	21	15	12	2	0
Placebo	199	179	131	91	61	43	33	29	26	23	1	0

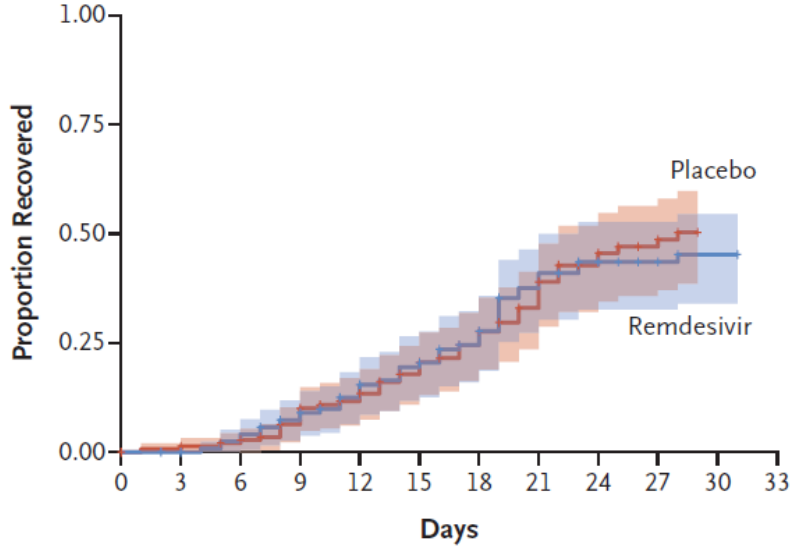
D Patients Receiving High-Flow Oxygen or Noninvasive Mechanical Ventilation



No. at Risk

Remdesivir	98	92	77	56	35	27	23	20	19	17	0	0
Placebo	99	96	80	62	47	37	34	23	18	17	1	0

Patients Receiving Mechanical Ventilation or ECMO



. at Risk

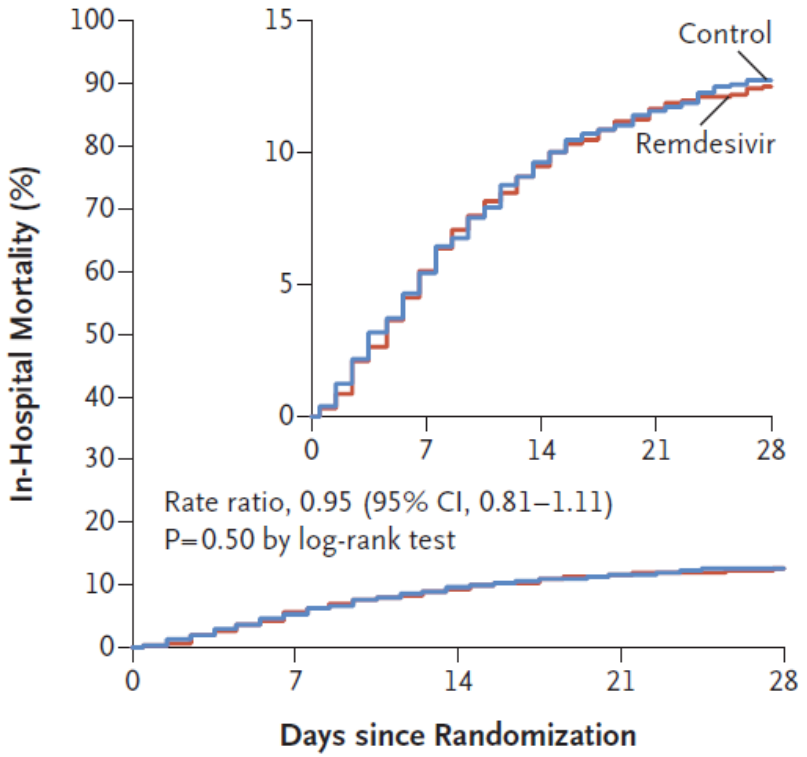
ndesivir	125	124	120	111	91	80	71	55	42	34	1	0
cebo	147	145	141	127	102	91	73	56	41	33	0	0

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

December 2, 2020, at NEJM.org

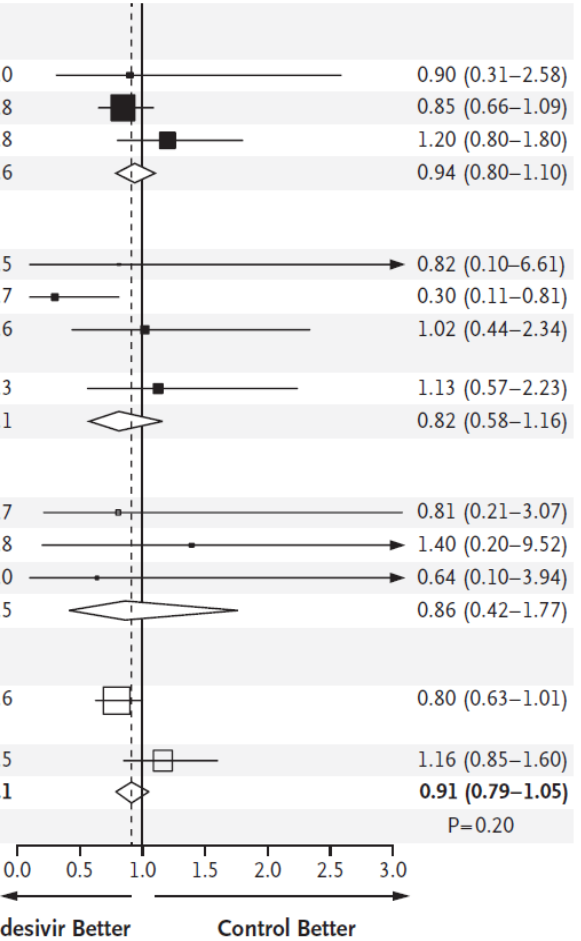
WHO Solidarity Trial Consortium*

A Remdesivir vs. Its Control



Denominator					
Remdesivir	2743	2159	2029	1918	1838
Control	2708	2138	2004	1908	1833
No. Who Died					
Remdesivir	129	90	48	18	16
Control	126	93	43	27	14

Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group: Value	Observed–Expected No. of Deaths in Remdesivir Group: Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)
Trials with few deaths (and randomization ratio of 2:1)					
Wuhan: low-flow oxygen	11/129 (8.5)	(7/68)×2 (10.3)	−0.8	3.7	0.81 (0.21–3.07)
Wuhan: high-flow oxygen or ventilation	11/29 (37.9)	(3/10)×2 (30.0)	0.6	1.8	1.40 (0.20–9.52)
International: no supplemental oxygen	5/384 (1.3)	(4/200)×2 (2.0)	−0.9	2.0	0.64 (0.10–3.94)
Stratified total: 2:1 trials	27/542 (5.0)	(14/278)×2 (5.0)	−1.1	7.5	0.86 (0.42–1.77)
Risk groups (calculated by summation of relevant strata)					
Lower risk: strata with no ventilation	231/3309 (7.0)	282/3277 (8.6)	−27.6	121.6	0.80 (0.63–1.01)
Higher risk	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 (0.85–1.60)
Stratified total	**387/3818 (10.1)**	**408/3782 (10.8)**	**−17.5**	**188.1**	**0.91 (0.79–1.05)**
Heterogeneity between trials (Solidarity vs. ACTT-1 vs. 2:1 trials): χ^2_2=0.5					P=0.20



World Health Organization

7. RECOMMENDATIONS FOR THERAPEUTICS

7.1 Remdesivir

Hospitalized patients with COVID-19, regardless of disease severity
Conditional recommendation
We suggest against administering remdesivir in addition to standard care.

Evidence to decision	
Benefits and harms	Possibly no benefit, or little difference, compared with usual care alone

"However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes".

Guidelines	DISEASE SEVERITY	TREATMENT
IDSA	Mechanical ventilation or ECMO	REMD 10 days
	On supplemental oxygen (noninvasive ventilation)	REMD 5 days
	NOT supplemental oxygen	NOT REMD
NIH	High-flow device, noninvasive ventilation, mechanical ventilation or ECMO	Cannot make a recommendation either for or against starting REMD
	On supplemental oxygen	REMD 5 days
	NOT supplemental oxygen	NOT REMD
WHO	Regardless of disease severity	NOT REMD
NHS	High-flow device, noninvasive ventilation, mechanical ventilation or ECMO	REMD 10 days
	On supplemental oxygen	REMD 5 days
	NOT supplemental oxygen	NOT REMD
AIFA	High-flow device, noninvasive ventilation, mechanical ventilation or ECMO	NOT REMD
	On supplemental oxygen	REMD 5 days
	NOT supplemental oxygen	NOT REMD

Prevalence and Risk Factors of Thromboembolism among Patients With Coronavirus Disease-19: A Systematic Review and Meta-Analysis

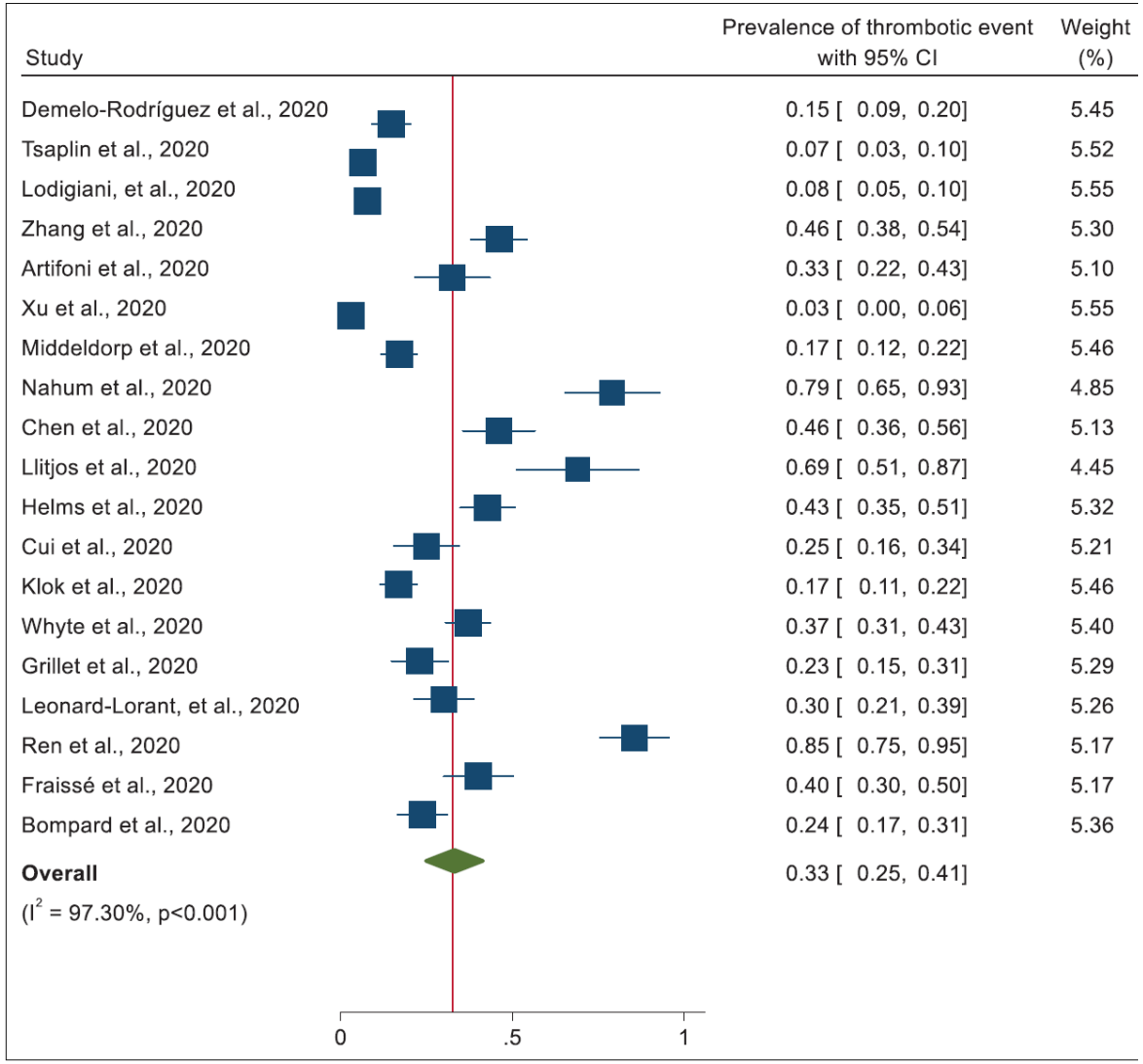


Figure 2. Forest plot illustrating the pooled analysis of 19 studies reporting thrombotic events in patients with COVID-19.

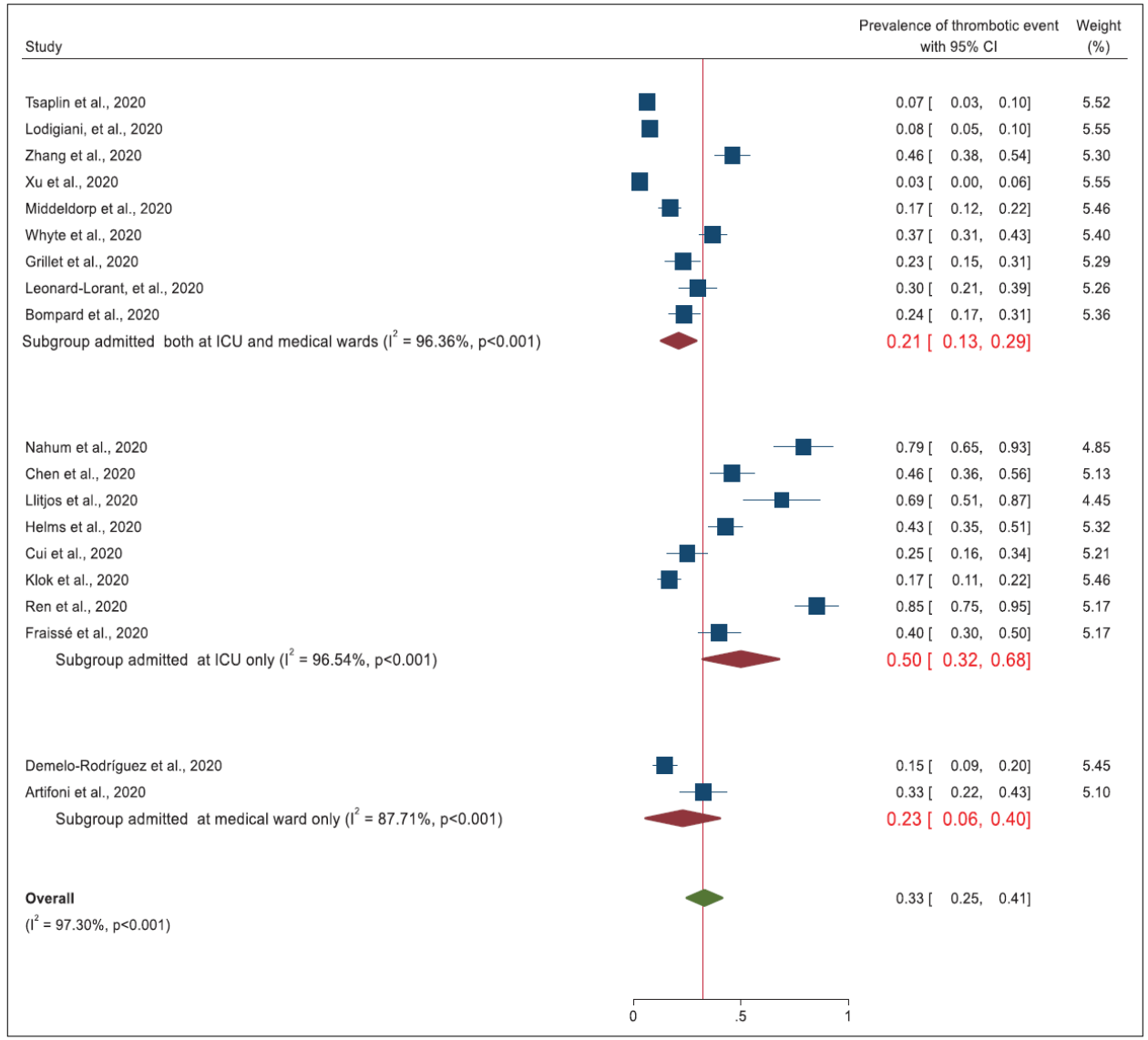


Figure 3. Subgroup analysis of thrombotic event by patient characteristics.

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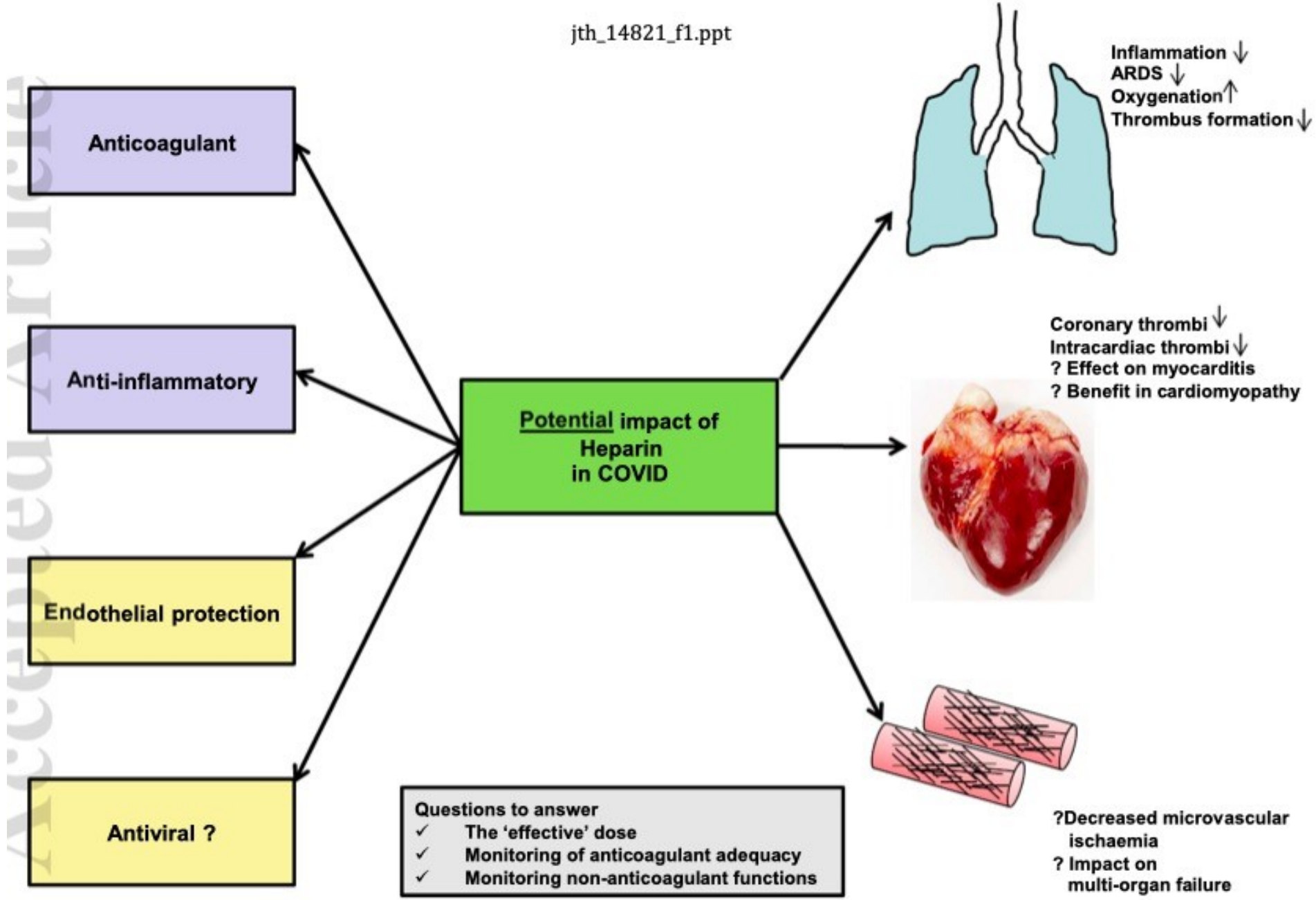
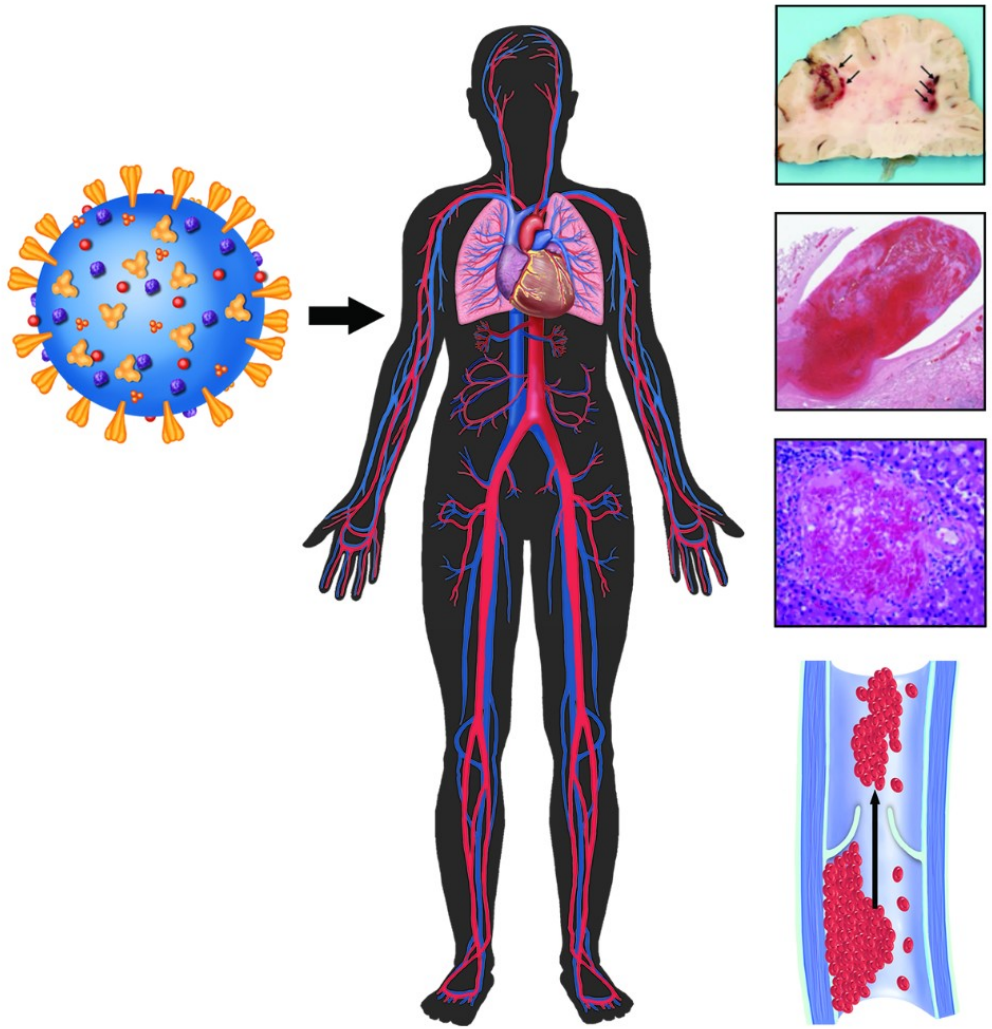
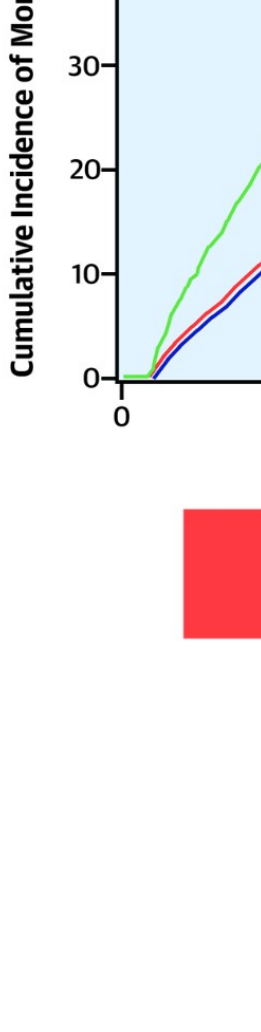


Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study

Thrombosis in COVID-19





Anticoagulation Associated With Better Outcomes

⬇ Clinical Trial ⬇

Therapeutic vs. Prophylactic LMWH vs. NOAC?

Nadkerni, data from 4,389 pts at Mount Sinai NY JACC 9.2020

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

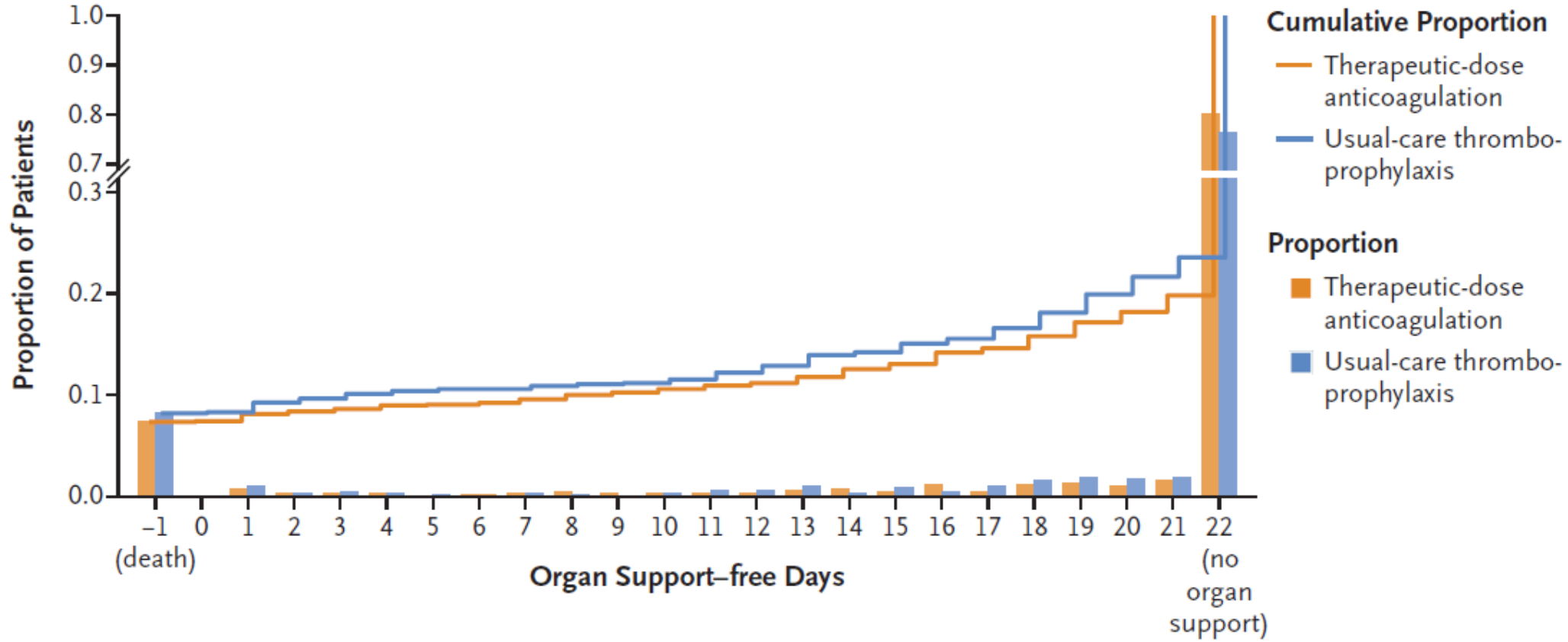
Table 3. Secondary Outcomes among All Patients with Moderate Disease.*

Outcome	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Effect of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Survival until hospital discharge	1085/1171 (92.7)	962/1048 (91.8)	1.3 (–1.1 to 3.2)	1.21 (0.87 to 1.68)§	87.1¶
Survival without organ support at 28 days‖	932/1175 (79.3)	789/1046 (75.4)	4.5 (0.9 to 7.7)	1.30 (1.05 to 1.61)	99.1¶
Progression to intubation or death**	129/1181 (10.9)	127/1050 (12.1)	–1.9 (–4.1 to 0.7)	0.82 (0.63 to 1.07)	92.2¶
Major thrombotic event or death	94/1180 (8.0)	104/1046 (9.9)	–2.6 (–4.4 to –0.2)	0.72 (0.53 to 0.98)	98.0¶
Major thrombotic event	13/1180 (1.1)	22/1046 (2.1)			
Death in hospital	86/1180 (7.3)	86/1046 (8.2)			
Major bleeding	22/1180 (1.9)	9/1047 (0.9)	0.7 (–0.1 to 2.3)	1.80 (0.90 to 3.74)	95.5††

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

A



Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

Table 2. Primary and Secondary Outcomes.

Outcome	Therapeutic-Dose Anticoagulation (N=536)	Usual-Care Thromboprophylaxis (N=567)	Adjusted Difference in Risk (95% Credible Interval)	Adjusted Odds Ratio (95% Credible Interval)*	Probability of Superiority	Probability of Futility	Probability of Inferiority
	median no. (IQR)		*percentage points*		%	%	%
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)	—	0.83 (0.67 to 1.03)	5.0	99.9	95.0
	no. of patients/total no. (%)						
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)	–4.1 (–10.7 to 2.4)	0.84 (0.64 to 1.11)	10.8	99.6	89.2
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)	1.0 (–5.6 to 7.4)	1.04 (0.79 to 1.35)	40.3	—	59.7
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)	1.5 (–4.9 to 8.0)	1.06 (0.81 to 1.38)	33.4	—	66.6
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Major bleeding§	20/529 (3.8)	13/562 (2.3)	1.1 (–0.6 to 4.4)	1.48 (0.75 to 3.04)	12.8	—	87.2

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

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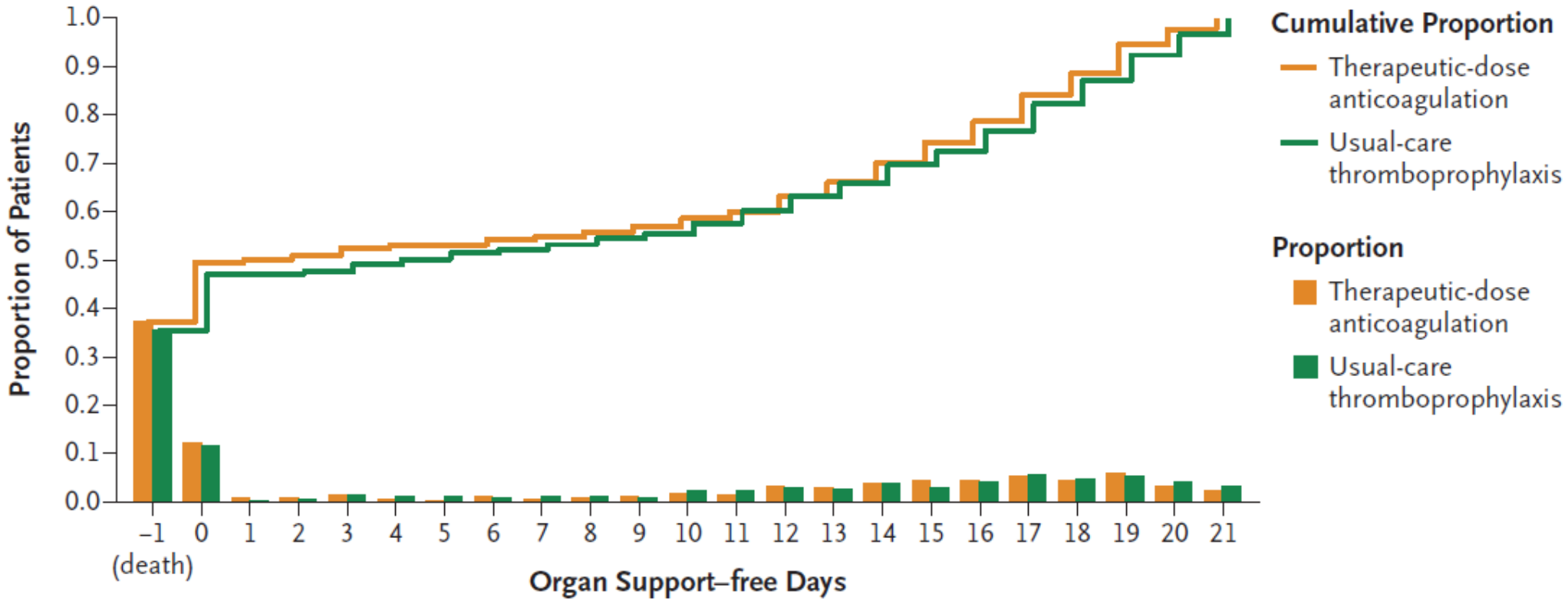


JAMA Internal Medicine | Original Investigation

Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19

The HEP-COVID Randomized Clinical Trial

Jama Intern Med 08 October 2021

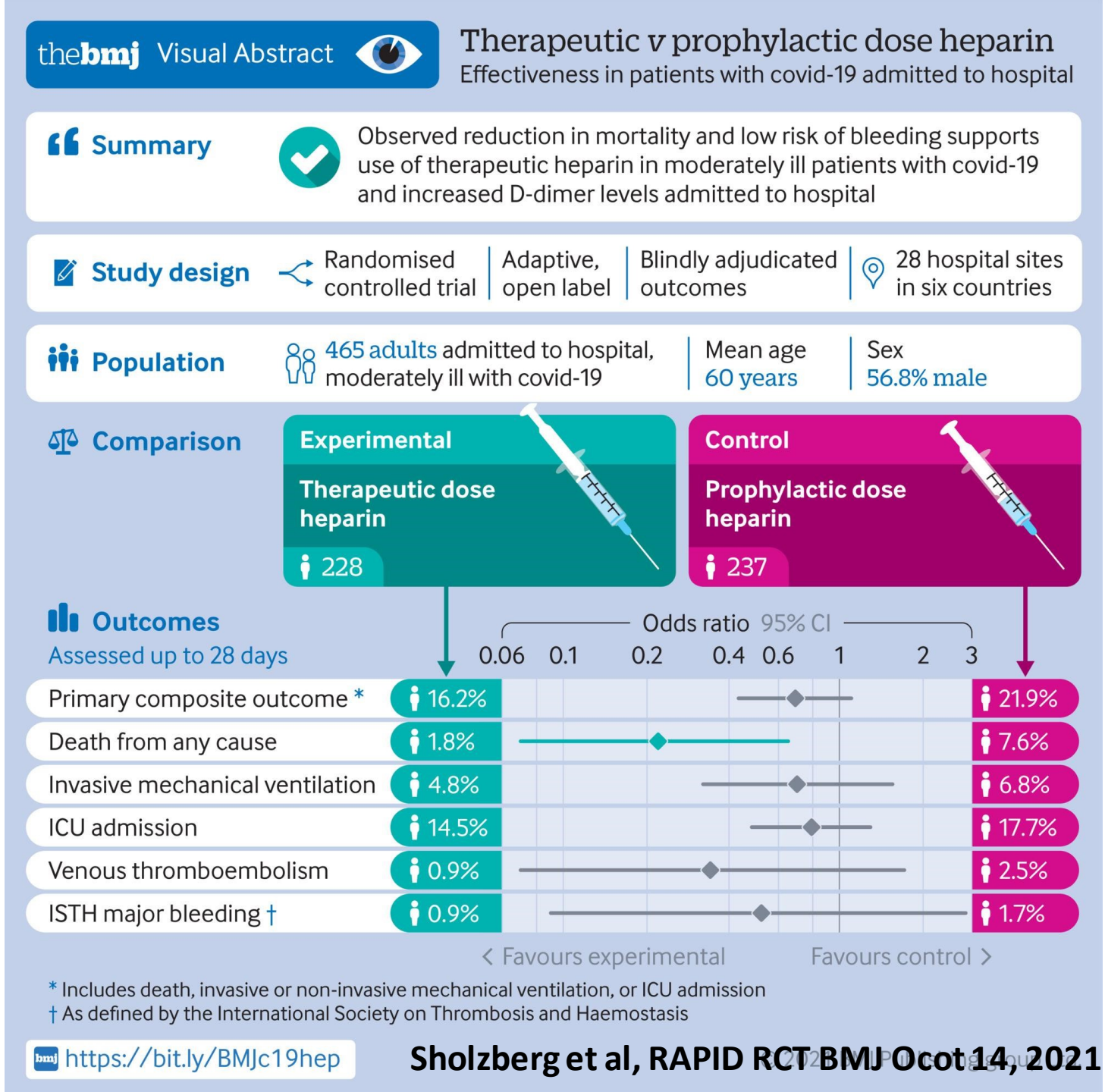
Table 2. Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Primary efficacy outcome				
VTE, ATE, or death	37/129 (28.7)	52/124 (41.9)	0.68 (0.49-0.96)	.03
Non-ICU stratum	14/84 (16.7)	31/86 (36.1)	0.46 (0.27-0.81)	.004
ICU stratum	23/45 (51.1)	21/38 (55.3)	0.92 (0.62-1.39)	.71
VTE + ATE	14/129 (10.9)	36/124 (29.0)	0.37 (0.21-0.66)	<.001
Death	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	.28
Secondary efficacy outcomes				
Primary efficacy outcome at day 14	30/129 (23.3)	45/124 (36.3)	0.64 (0.43-0.95)	.02
Progression to ARDS	11/127 (8.7)	6/121 (5.0)	1.75 (0.67-4.58)	.25
Rehospitalization	1/129 (0.8)	3/124 (2.4)	0.32 (0.03-3.04)	.36
Intubation	17/122 (13.9)	21/121 (17.4)	0.80 (0.45-1.45)	.46
ECMO	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.20)	>.99
Nonfatal cardiac arrest	0	2/124 (1.6)	0.19 (0.01-3.97)	.24
Acute kidney injury[b]	17/129 (13.2)	12/124 (9.7)	1.36 (0.68-2.73)	.38
New-onset atrial fibrillation	4/129 (3.1)	5/124 (4.0)	0.77 (0.21-2.80)	.75
Principal safety outcome				
Major bleeding	6/129 (4.7)	2/124 (1.6)	2.88 (0.59-14.02)	.28
Non-ICU stratum	2/84 (2.4)	2/86 (2.3)	1.02 (0.15-7.10)	>.99
ICU stratum	4/45 (8.9)	0	7.62 (0.42-137.03)	.12

Abbreviations: ARDS, acute respiratory distress syndrome; ATE, arterial thromboembolism; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RR, relative risk; VTE, venous thromboembolism.

[a] Modified intention-to-treat population (2-sided *P* value for superiority).

[b] Acute kidney injury defined as (1) increase in serum creatinine by 0.3 mg/dL or greater within 48 hours, (2) increase in serum creatinine by a factor of 1.5 times baseline or greater, or (3) decrease in urine volume to less than 0.5 mg/kg/h for 6 hours per Kidney Disease: Improving Global Outcomes standard definition.



Sholzberg et al, RAPID RCT BMJ Ocot 14, 2021

WHAT IS ALREADY KNOWN ON THIS TOPIC

RCT suggest that therapeutic heparin is beneficial in moderately ill COVID inpatients, but of no benefit and potential harm when provided to critically ill patients

Given the disparate findings in these two patient populations, there is hesitancy to adopt therapeutic heparin as SoC

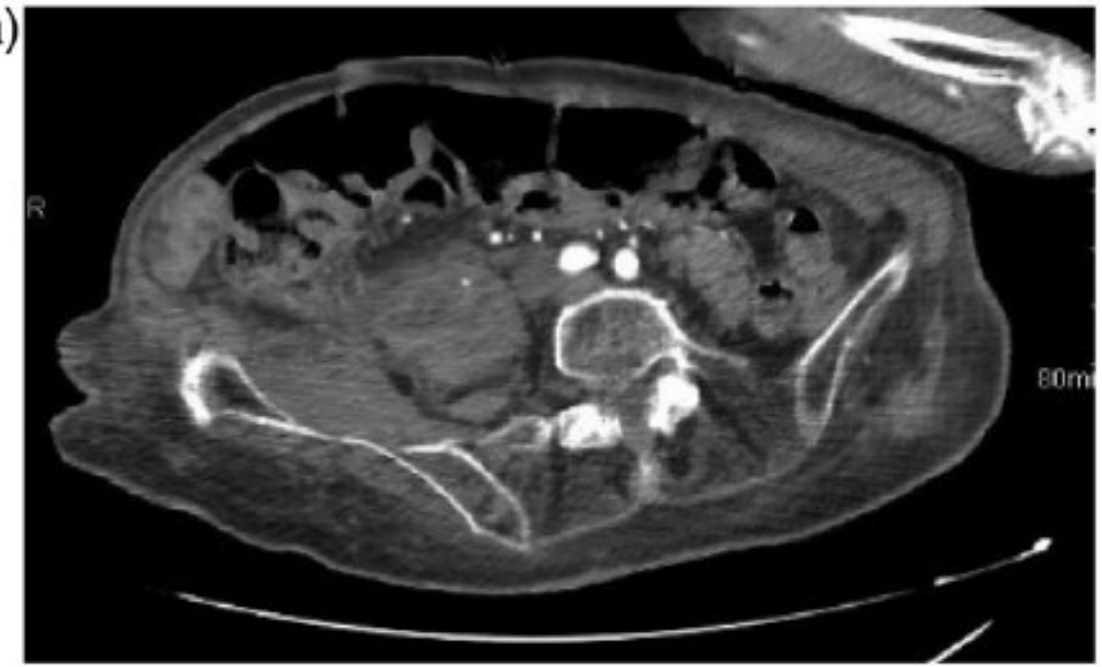
WHAT THIS STUDY ADDS

Use of therapeutic heparin in moderately ill patients and increased D-dimer levels was not associated with a significant reduction in the primary composite outcome of death, NiV-MV, or ICU admission

Although the difference was not significant, a noticeable reduction in mortality and low risk of bleeding was observed with therapeutic heparin

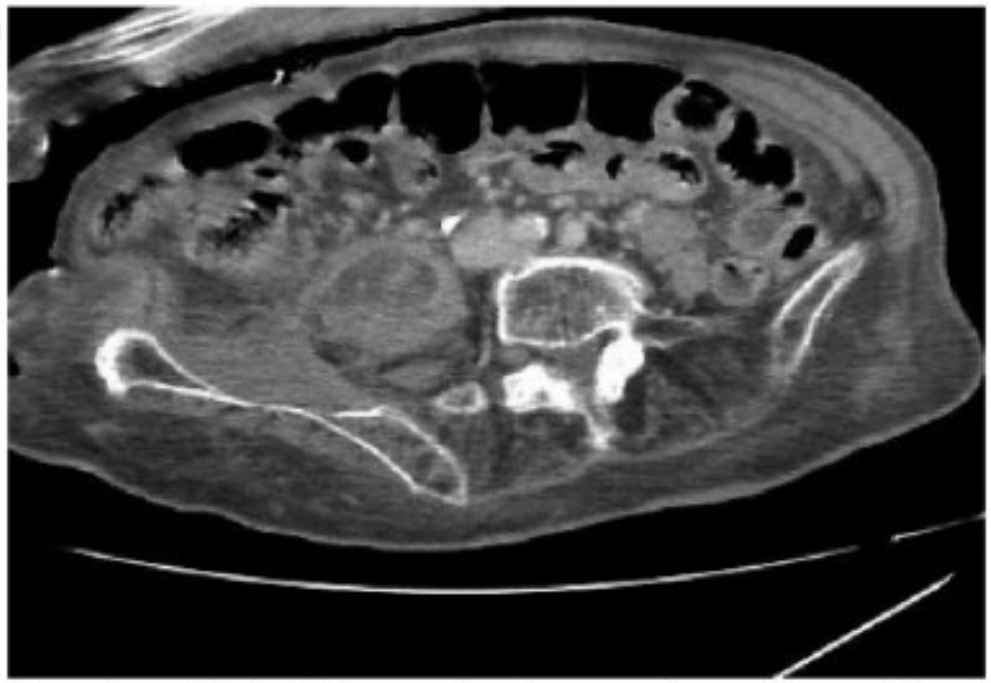
Spontaneous ilio-psoas haematomas (IPHs): a warning for COVID-19 inpatients

(a)



Angio-CT: Iliopsoas hematoma with small arterial intralesional blush

(b)



Angio-CT: delayed phase shows pooling (increased size of blush) of iv contrast media in same patient.

Vergori Ann Med 01.2021

Prophylaxis vs Therapeutic dosage in COVID-19

- In non critical not VTE, full therapeutic doses if
  1. D-dimer > 2 or 4 UNV OR
  2. SIC Score >4 (plt, INR, SOFA score)

- In critical patients not VTE prophylaxys only

Steroids for Covid 19

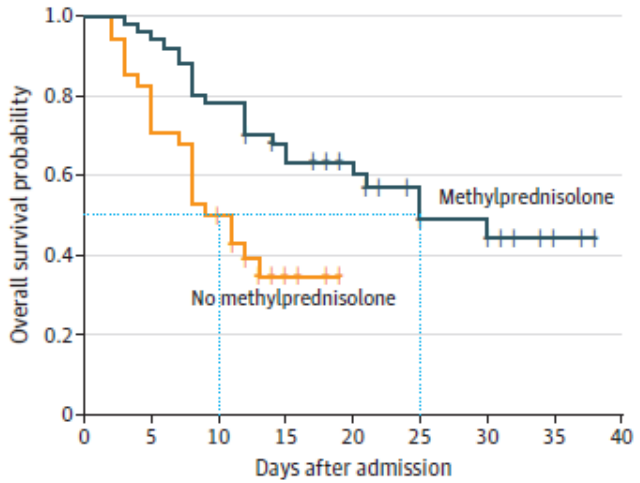
JAMA Internal Medicine | Original Investigation

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

Table 1. Demographic Characteristics of Patients With Coronavirus Disease 2019 Pneumonia (continued)

Study population	No. (%)
Clinical outcomes	
ARDS	84 (41.8)
ICU admission	53 (26.4)
Death	44 (21.9)

Figure. Survival Curve in Patients With Acute Respiratory Distress Syndrome Who Did and Did Not Receive Methylprednisolone Treatment



Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20-0.72; *P* = .003).

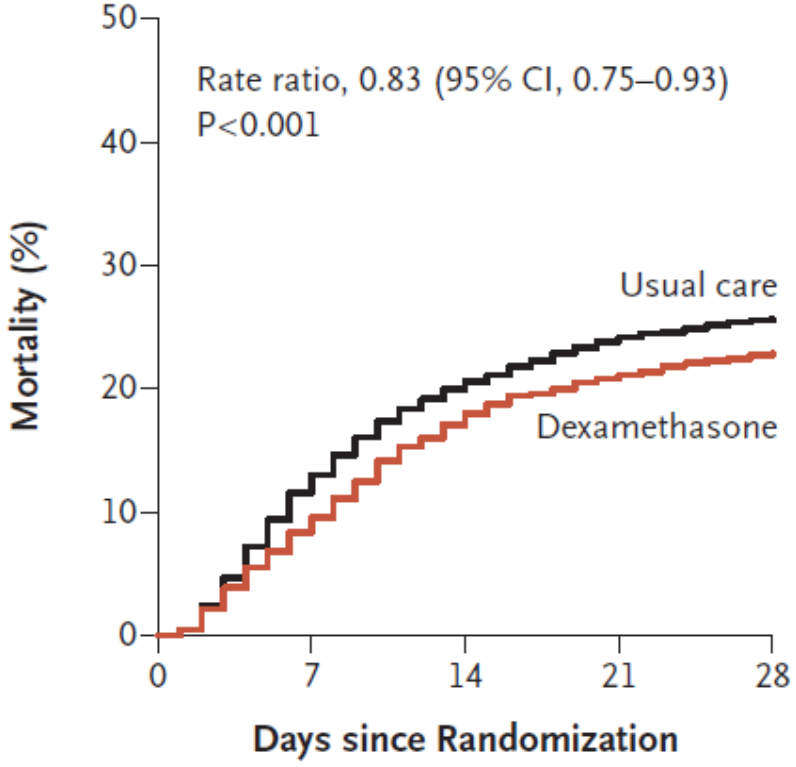
Clinical characteristics	All patients: Without ARDS, No. (%) (n = 117)	With ARDS, No. (%) (n = 84)	Difference (95% CI)[a]	*P* value[b]	Patients with ARDS: Alive, No. (%) (n = 40)	Died, No. (%) (n = 44)	Difference (95% CI)[a]	*P* value[b]
Treatment in hospital								
Oxygen therapy[c]								
Nasal cannula	81 (69.2)	17 (20.2)	−49.0 (−62.0 to −36.0)	<.001	17 (42.5)	0	−42.5 (−60.2 to −24.8)	<.001
NMV	0	61 (72.6)	72.6 (62.1 to 83.2)		23 (57.5)	38 (86.4)	28.9 (8.1 to 49.6)	
IMV	0	5 (6.0)	6.0 (−0.1 to 12.0)		0	5 (11.4)	11.4 (−0.4 to 23.1)	
IMV with ECMO	0	1 (1.2)	1.2 (−2.2 to 4.5)		0	1 (2.3)	2.3 (−4.4 to 8.9)	
Methylprednisolone	12 (10.3)	50 (59.5)	49.3 (36.4 to 62.1)	<.001	27 (67.5)	23 (52.3)	−15.2 (−38.3 to 7.9)	.16
Antibiotic therapy	113 (96.6)	83 (98.8)	2.2 (−2.8 to 7.3)	.59	40 (100.0)	43 (97.7)	−2.3 (−8.9 to 4.4)	>.99
Antiviral therapy	106 (90.6)	64 (76.2)	−14.4 (−26.0 to −2.9)	.005	39 (97.5)	25 (56.8)	−40.7 (−58.5 to −22.9)	<.001

Wu et al JAMA 13.03.2020

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

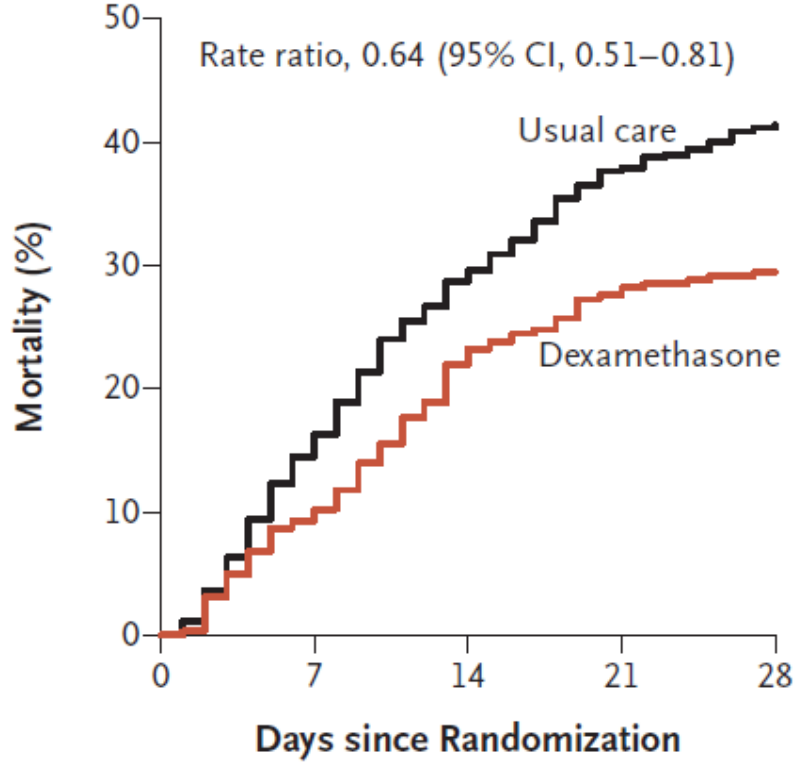
The RECOVERY Collaborative Group*

A **All Participants (N=6425)**



No. at Risk					
Usual care	4321	3754	3427	3271	3205
Dexamethasone	2104	1903	1725	1659	1621

B **Invasive Mechanical Ventilation (N=1007)**

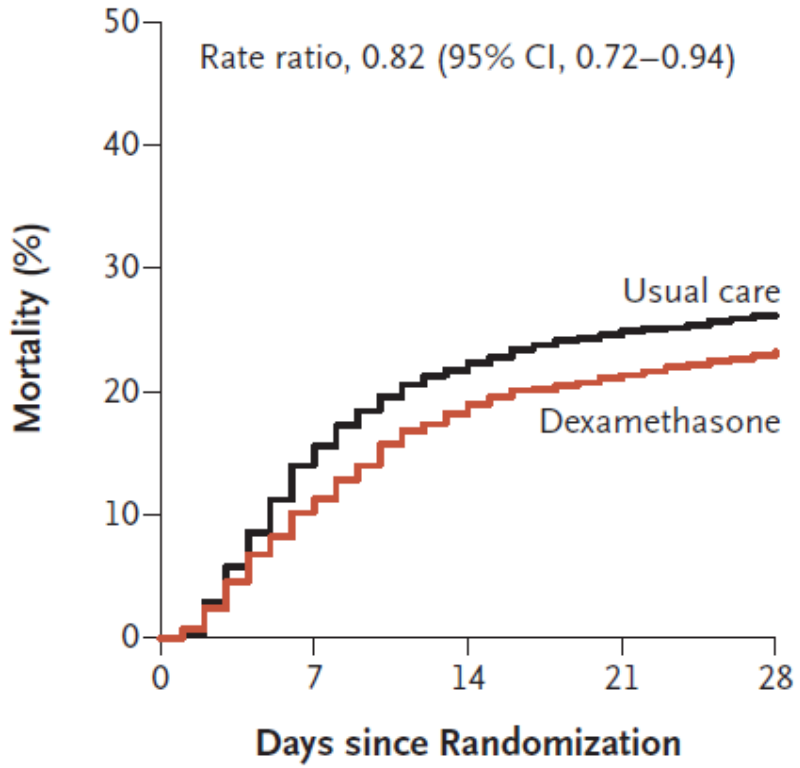


No. at Risk					
Usual care	683	572	481	424	400
Dexamethasone	324	290	248	232	228

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

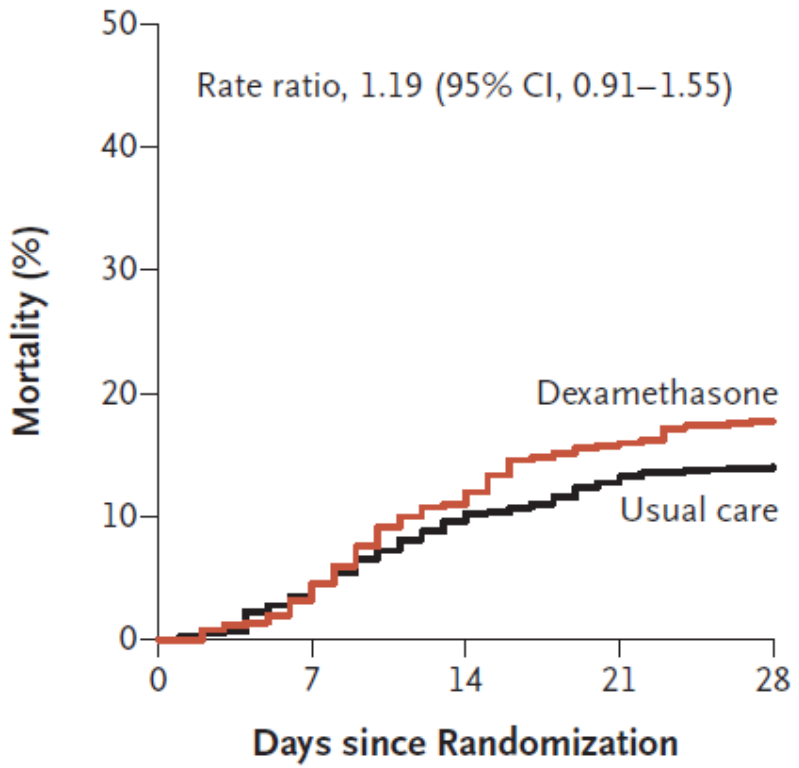
The RECOVERY Collaborative Group*

C Oxygen Only (N=3883)



No. at Risk					
Usual care	2604	2195	2018	1950	1916
Dexamethasone	1279	1135	1036	1006	981

D No Oxygen Received (N=1535)



No. at Risk					
Usual care	1034	987	928	897	889
Dexamethasone	501	478	441	421	412

Corticosteroids for COVID-19

LIVING GUIDANCE
2 SEPTEMBER 2020

World Health Organization

Recommendations: The panel made two recommendations: a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.

Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia
The COVID STEROID 2 Randomized Trial

Table 2. Primary and Secondary Outcomes

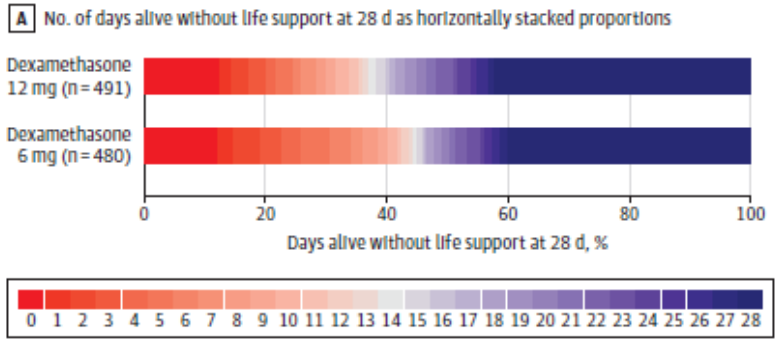
Outcome[a]	12 mg of dexamethasone (n = 491)	6 mg of dexamethasone (n = 480)	Adjusted mean difference (95% CI)[b]	Adjusted relative risk (99% CI)[b]	*P* value
Primary outcome					
No. of days alive without life support at 28 d, median (IQR)[c]	22.0 (6.0 to 28.0)	20.5 (4.0 to 28.0)	1.3 (0 to 2.6)		.07[d]
Single components of the composite primary outcome[b]					
No. of days alive without invasive mechanical ventilation at 28 d, median (IQR)	23.0 (7.0 to 28.0)	22.0 (5.0 to 28.0)			
No. of days alive without circulatory support at 28 d, median (IQR)	26.0 (13.0 to 28.0)	25.0 (9.0 to 28.0)			
No. of days alive without kidney replacement therapy at 28 d, median (IQR)	28.0 (18.0 to 28.0)	28.0 (13.8 to 28.0)			
Secondary analysis of the primary outcome					
No. of days alive without life support at 28 d[e]			1.2 (−0.1 to 2.4)		.06
Unadjusted analysis			1.3 (−0.1 to 2.7)		.07
Secondary outcomes					
No. of days alive without life support at 90 d, median (IQR)	(n = 489) 84.0 (9.3 to 90.0)	(n = 478) 80.0 (6.0 to 90.0)	4.4 (−1.6 to 10.4)		.15[f]
No. of days alive out of the hospital at 90 d, median (IQR)	(n = 490) 61.5 (0 to 78.0)	(n = 478) 48.0 (0 to 76.0)	4.1 (−1.3 to 9.5)		.09
Mortality					
At 28 d, No. (%)	133 (27.1)	155 (32.3)	−4.5 (−11.5 to 2.3)[g]	0.86 (0.68 to 1.08)	.10[h]
At 90 d, No./total (%)	157/490 (32.0)	180/478 (37.7)	−4.9 (−12.1 to 2.4)[g]	0.87 (0.70 to 1.07)	.09[i]
≥1 serious adverse reactions, No./total (%)[j]	56/497 (11.3)	65/485 (13.4)	−2.2 (−7.3 to 3.1)[g]	0.83 (0.54 to 1.29)	.27[k]
New episodes of septic shock, No. (%)	42 (8.5)	50 (10.3)			
Invasive fungal infection, No. (%)	15 (3.0)	21 (4.3)			
Clinically important gastrointestinal bleeding, No. (%)	9 (1.8)	5 (1.0)			
Anaphylactic reaction to dexamethasone, No.	0	0			

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia
The COVID STEROID 2 Randomized Trial

JAMA. 2021;326(18):1807-1817. doi:10.1001/jama.2021.18295 online October 21, 2021

Figure 2. Distributions of the Primary Outcome and Time to Death Curves to Day 90



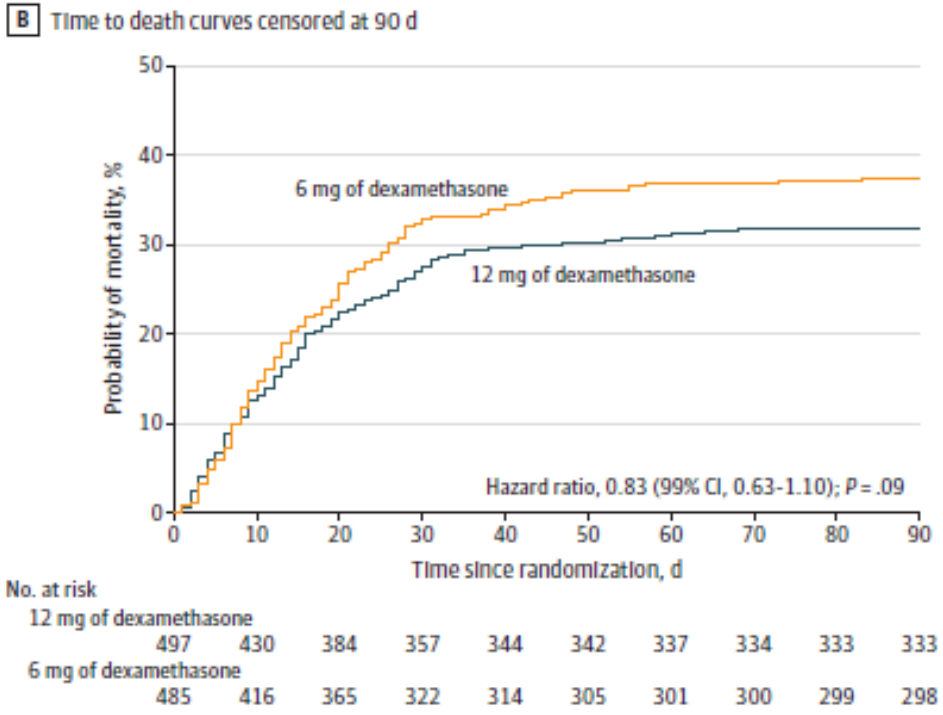
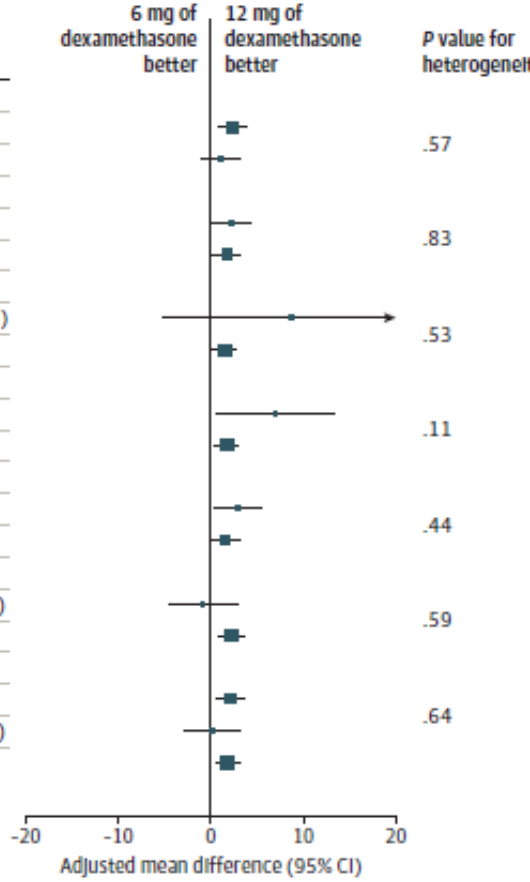


Figure 3. Median Days Alive Without Life Support and the Adjusted Mean Differences in the 7 Predefined Subgroups

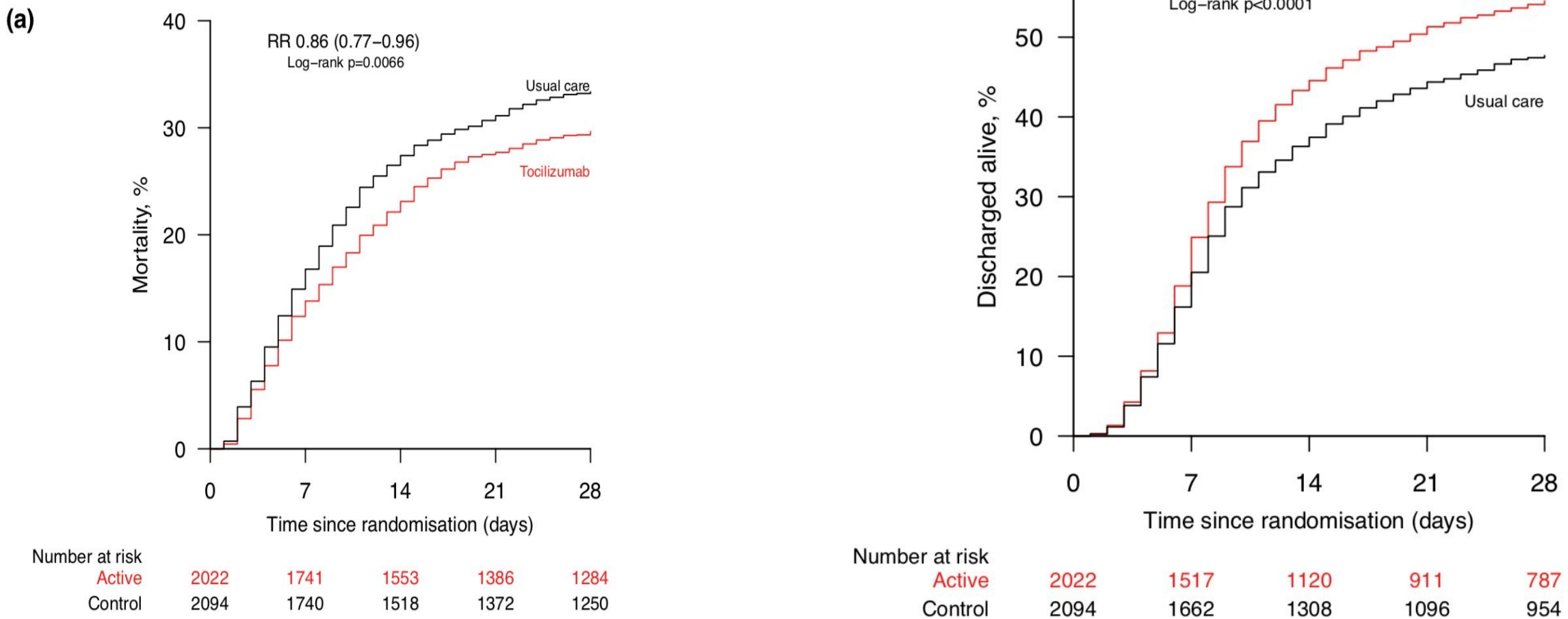
Subgroup	Days alive without life support by dexamethasone dose, median (IQR) 12 mg	6 mg	Adjusted mean difference (95% CI)[a]
Enrollment geographic region			
Europe	22.0 (7.0 to 28.0) (n = 298)	20.0 (4.0 to 28.0) (n = 315)	1.8 (0.2 to 3.4)
India	28.0 (4.8 to 28.0) (n = 187)	25.0 (5.0 to 28.0) (n = 182)	0.5 (-1.7 to 2.6)
Age, y			
≥70	12.0 (3.0 to 28.0) (n = 167)	8.0 (3.0 to 28.0) (n = 167)	1.6 (-0.7 to 4.0)
<70	26.0 (9.0 to 28.0) (n = 318)	25.0 (5.0 to 28.0) (n = 330)	1.2 (-0.4 to 2.8)
Chronic use of systemic glucocorticoids at baseline			
Yes	22.0 (6.0 to 28.0) (n = 16)	5.0 (0.8 to 8.0) (n = 13)	8.4 (-5.9 to 22.7)
No	22.0 (6.0 to 28.0) (n = 469)	21.5 (4.0 to 28.0) (n = 484)	1.0 (-0.3 to 2.3)
Limitations in care[b]			
Yes	9.0 (3.3 to 28.0) (n = 25)	6.0 (3.0 to 28.0) (n = 30)	6.6 (0.1 to 13.1)
No	22.0 (7.0 to 28.0) (n = 460)	22.0 (5.0 to 28.0) (n = 467)	1.2 (-0.1 to 2.5)
Required invasive mechanical ventilation			
Yes	9.0 (0 to 21.0) (n = 99)	2.5 (0 to 15.0) (n = 107)	2.4 (-0.2 to 5.0)
No	28.0 (9.0 to 28.0) (n = 386)	28.0 (6.0 to 28.0) (n = 390)	1.1 (-0.5 to 2.6)
Prior use of IL-6 receptor antagonists			
Yes	27.0 (9.5 to 28.0) (n = 47)	28.0 (24.0 to 28.0) (n = 52)	-1.4 (-5.3 to 2.4)
No	22.0 (5.0 to 28.0) (n = 438)	18.0 (4.0 to 28.0) (n = 445)	1.7 (0.3 to 3.1)
Prior use of dexamethasone before randomization, d			
0-2	22.0 (4.5 to 28.0) (n = 355)	23.0 (5.0 to 28.0) (n = 384)	1.6 (0.1 to 3.1)
3-4	22.0 (6.8 to 28.0) (n = 130)	19.0 (4.0 to 28.0) (n = 113)	-0.4 (-3.4 to 2.7)
All patients	22.0 (6.0 to 28.0) (n = 491)	20.5 (4.0 to 28.0) (n = 480)	1.3 (0 to 2.6)



Immunodulants for Covid 19

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

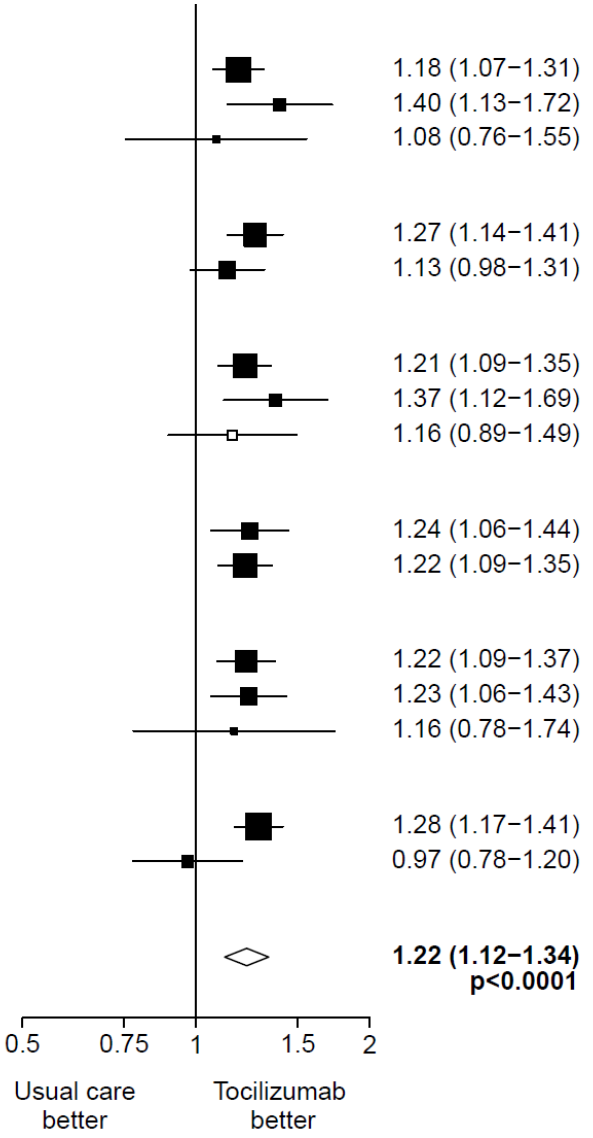
Figure 2: Effect of allocation to tocilizumab on (a) 28–day mortality and (b) discharge from hospital alive within 28 days of randomisation



Lancet May 2021

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Age, years (χ^2_1=0.2; p=0.65)			
<70	832/1332 (62%)	766/1354 (57%)	1.18 (1.07–1.31)
≥70 <80	204/477 (43%)	159/480 (33%)	1.40 (1.13–1.72)
≥80	57/213 (27%)	65/260 (25%)	1.08 (0.76–1.55)
Sex (χ^2_1=1.4; p=0.23)			
Men	706/1335 (53%)	644/1437 (45%)	1.27 (1.14–1.41)
Women	387/687 (56%)	346/657 (53%)	1.13 (0.98–1.31)
Ethnicity (χ^2_1=1.1; p=0.30)			
White	760/1356 (56%)	700/1426 (49%)	1.21 (1.09–1.35)
Black, Asian, or Minority Ethnic	201/341 (59%)	179/357 (50%)	1.37 (1.12–1.69)
Unknown	132/325 (41%)	111/311 (36%)	1.16 (0.89–1.49)
Days since symptom onset (χ^2_1=0.0; p=0.84)			
≤7	365/668 (55%)	314/660 (48%)	1.24 (1.06–1.44)
>7	728/1354 (54%)	676/1433 (47%)	1.22 (1.09–1.35)
Respiratory support at randomization (χ^2_1=0.0; p=0.94)			
No ventilator support*	668/935 (71%)	602/933 (65%)	1.22 (1.09–1.37)
Non–invasive ventilation†	376/819 (46%)	341/867 (39%)	1.23 (1.06–1.43)
Invasive mechanical ventilation‡	49/268 (18%)	47/294 (16%)	1.16 (0.78–1.74)
Use of corticosteroids$ (χ^2_1=5.4; p=0.02)			
Yes	930/1664 (56%)	817/1721 (47%)	1.28 (1.17–1.41)
No	162/357 (45%)	170/367 (46%)	0.97 (0.78–1.20)
Unknown	1/1 (100%)	3/6 (50%)	
All participants	**1093/2022 (54%)**	**990/2094 (47%)**	**1.22 (1.12–1.34) p<0.0001**



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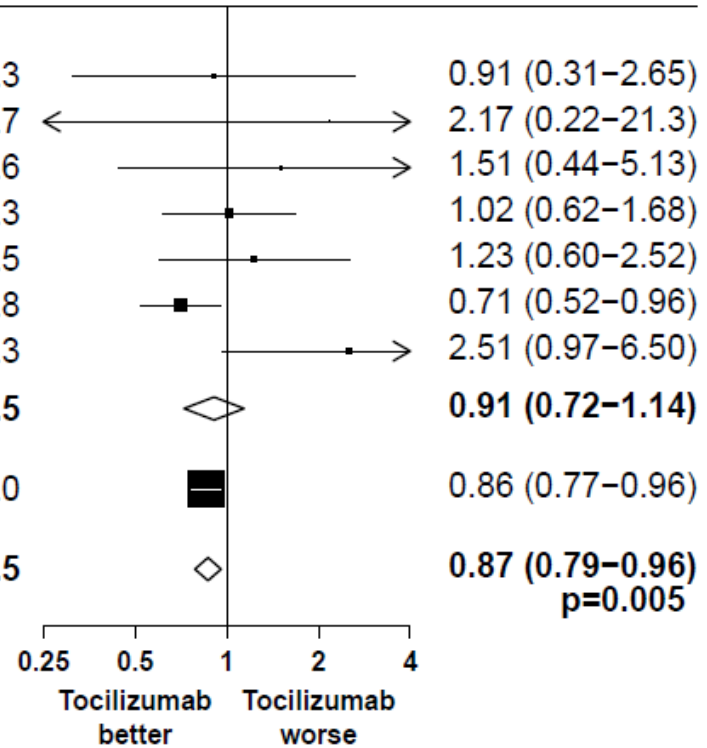
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

	Deaths / Patients randomised (%)		Observed−Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O−E)*	Var(O−E)	
COR−IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22−21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	98/353 (27.8)	142/402 (35.3)	−14.2	40.8	0.71 (0.52−0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97−6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	−48.2	316.0	0.86 (0.77−0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**−55.4**	**390.5**	**0.87 (0.79−0.96) p=0.005**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



* Log−rank O−E for RECOVERY, O−E from 2x2 tables for the other trials. RR is calculated by taking ln RR to be (O−E)/V with Normal variance 1/V. Subtotals or totals of (O−E) and of V yield inverse−variance−weighted averages of the ln RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

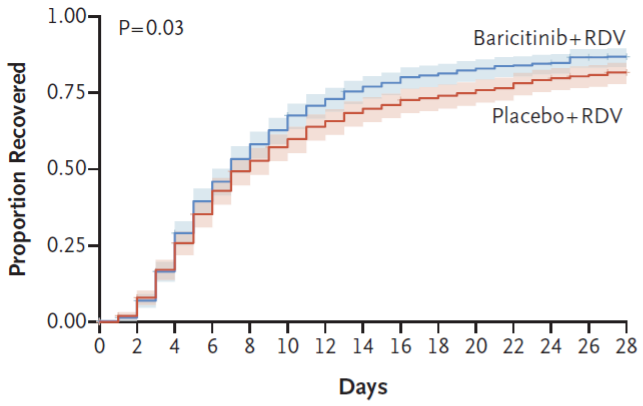
Lancet May 2021

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

NEJM Dec 11, 2020

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan,

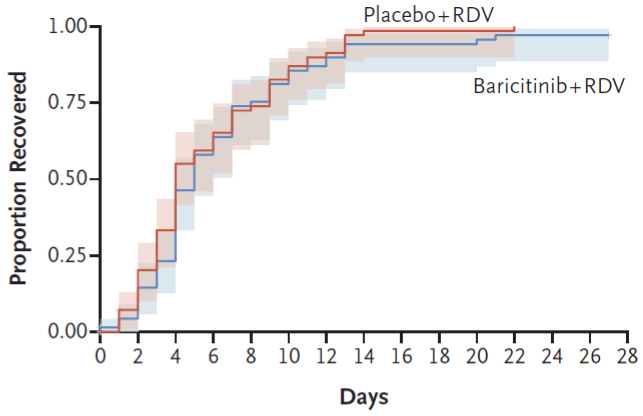
A Overall



No. at Risk

Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44

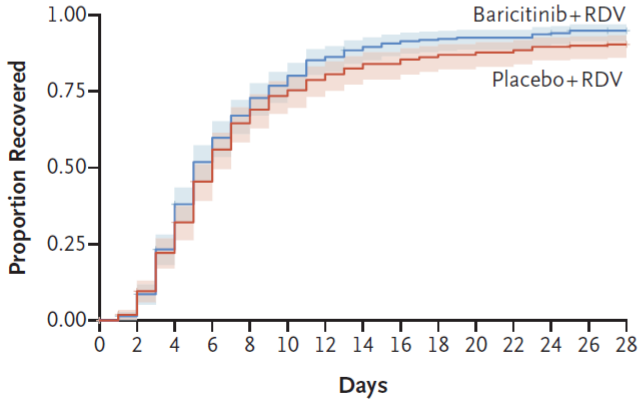
B Baseline Ordinal Score of 4



No. at Risk

Baricitinib+RDV	70	66	53	29	18	13	9	4	4	4	4	2	2	2	0
Placebo+RDV	72	64	46	28	19	12	7	2	1	1	1	1	0	0	0

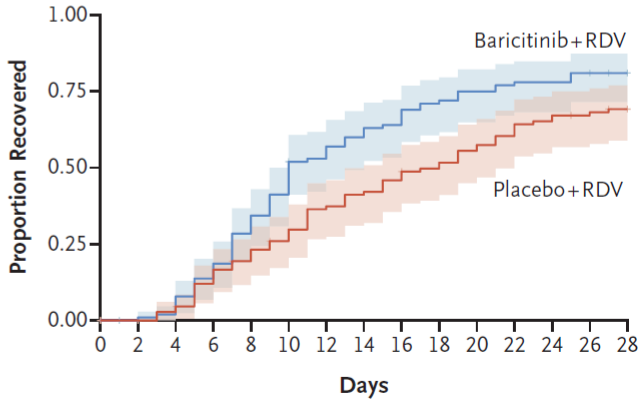
C Baseline Ordinal Score of 5



No. at Risk

Baricitinib+RDV	288	276	213	133	91	64	41	31	25	22	20	20	17	12	5
Placebo+RDV	276	267	211	146	95	71	57	47	43	37	35	33	28	26	12

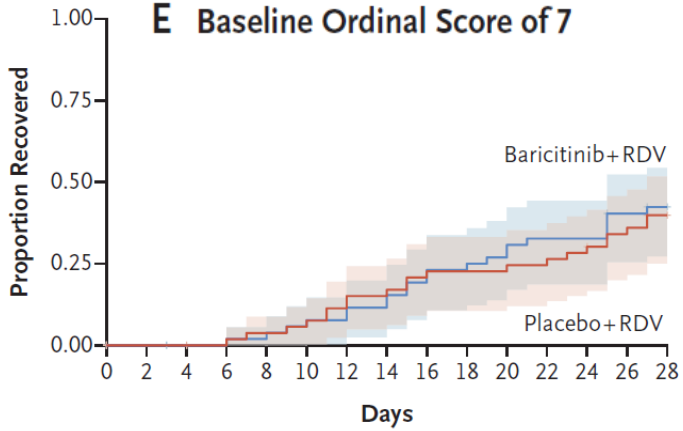
D Baseline Ordinal Score of 6



No. at Risk

Baricitinib+RDV	103	102	100	88	73	60	47	40	36	29	25	23	22	19	10
Placebo+RDV	113	110	106	95	86	78	67	62	57	52	46	41	36	32	16

E Baseline Ordinal Score of 7



No. at Risk

Baricitinib+RDV	54	53	52	52	51	49	48	46	42	40	38	35	35	30	15
Placebo+RDV	57	54	54	53	51	50	47	45	42	41	41	40	38	34	16

Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

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Table 2

Outcome	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Baricitinib (N=515)	Placebo (N=518)	Baricitinib (N=70)	Placebo (N=72)	Baricitinib (N=288)	Placebo (N=276)	Baricitinib (N=103)	Placebo (N=113)	Baricitinib (N=54)	Placebo (N=57)
Recovery										
No. of recoveries	433	406	67	69	262	243	82	73	22	21
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)	5 (4–6)	4 (4–6)	5 (5–6)	6 (5–6)	10 (9–13)	18 (13–21)	NE (25–NE)	NE (26–NE)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])		0.88 (0.63–1.23)		1.17 (0.98–1.39)		1.51 (1.10–2.08)		1.08 (0.59–1.97)	
Mortality over first 14 days‡										
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)		NE		0.73 (0.16–3.26)		0.21 (0.02–1.80)		0.69 (0.19–2.44)	
No. of deaths by day 14	8	15	0	0	3	4	1	5	4	6
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)	0 (NE–NE)	0 (NE–NE)	1.1 (0.4–3.4)	1.5 (0.6–3.9)	1.0 (0.1–6.7)	4.6 (2.0–10.8)	7.6 (2.9–19.1)	11.3 (5.3–23.5)
Mortality over entire trial period‡										
Hazard ratio (95% CI)	0.65 (0.39–1.09)		NE		0.40 (0.14–1.14)		0.55 (0.22–1.38)		1.00 (0.45–2.22)	
No. of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)	0 (NE–NE)	0 (NE–NE)	1.9 (0.8–4.4)	4.7 (2.7–8.1)	7.5 (3.6–15.2)	12.9 (7.7–21.3)	23.1 (13.8–37.1)	22.6 (13.5–36.4)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	177 (34.4)	165 (31.9)	33 (47.1)	44 (61.1)	114 (39.6)	101 (36.6)	27 (26.2)	17 (15.0)	3 (5.6)	3 (5.3)
2	177 (34.4)	163 (31.5)	25 (35.7)	20 (27.8)	120 (41.7)	115 (41.7)	30 (29.1)	24 (21.2)	2 (3.7)	4 (7.0)
3	8 (1.6)	3 (0.6)	5 (7.1)	2 (2.8)	2 (0.7)	1 (0.4)	0	0	1 (1.9)	0
4	31 (6.0)	18 (3.5)	7 (10.0)	6 (8.3)	14 (4.9)	7 (2.5)	7 (6.8)	3 (2.7)	3 (5.6)	2 (3.5)
5	43 (8.3)	50 (9.7)	0	0	18 (6.2)	27 (9.8)	15 (14.6)	20 (17.7)	10 (18.5)	3 (5.3)
6	20 (3.9)	19 (3.7)	0	0	9 (3.1)	1 (0.4)	7 (6.8)	16 (14.2)	4 (7.4)	2 (3.5)
7	48 (9.3)	83 (16.0)	0	0	8 (2.8)	19 (6.9)	15 (14.6)	28 (24.8)	25 (46.3)	36 (63.2)
8	11 (2.1)	17 (3.3)	0	0	3 (1.0)	5 (1.8)	2 (1.9)	5 (4.4)	6 (11.1)	7 (12.3)
Odds ratio (95% CI)	1.3 (1.0–1.6)		0.6 (0.3–1.1)		1.2 (0.9–1.6)		2.2 (1.4–3.6)		1.7 (0.8–3.4)	

* Patients in both groups received RDV in addition to either baricitinib or placebo. Neither the P value nor any confidence intervals have not been adjusted for multiple comparisons

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

ABSTRACT

Background: Baricitinib, an oral selective Janus kinase 1 and 2 inhibitor, improved outcomes in a previous randomized controlled trial of hospitalized adults with COVID-19, in combination with remdesivir.

Methods: In this phase 3, global, double-blind, randomized, placebo-controlled trial, 1525 hospitalized adults with COVID-19 receiving standard of care (SOC) were randomly assigned (1:1) to once-daily baricitinib 4-mg (N=764) or placebo (N=761) for up to 14 days. SOC included systemic corticosteroids in ~79% of participants (dexamethasone ~90%). The primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28. A key secondary endpoint was all-cause mortality by day 28.

Results: Overall, 27.8% of participants receiving baricitinib vs 30.5% receiving placebo progressed (primary endpoint, odds ratio 0.85, 95% CI 0.67-1.08; p=0.18). The 28-day all-cause mortality was 8.1% for baricitinib and 13.1% for placebo, corresponding to a 38.2% reduction in mortality (hazard ratio [HR] 0.57, 95% CI 0.41-0.78; nominal p=0.002); 1 additional death was prevented per 20 baricitinib-treated participants. Reduction in mortality was seen for all pre-specified subgroups of baseline severity (most pronounced for participants on high-flow oxygen/non-invasive ventilation at baseline [17.5%, baricitinib vs 29.4%, placebo; HR 0.52, 95% CI 0.33-0.80; nominal p=0.007]). The frequency of adverse events, serious adverse events, serious infections, and venous thromboembolic events was similar between groups.

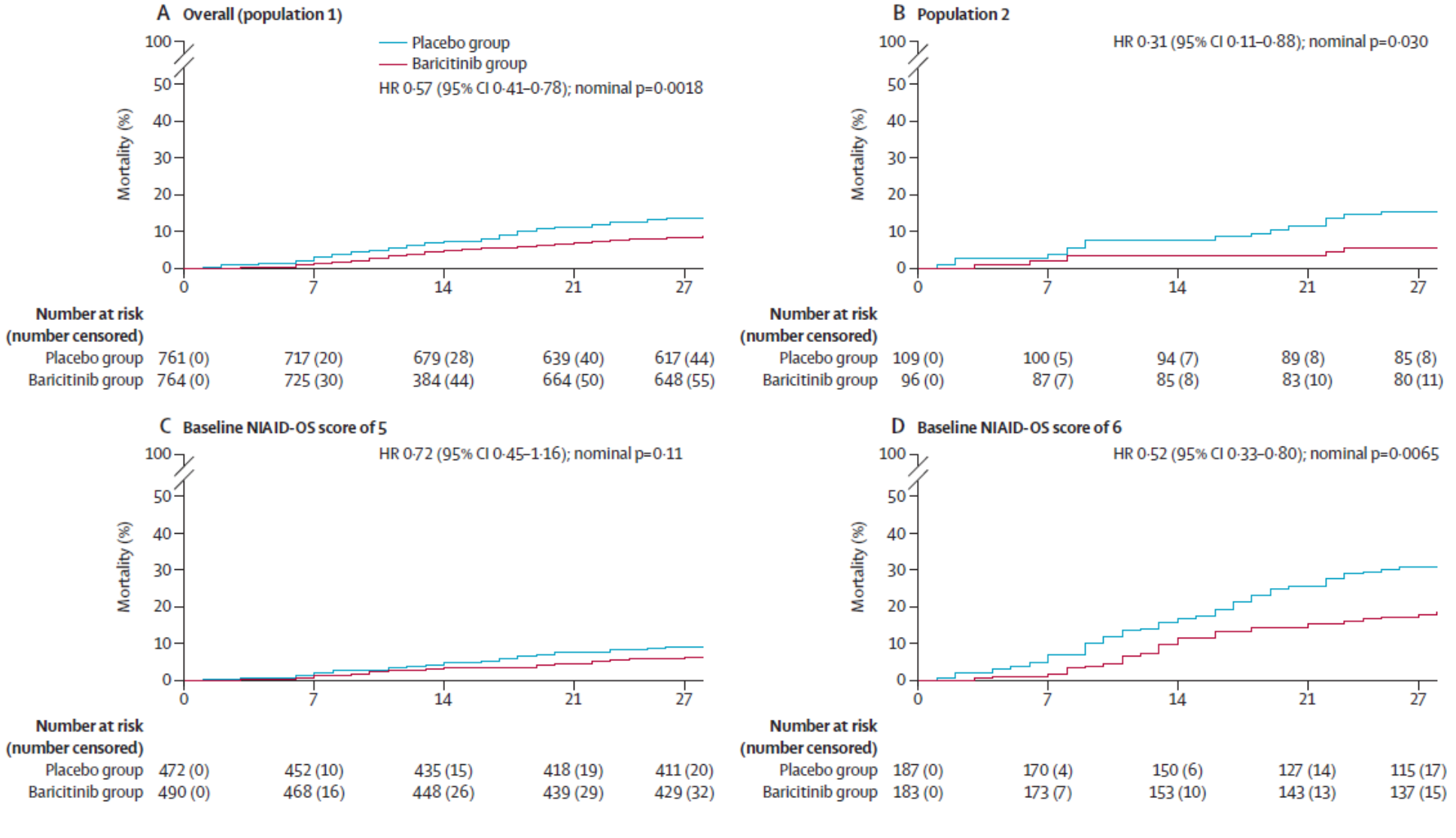
Conclusions: While reduction of disease progression did not achieve statistical significance, treatment with baricitinib in addition to SOC (predominantly dexamethasone) significantly reduced mortality with a similar safety profile between groups of hospitalized COVID-19 participants.

Table 2. Primary and key secondary outcomes in the intent-to-treat population

	Placebo + SOC (N=761)		Baricitinib 4-mg + SOC (N=764)	
Outcome			Comparison with placebo (95% CI)	Nominal p value*
Primary outcome				
Progressed to high-flow oxygen, non-invasive ventilation oxygen, invasive mechanical ventilation†, or death by Day 28, (%)‡§				
Population 1¶**	30.5	27.8	0.85 (0.67 to 1.08)	0.18
Population 2††‡‡	27.1	28.9	1.12 (0.58 to 2.16)	0.73
Key secondary outcomes				
All-cause mortality, n (%)¶¶	100 (13.1)	62 (8.1)	0.57 (0.41 to 0.78)	0.002

Lancet Respir Med Sept 1, 2021

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial



Lancet Respir Med Sept 1, 2021

Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomised, Placebo-Controlled Trial.

Table 2: Overview of efficacy outcomes in the intent-to-treat population by day 28

	Placebo + SOC (N= 50)	Baricitinib + SOC (N= 51)	Comparison with placebo (95% CI)	p value*
All-cause mortality				
n (%)‡	29 (58·0)	20 (39·2)	0·54 (0·31, 0·96)	0·030
KM Estimates (95% CI)	59·0 (41·1, 77·7)	40·6 (25·8, 59·7)	··	··
Time to mortality, days; median (95% CI)	17·0 (11·0, NA)	NA (24·0, NA)	··	··
VFDs (days) †	5·5 (8·4)	8·1 (10·2)	2·36 (-1·38, 6·09)	0·21
Likelihood of overall improvement on the NIAID-OS				
Day 4	··	··	14·37 (1·79, 115·65)	0·012
Day 7	··	··	2·87 (1·12, 7·36)	0·028
Day 10	··	··	2·08 (0·96, 4·49)	0·062
Day 14	··	··	1·97 (0·95, 4·09)	0·068
Day 21	··	··	2·16 (1·04, 4·49)	0·040
Day 28	··	··	1·82 (0·87, 3·81)	0·11
≥1-point improvement on NIAID-OS				

Submitted Lancet Resp Med 10-21

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

nature medicine

Background In a previous open-label trial early anakinra treatment guided by elevated soluble urokinase plasminogen activator receptor (suPAR) prevented progression of COVID-19 pneumonia into respiratory failure.

Methods In the SAVE-MORE multicenter trial, hospitalized patients with moderate and severe COVID-19 pneumonia and plasma suPAR 6 ng/ml or more and receiving standard-of-care (SoC) were 1:2 randomized to subcutaneous treatment with placebo or 100mg anakinra once daily for 10 days. The primary endpoint was the 11-point World Health Organization ordinal Clinical Performance Scale (WHO-CPS) by day 28. The changes of the WHO-CPS and of the sequential organ failure assessment (SOFA) score were the main secondary endpoints. The trial was designed following advice by the COVID-ETF of the European Medicines Agency.

Results Anakinra-treated patients were allocated to significantly lower strata of disease severity by day 28 (adjusted odds ratio-OR 0.36; 95%CI 0.26-0.50; P<0.0001). Significantly lower disposition into severe disease or death (6 or more points of WHO-CPS) was found (OR: 0.46; P: 0.01). The median absolute changes of WHO-CPS in the placebo and anakinra groups from baseline was -3 and -4 at day 28 (OR 0.40; P<0.0001); and -2 and -3 at day 14 (OR 0.63; P: 0.003); the absolute change of SOFA score was 0 and -1 (OR 0.63; P: 0.004). Hospital stay was shorter.

Conclusions Early start of anakinra treatment guided by suPAR is leading to 64% global improvement in moderate and severe COVID-19 pneumonia .

(Sponsored by the Hellenic Institute for the Study of Sepsis ClinicalTrials.gov identifier, NCT04680949) Consider adding the mortality benefit and the shorter ICU stay.

Kyriazopoulou, E., Poulakou, G., Milionis, H. et al. Nat Med (2021). https://doi.org/10.1038/s41591-021-01499-z

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

nature medicine

Criteri di inclusione:

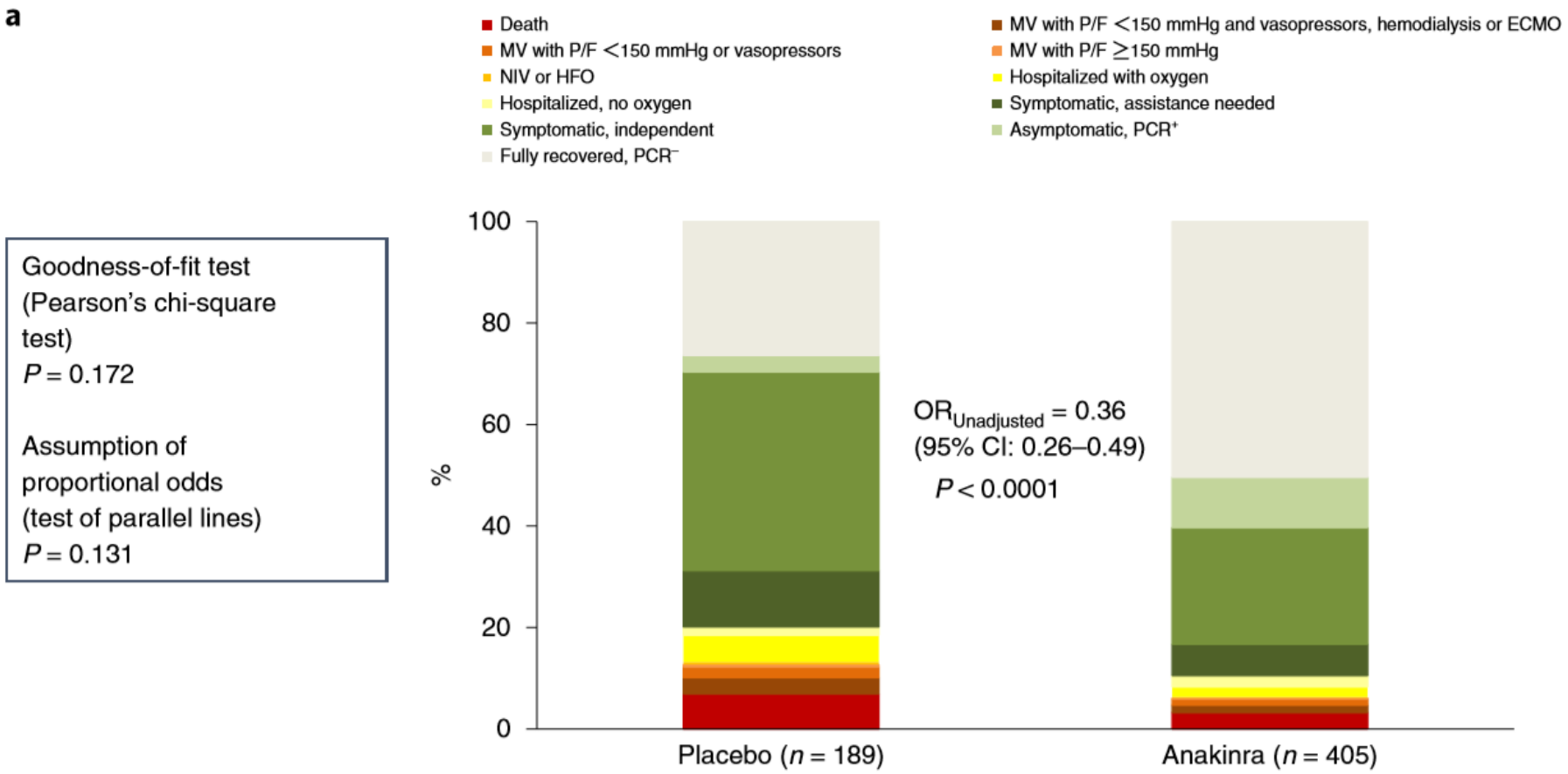
- Pazienti adulti
- Diagnosi di infezione da SARS-CoV-2
- Polmonite (Rx o TC)
- Indicazione a ospedalizzazione
- suPAR≥6

Criteri di esclusione:

- P/F < 150
- Bisogno di NIV o VM
- Neutropenia
- Neoplasia stadio IV
- Malattia renale terminale
- Insufficienza epatica grave
- Immunodeficienze
- Terapia cronica con corticosteroidi
- Uso di anticitochine nell'ultimo mese

Kyriazopoulou, E., Poulakou, G., Milionis, H. et al. Nat Med (2021). https://doi.org/10.1038/s41591-021-01499-z

PRIMARY ENDPOINT: distribution of the WHO-CPS scores at day 28 (primary outcome) of patients allocated to treatment with placebo and to treatment with anakinra



50.4% (204/405) of patients receiving anakinra had fully recovered with no viral RNA detected on day 28 compared to 26.5% (50/189) of patients receiving placebo, and 3.2% (13/405) and 6.9% (13/189) of patients in the anakinra and placebo arms, respectively, died.

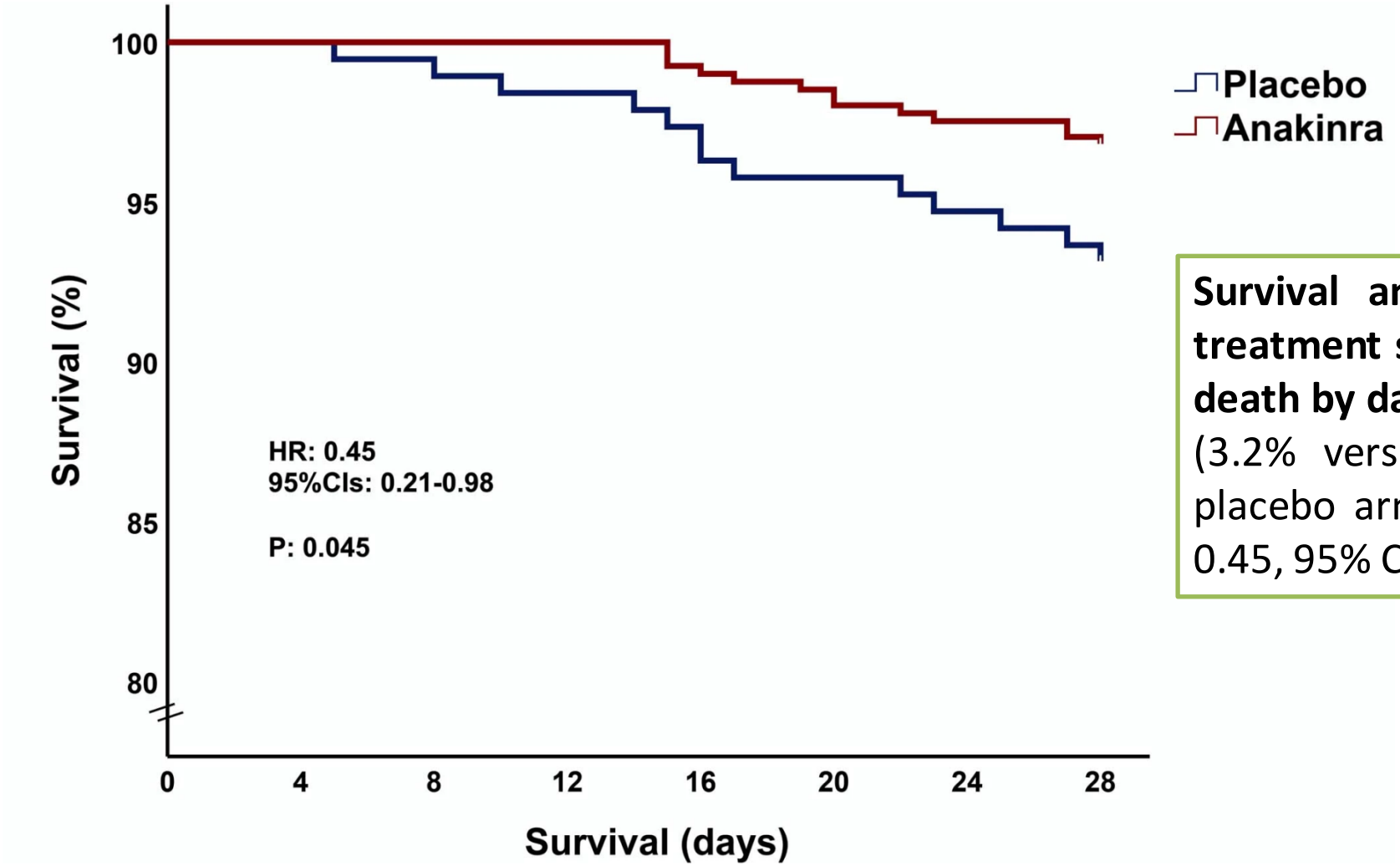
PRIMARY ENDPOINT: univariate and multivariate ordinal regression analysis of the WHO-CPS scores at day 28

b

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Group of treatment (Anakinra vs placebo)	0.36	0.26–0.49	<0.0001	0.36	0.26–0.50	<0.0001
Intake of dexamethasone (Yes/No)	1.90	1.28–2.83	0.002	1.49	0.59–3.80	0.395
Severe COVID-19 by WHO (Yes/No)	1.95	1.31–2.90	0.001	1.29	0.51–3.27	0.582
BMI >30 kg m^{-2} (Yes/No)	1.27	0.87–1.61	0.267	1.10	0.81–1.50	0.530
Country (Italy vs Greece)	1.18	0.74–1.88	0.482	1.25	0.77–2.03	0.350

Covariates entered in the multivariate model were those used for stratified randomization according to advice received from the COVID-ETF (disease severity, intake of dexamethasone, body mass index (BMI) and country) and the treatment with anakinra was the only independent variable associated with the primary outcome.

PRIMARY ENDPOINT: Survival analysis of enrolled patients at day 28 (univariate Cox regression analysis)



Patients at risk (n)

Placebo	189	189	187	186	182	181	179	176
Anakinra	405	405	405	405	401	397	395	392

Survival analysis showed that anakinra treatment significantly reduced the risk of death by day 28 compared to placebo
(3.2% versus 6.9% in the anakinra and placebo arms, respectively; hazard ratio = 0.45, 95% CI 0.21–0.98, *P* = 0.045)

TAKE HOME MESSAGE

- Attenuation of the early hyperinflammatory phase is already managed in other IDs: TB and crypto meningitis
- Attenuation of the hyperinflammatory phase of COVID-19 could protect COVID-19 patients by preventing clinical progression and death
- Anti-Jak and anti IL-6 have a role as immune suppressant drugs
- **suPAR** can represent an innovative early marker of disimmune regolation, personalizing treatment approach, because early increase of suPAR is indicative of excess release of DAMPs, leading to pro-inflammatory phenomena
- Early start of **anakinra** treatment guided by **suPAR** is leading to 64% global improvement in moderate and severe COVID-19 pneumonia
- The proportion of patients who fully recovered exceeded 50% and the number of patients who remained with severe disease was reduced by 54%.
- Relative decrease of mortality was 55% and reached 80% for patients likely having cytokine storm.

Terapia con immunomodulanti secondo indicazioni AIFA update del 28.09.21

		Indicazioni	dosaggio	Controindicazioni
Tocilizumab	anti IL-6	Soggetti adulti ospedalizzati con COVID-19 grave e/o con livelli elevati degli indici di infiammazione sistemica. • ricoverati in terapia intensiva da < di 24/48 h in ventilazione meccanica o ossigeno ad alti flussi; oppure • recentemente ospedalizzati con fabbisogno di O2 in rapido aumento in ventilazione meccanica NON invasiva o ossigeno ad alti flussi + elevati indici di flogosi (PCR ≥7.5 mg/dL). • rapida progressione clinica dopo 24/48 h di desametasone, o altri cortisonici. Fabbisogno di ossigeno in rapido aumento, pur senza necessità di ventilazione non invasiva o ossigeno ad alti flussi, e con elevati livelli di indici di flogosi (CRP≥7,5 mg/dL).	8 mg/kg ev in 60min Seconda dose dopo almeno 8 ore se non migliora (max 800 mg ad infusione)	- Infezioni attive in atto (diverse da COVID-19) che potrebbero peggiorare con l'utilizzo di tocilizumab (vedi quantiferon e PCT) - Storia di ulcerazione intestinale o diverticolite - Epatopatia attiva e compromissione epatica - Trattamento con altri inibitori delle interleuchine o con altri JAK-inibitori
Baricitinib	Anti JAK1/JAK2	Pazienti recentemente ospedalizzati con fabbisogno di ossigeno in rapido aumento (condizioni cliniche rapidamente ingravescenti) che richiedono ventilazione meccanica NON invasiva o ossigeno ad alti flussi in presenza di elevati livelli di indici di flogosi (PCR ≥7.5 mg/dL). Utilizzo off label in pazienti in ventilazione meccanica invasiva o ECMO*	4 mg per o.s./die per 14 giorni (o fino a dimissione dall'ospedale per risoluzione clinica, se antecedente) eGFR 30-<60: 2 mg PO QD eGFR <30: non somministrare	- Neutropenia e infezioni gravi - Eventi epatici - Diverticolite e di perforazione gastrointestinale **- Tromboembolismo venoso** (Usato con attenzione nei pazienti con fattori di rischio per TVP/EP. Se compaiono manifestazioni cliniche di TVP/EP deve essere interrotto). - Trattamento con altri inibitori delle interleuchine o con altri JAK-inibitori
Anakinra	anti IL 1	Soggetti adulti ospedalizzati con polmonite da COVID-19 moderata/severa (con pO2/FiO2>150, e NON sottoposti a CPAP o ventilazione meccanica) e con (suPAR) ≥ 6ng/ml.	100 mg/die per 10 giorni SC	- Neutropenia e infezioni gravi - Eventi epatici - Trattamento con altri inibitori delle interleuchine o con altri JAK-inibitori
Sarilumab	Anti IL-6	si ritiene che sarilumab possa essere utilizzato in alternativa a tocilizumab quando quest'ultimo non fosse disponibile	400 mg ev in 60 min	

* Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomised, Placebo-Controlled Trial.

https://www.aifa.gov.it/-/aifa-rende-disponibili-i-medicinali-anakinra-baricitinib-e-sarilumab-per-il-trattamento-del-covid-19

Take home message

- **Strict monitoring of peripheral oxygen saturation** is mandatory at home

There is now **evidence-based clinical management of COVID-19 patients**

- **Non-pharmacological based management**
  - **HCWs – patient empathy**
  - **Pronation** is indicated in all patients apart if mechanically ventilated or not
  - **correct O2 therapy** in all health care settings to ***maintain a PaO2>95%*** with all available and feasible medical devices starting form Venturi mask, to CPaP, NIV or OTV;

- **Pharmacological based management**
  - **MoAbs** and **other oral antiviral drugs** in early phase of infection in at risk outpatients,
  - **MoAbs** permitted use in persistent COVID patients, and in-patients
  - early **Remdesevir** use as antiviral in case of pneumonia,
  - **LMWH for prophylaxis/treatment** in all hospitalized patients,
  - **Steroids** is a save life drug but only in case of oxygen support,
  - **Immunemodulant drugs** (tocilizumab/sarilumab , baricitinib & anakinra according to EMA/AIFA assessment)