La terapia del COVID-19 nelle sue varie fasi

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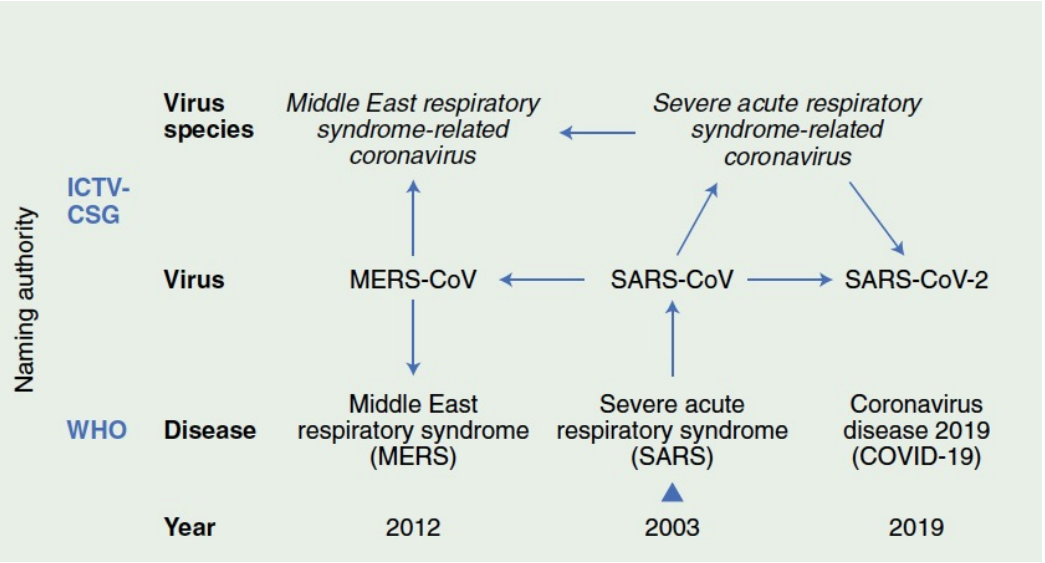
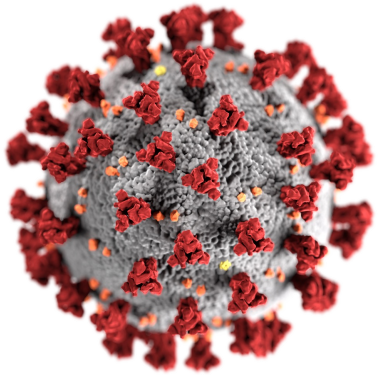
Indice

- SARS-CoV2: l’infezione
- COVID-19: le fasi della malattia
- Antivirali
- Eparine
- Corticosteroidi
- Altre terapie sperimentate senza successo: Azitromicina

Classificazione e denominazione del nuovo coronavirus 2019-nCoV in SARS-CoV-2





Da Centers for Disease Control and Prevention, Public Health Image Library, n°23312.

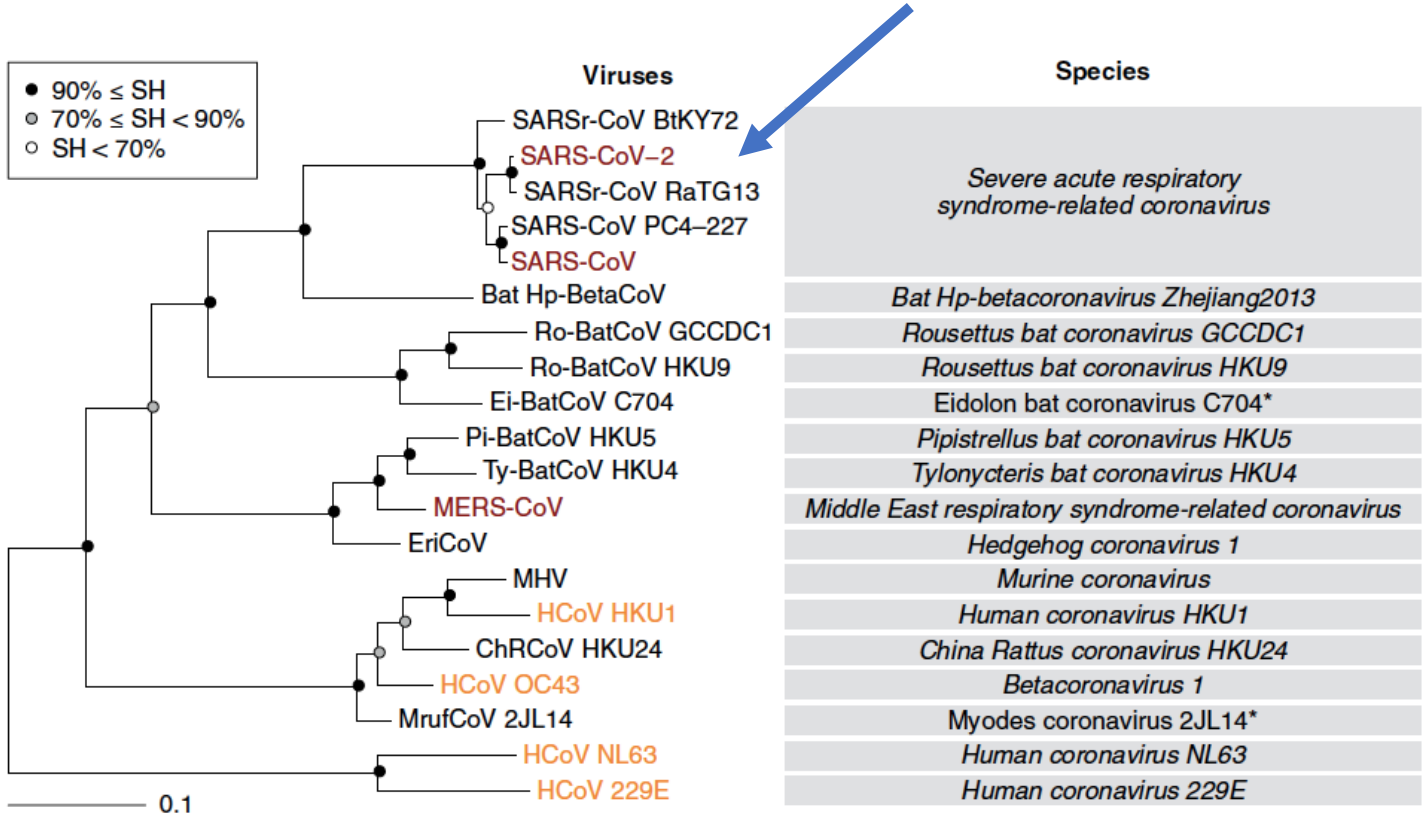
CONSENSUS STATEMENT

nature microbiology

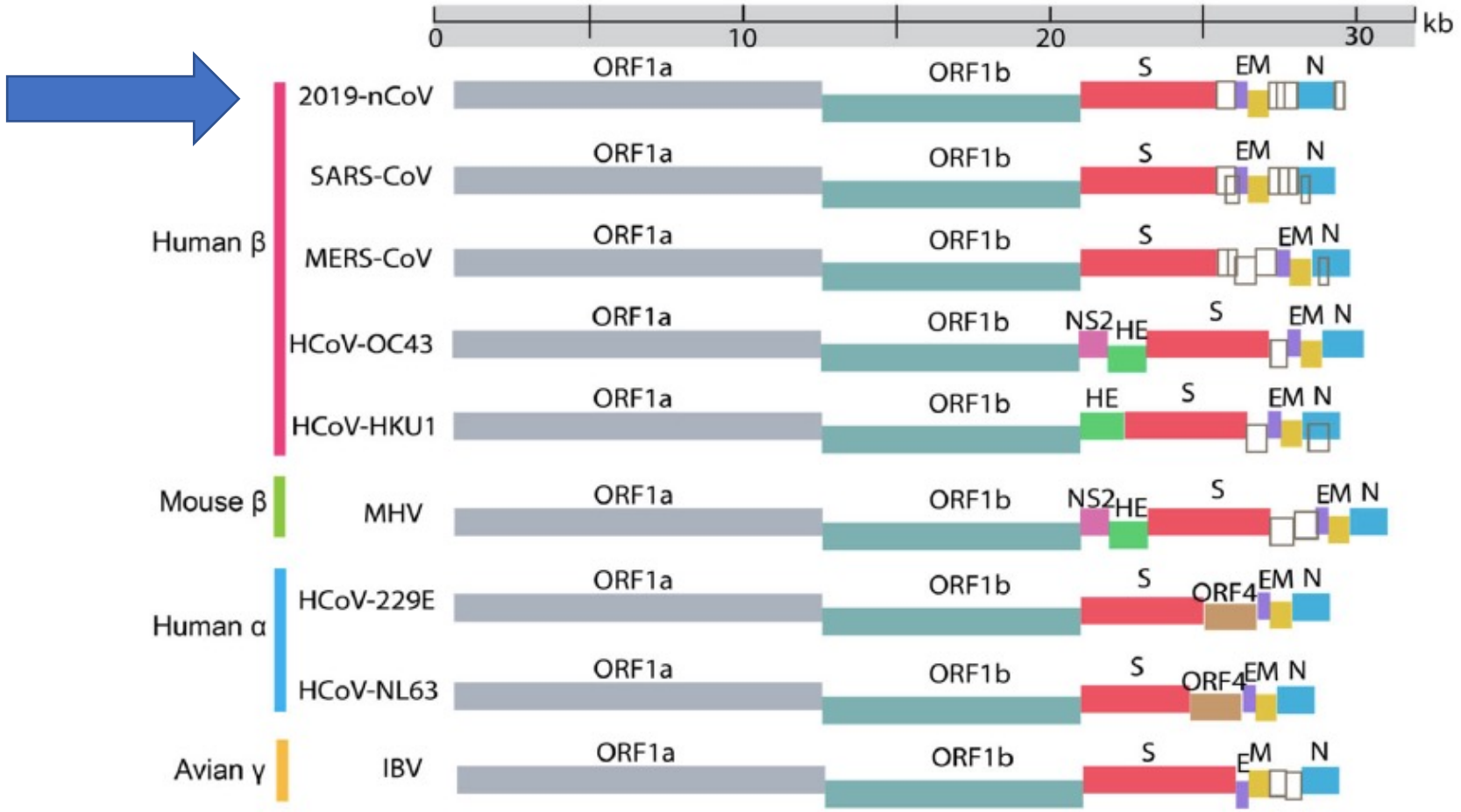
OPEN

The species *Severe acute respiratory syndrome-related coronavirus*: classifying 2019-nCoV and naming it SARS-CoV-2

Coronaviridae Study Group of the International Committee on Taxonomy of Viruses*



SARS-CoV-2: sequenza genica a confronto con gli altri coronavirus



Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Zhou et al., 2020. Cell discovery 6:14

SARS-CoV-2: proteine codificate dal genoma

ORF1ab related proteins

Target description	Target description
Leader protein nsp1	Nonstructural protein 7
Papain-like protease nsp3	Nonstructural protein 8
Papain-like protease nsp3	Nonstructural protein 9
Papain-like protease nsp3	Nonstructural protein 10
Papain-like protease nsp3	RNA-directed RNA polymerase nsp12
Papain-like protease nsp3	Helicase nsp13
Papain-like protease nsp3	Guanine-N7 methyltransferase nsp14
Nonstructural protein 4	Uridylate-specific endoribonuclease nsp15
3C-like protease nsp5	2'-O-methyltransferase nsp16

Drugs targets

Drug target

Target description
S protein
E protein
ORF7a
N protein
N protein

Dong, S, et al. A guideline for homology modeling of the proteins from newly discovered betacoronavirus, 2019 novel coronavirus (2019-nCoV). J Med Virol. 2020; 1– 7.

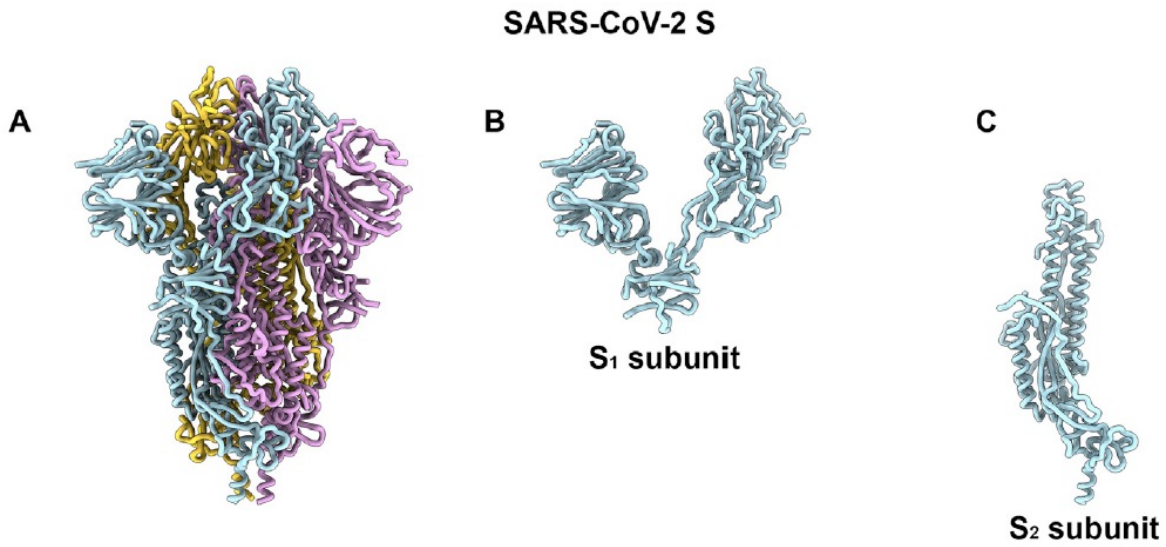
Cell

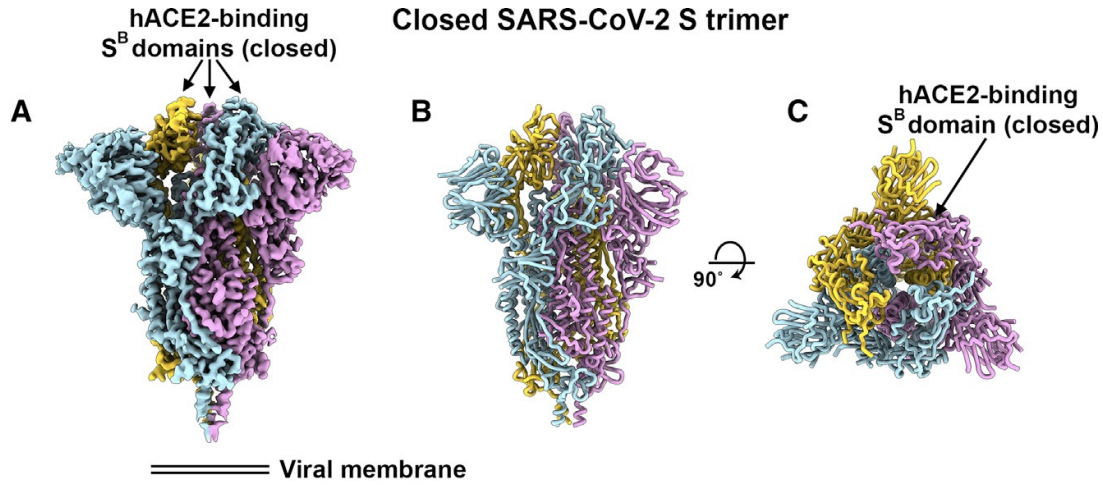
Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein

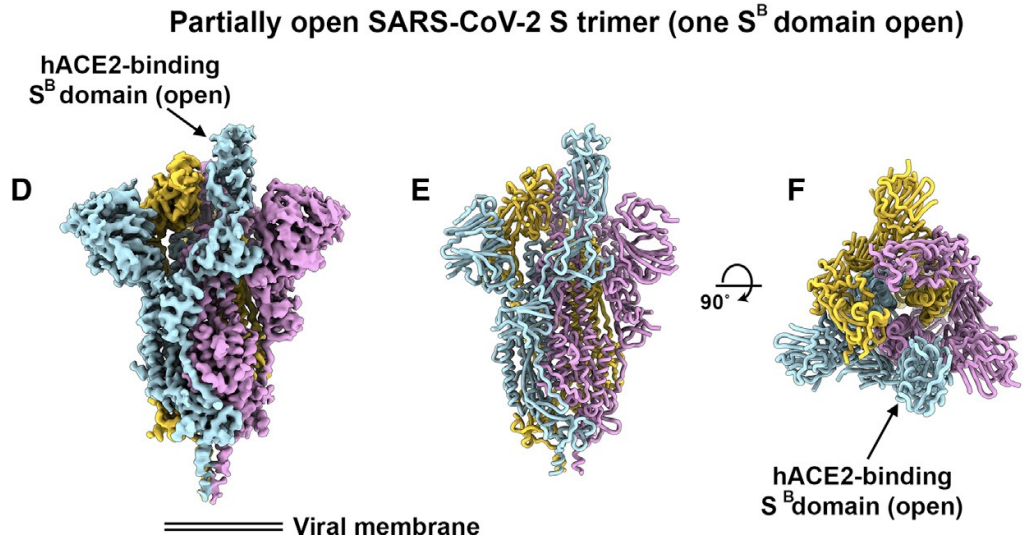
Authors

Alexandra C. Walls, Young-Jun Park, M. Alejandra Tortorici, Abigail Wall, Andrew T. McGuire, David Veesler

Walls et al., 2020, Cell *180*, 1–12
March 19, 2020





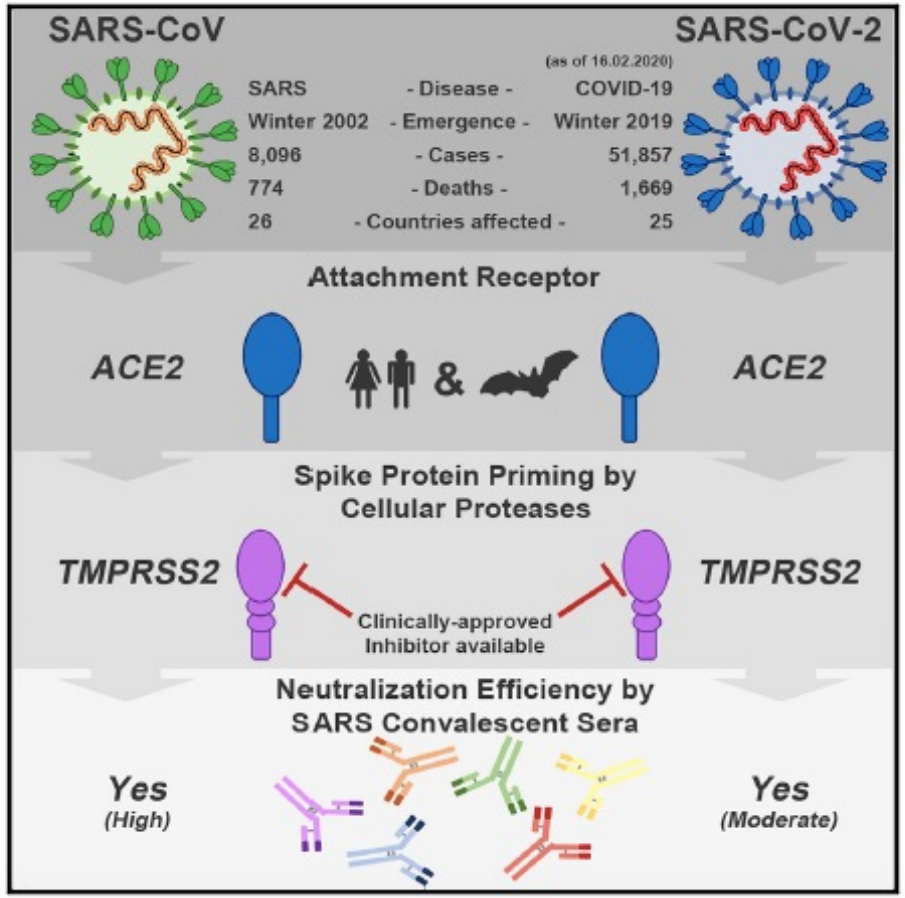


Cell

Hoffmann et al., 2020, Cell *181*, 1–10
April 16, 2020 © 2020 Elsevier Inc.

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

Graphical Abstract



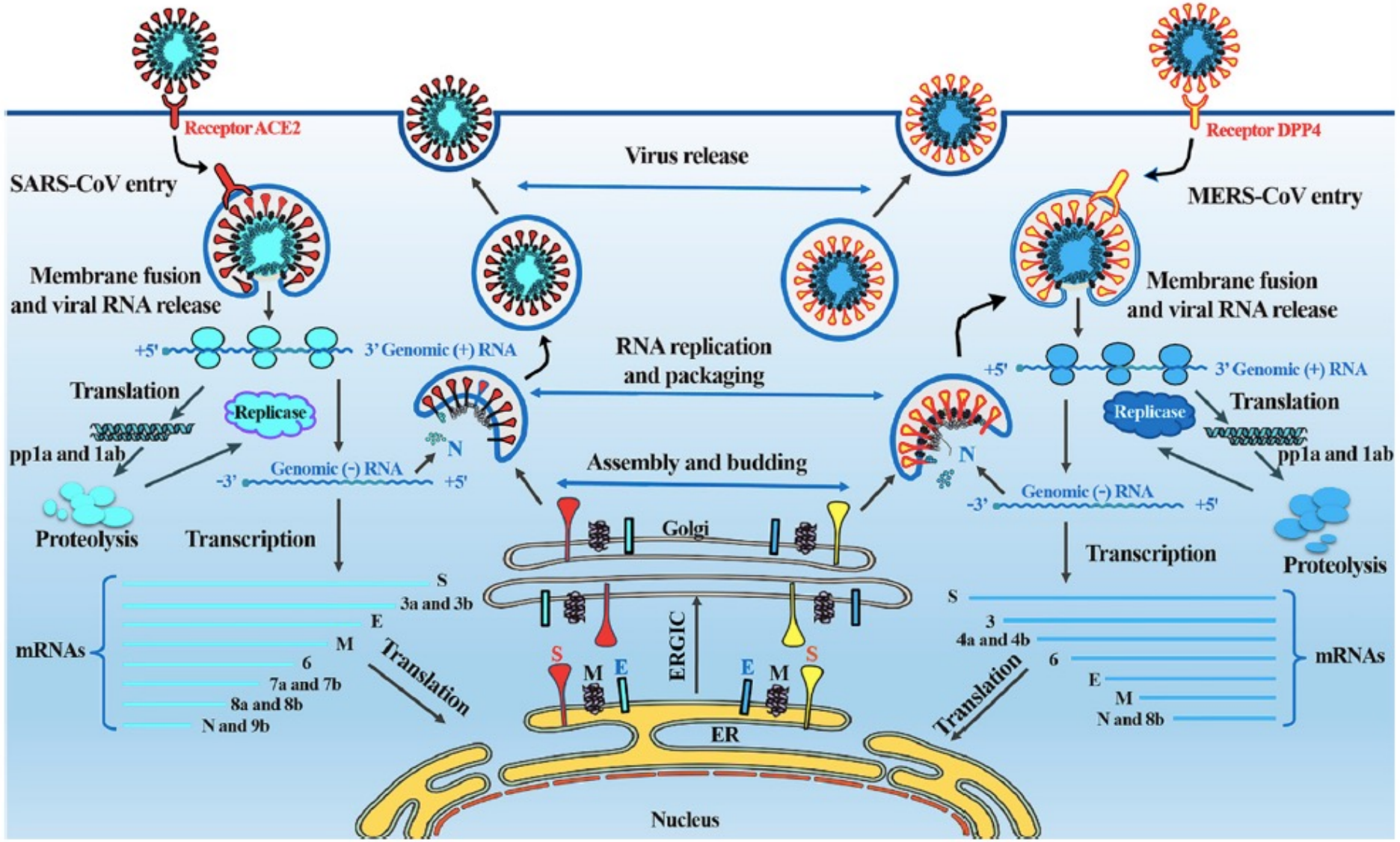
Highlights

- SARS-CoV-2 uses the SARS-CoV receptor ACE2 for host cell entry
- The spike protein of SARS-CoV-2 is primed by TMPRSS2
- Antibodies against SARS-CoV spike may offer some protection against SARS-CoV-2

The Cellular Serine Protease TMPRSS2 Primes SARS-2-S for Entry, and a Serine Protease Inhibitor Blocks SARS-CoV-2 Infection of Lung Cells

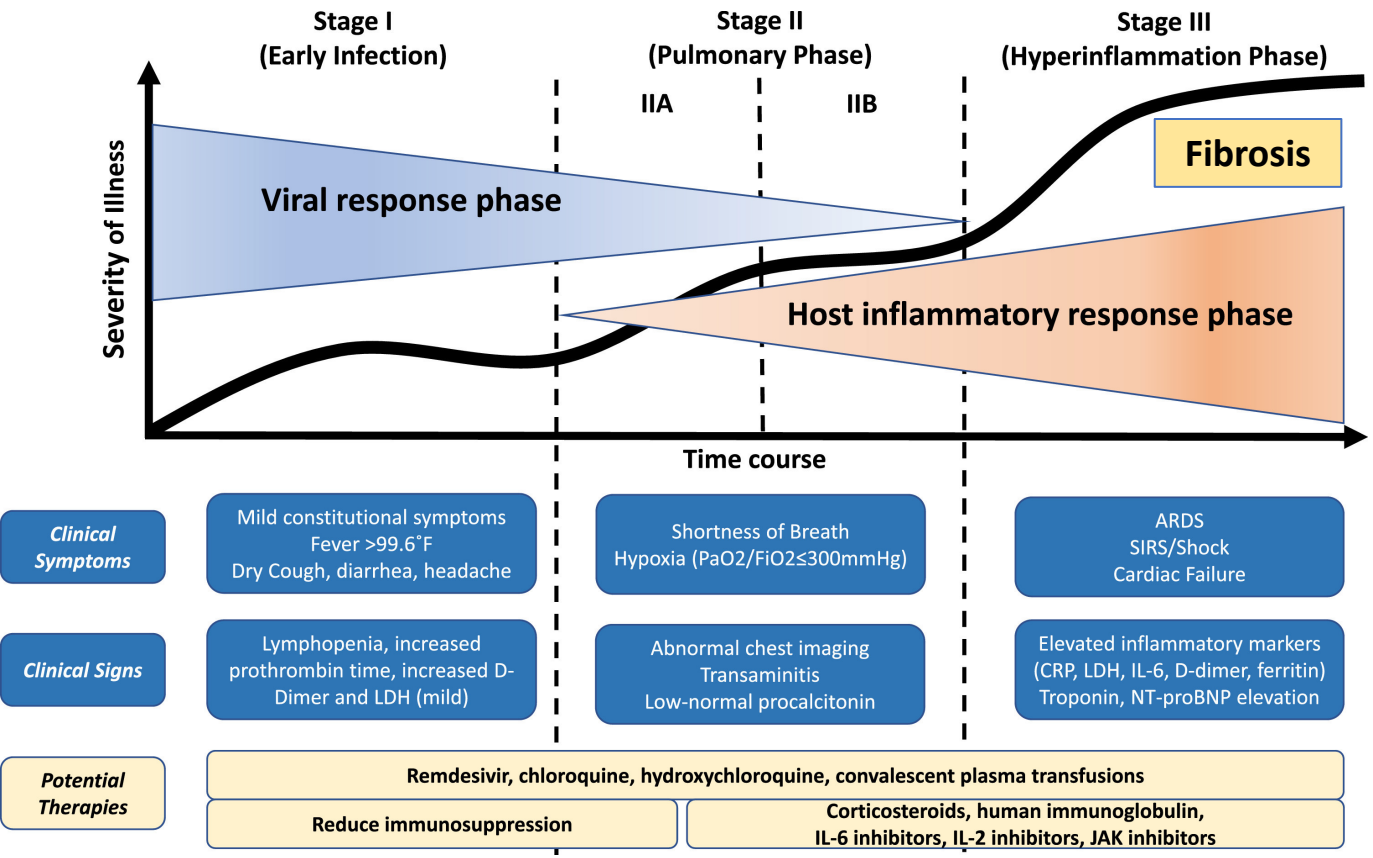
L'inibitore delle proteasi camostat mesylate, attivo nei confronti di TMPRSS2, blocca parzialmente l'ingresso di SARS-CoV2 in modelli cellulari (Caco-2 e Vero).

Ciclo replicativo dei coronavirus



From SARS to MERS, Thrusting Coronaviruses into the Spotlight. Song et al., 2019 Viruses, 11, 59;

COVID-19: le fasi della malattia



Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405-407.

Il decorso clinico del COVID mostra **3 distinte fasi cliniche** della malattia:

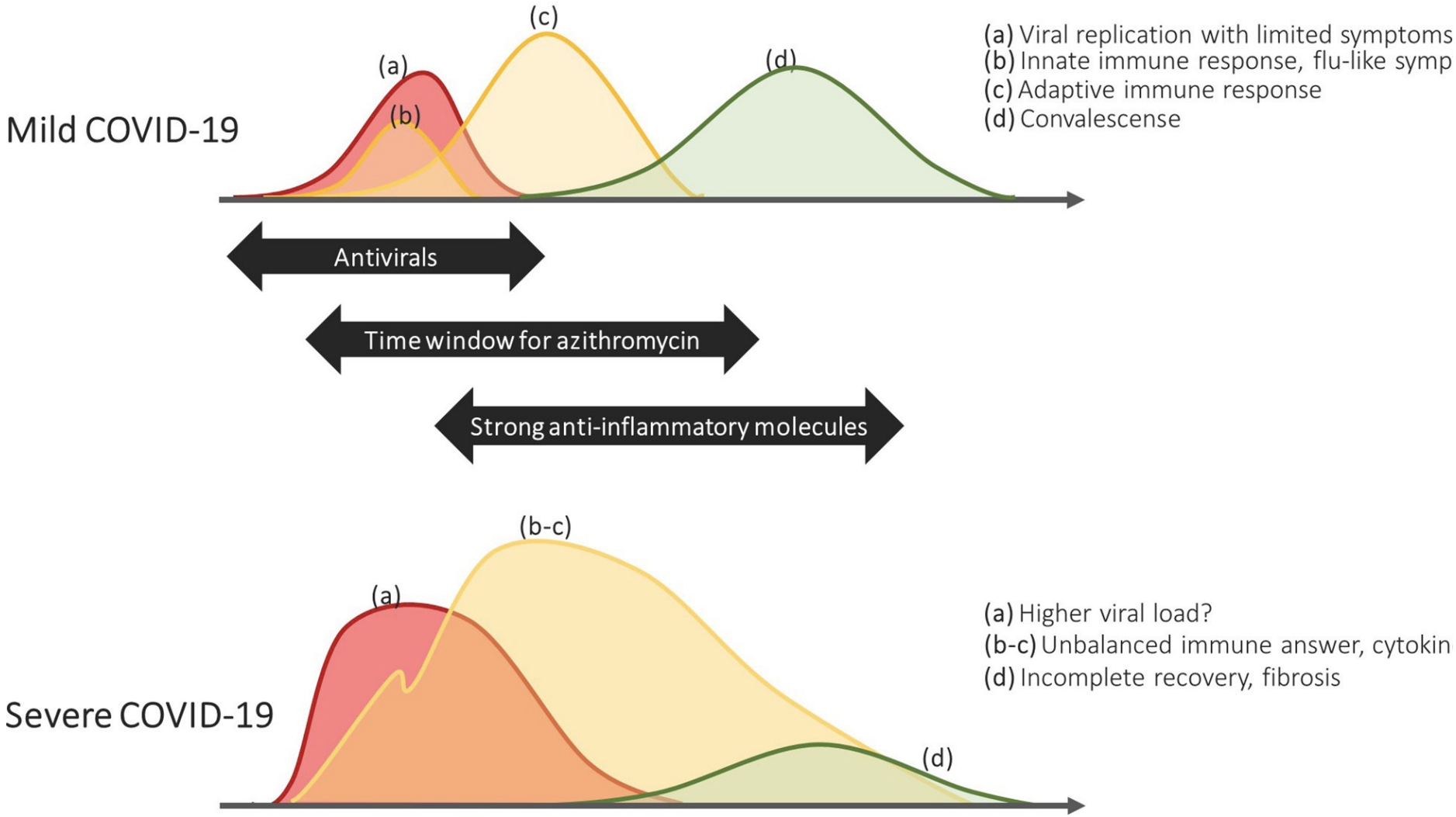
1. Fase iniziale durante la quale il virus si replica all'interno delle cellule dell'ospite. Tale fase si caratterizza per malessere generale, febbre e tosse secca. I casi in cui l'infezione si ferma in questo stadio hanno un decorso benigno.

2. La malattia può evolvere verso una seconda fase con alterazioni a livello polmonare causate sia dagli effetti diretti del virus sia dalla risposta immunitaria dell'ospite. Tale fase si caratterizza per un quadro di polmonite interstiziale bilaterale associata, ad una sintomatologia respiratoria prima stabile e senza ipossiemia, ma che può peggiorare progressivamente

3. Tale scenario può evolvere verso un quadro clinico dominato dalla tempesta citochinica e dallo stato iperinfiammatorio che determina conseguenze locali e sistemiche producendo, a livello polmonare, quadri di danno vascolare con trombizzazione dei piccoli vasi ed evoluzione verso lesioni polmonari gravi e talvolta permanenti (fibrosi polmonare). Questo gravissimo quadro clinico porta a una ARDS grave e talvolta alla CID.

Qual è il giusto momento per le diverse terapie?

PRINCIPLE cohort



RECOVERY cohort

Gyselinck I, et al. BMJ Open Resp Res 2021;8:e000806.

Terapie per il COVID-19: a che punto siamo?

AGENZIA ITALIANA DEL FARMACO

Gestione domiciliare:

- **FANS, PARACETAMOLO**
- **REMDESIVIR** (Veklury)
- **NIRMATRELVIR/RITONAVIR** (Paxlovid)
- **MOLNUPIRAVIR** (Lagevrio)
- **ANTICORPI MONOCLONALI:**
  - Bamlanivimab-Etesevimab (Eli-Lilly);
  - Casirivimab-Imdevimab (Regeneron/Roche);
  - Sotrovimab (GlaxoSmithKline);
- **CORTICOSTEROIDI**
- **EPARINE**

Gestione ospedaliera:

- **CORTICOSTEROIDI (desametasone)**
- **EPARINE A BASSO PESO MOLECOLARE**
- **REMDESIVIR**
- **TOCILIZUMAB**
- **SARILUMAB**
- **BARICITINIB**
- **ANAKINRA**

GLI ANTIVIRALI CONTRO SARS-COV-2

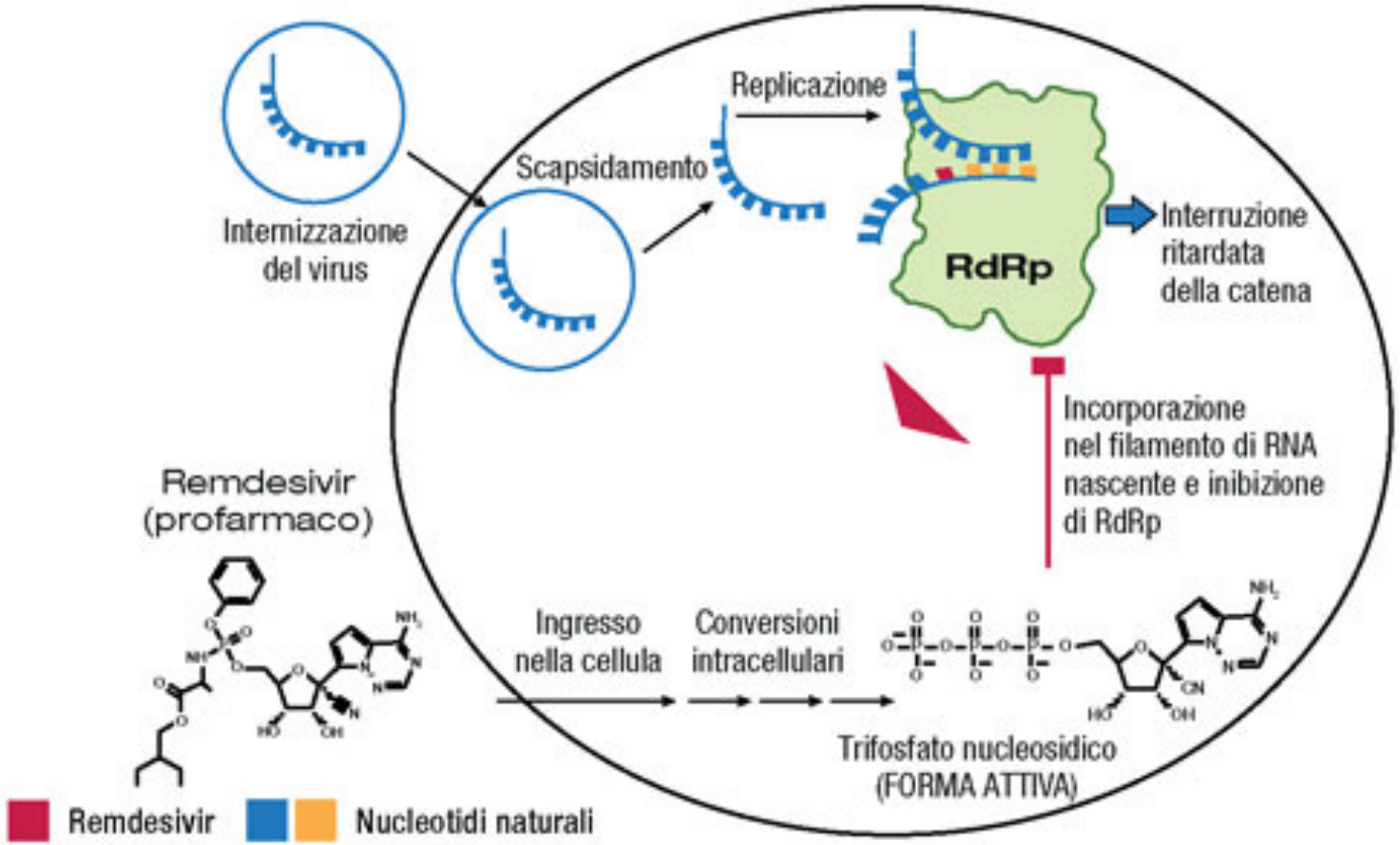
Drug	Setting	Patient population	Dosing regimen	Dose adjustment for kidney dysfunction	Date of FDA EUA or approval	Date of EMA authorization
Antiviral agents						
Remdesivir	Inpatient and outpatient	Symptoms (mild to moderate) for < 7 days	200 mg i.v. on day 1, then 100 mg i.v. daily from day 2 (3 days for non-hospitalized, 5 days or until discharge for hospitalized)	eGFR < 30: NR	EUA, 1 May 2020; FDA approved, 22 October 2020	3 July 2020
Nirmatrelvir–ritonavir (Paxlovid)	Outpatient	Symptoms (mild to moderate) for < 5 days	300 mg/100 mg oral twice daily for 5 days	eGFR 30–59: 150/100 mg twice daily for 5 days; eGFR < 30: NR	EUA, 22 December 2021	28 January 2022
Molnupiravir	Outpatient	Symptoms (mild to moderate) for < 5 days	800 mg orally twice daily for 5 days	None	EUA, 23 December 2021	Under review

Recentemente sono stati resi disponibili tre antivirali (remdesivir, nirmatrelvir/ritonavir e molnupiravir) per il trattamento di soggetti adulti con COVID-19 che non necessitano di ossigenoterapia supplementare e che sono a maggior rischio di progressione verso forme severe di COVID-19.

REMDESIVIR

REMDESIVIR È UN ANALOGO NUCLEOTIDICO DELL'ADENOSINA IN GRADO DI INIBIRE DIVERSE RNA POLIMERASI RNA-DIPENDENTI VIRALI

FIG. **1** Il meccanismo d'azione di remdesivir ne definisce la potente azione antivirale diretta sul SARS-CoV-2 (1-4)



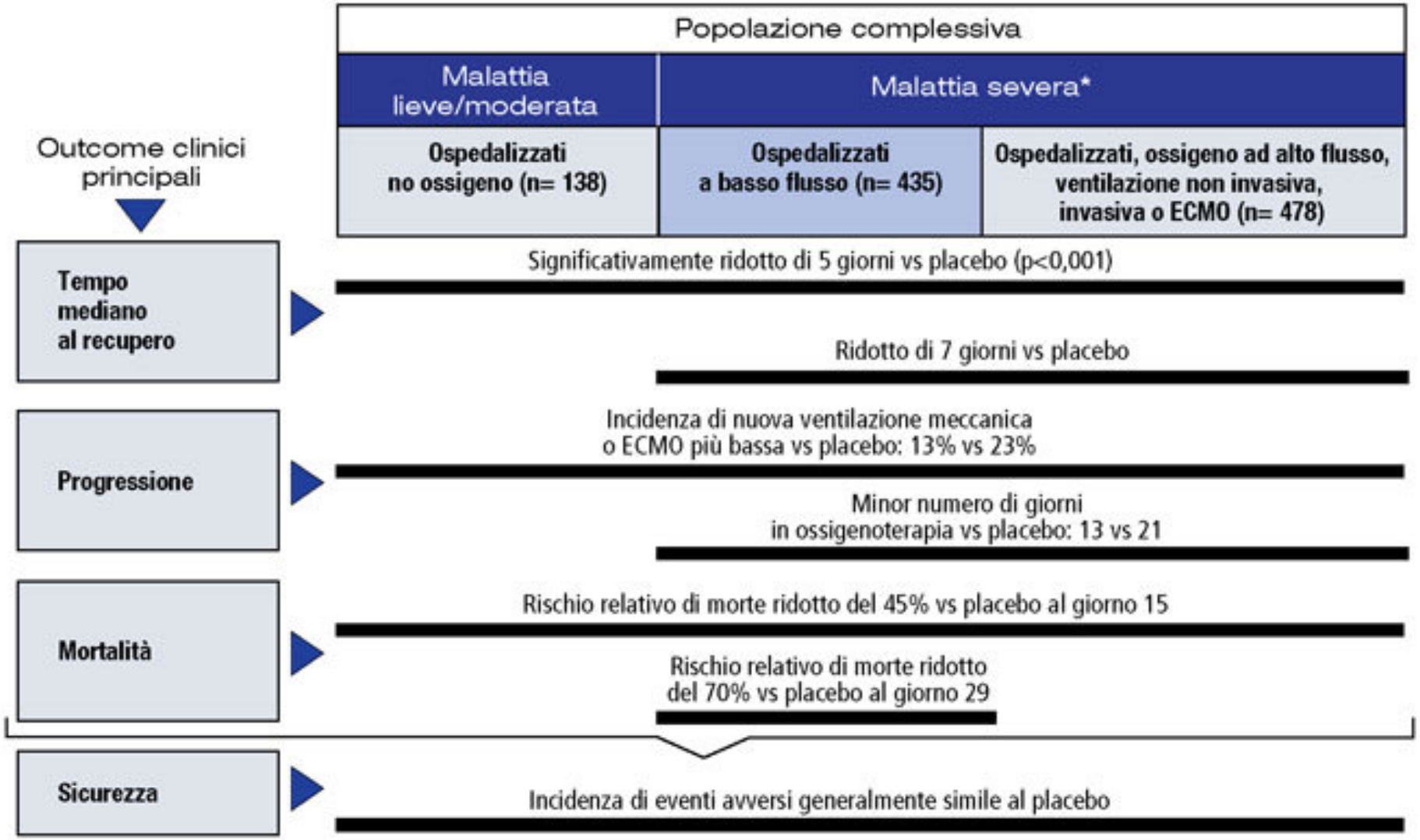
Remdesivir inibisce **la sintesi dell'RNA virale** attraverso un effetto sull'attività della RNA polimerasi RNA-dipendente (RdRp) e della esoribonucleasi (4-6).

Effetto sull'attività della RdRp virale (6)
A livello intracellulare, remdesivir viene convertito nella sua forma attiva, il trifosfato nucleosidico, che inibisce la RdRp e che, incorporato nel filamento dell'RNA nascente, determina un arresto ritardato del processo di replicazione (3).

Effetto sull'attività della esoribonucleasi (6)
La esoribonucleasi del virus, deputata a correggere gli errori di replicazione (processo di proofreading), non può funzionare contro la forma attiva di remdesivir (3).

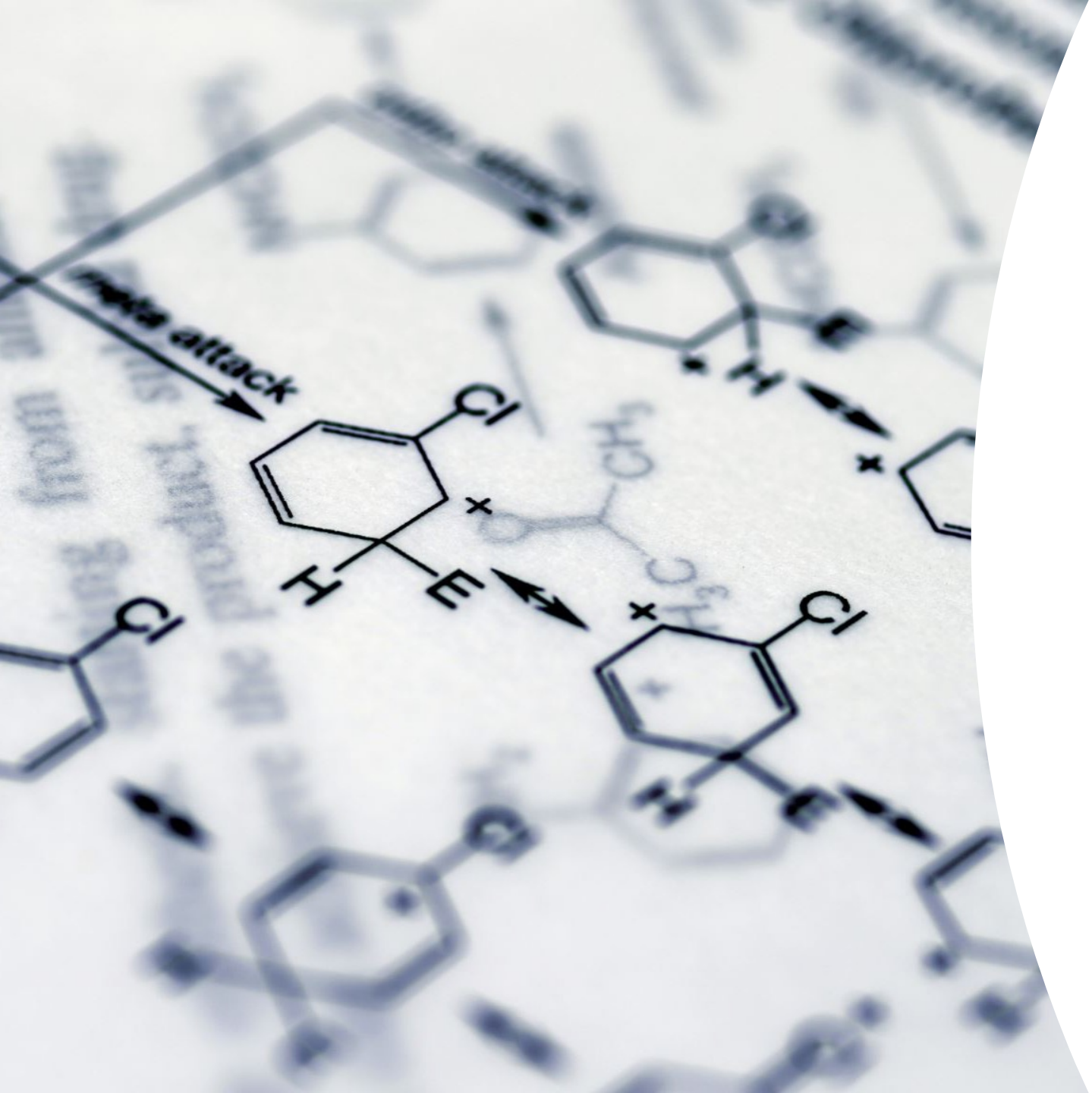
1. Gordon CJ, et al. J Biol Chem. 2020 2. VEKLURY. RCP. 3. Hashemian SM, et al. Drug Des Devel Ther. 2020.
4. Jorgensen SCJ, et al. Pharmacotherapy. 2020. 5. Ribaudo G, et al. J Biomol Struct Dyn. 2020. 6. Al-Tannak NF, et al. Sci. Pharm. 2020

TAB. **1** Risultati dello studio NIAID ACTT-1



*Malattia severa: Pazienti con malattia severa: in ventilazione meccanica invasiva o non invasiva, ossigeno supplementare, SpO2 ≤ 94% in aria ambiente o tachipnea (frequenza respiratoria ≥24 respiri/minuto)

Beigel JH et al; for the ACTT-1 Study Group Members. N Engl J Med. 2020

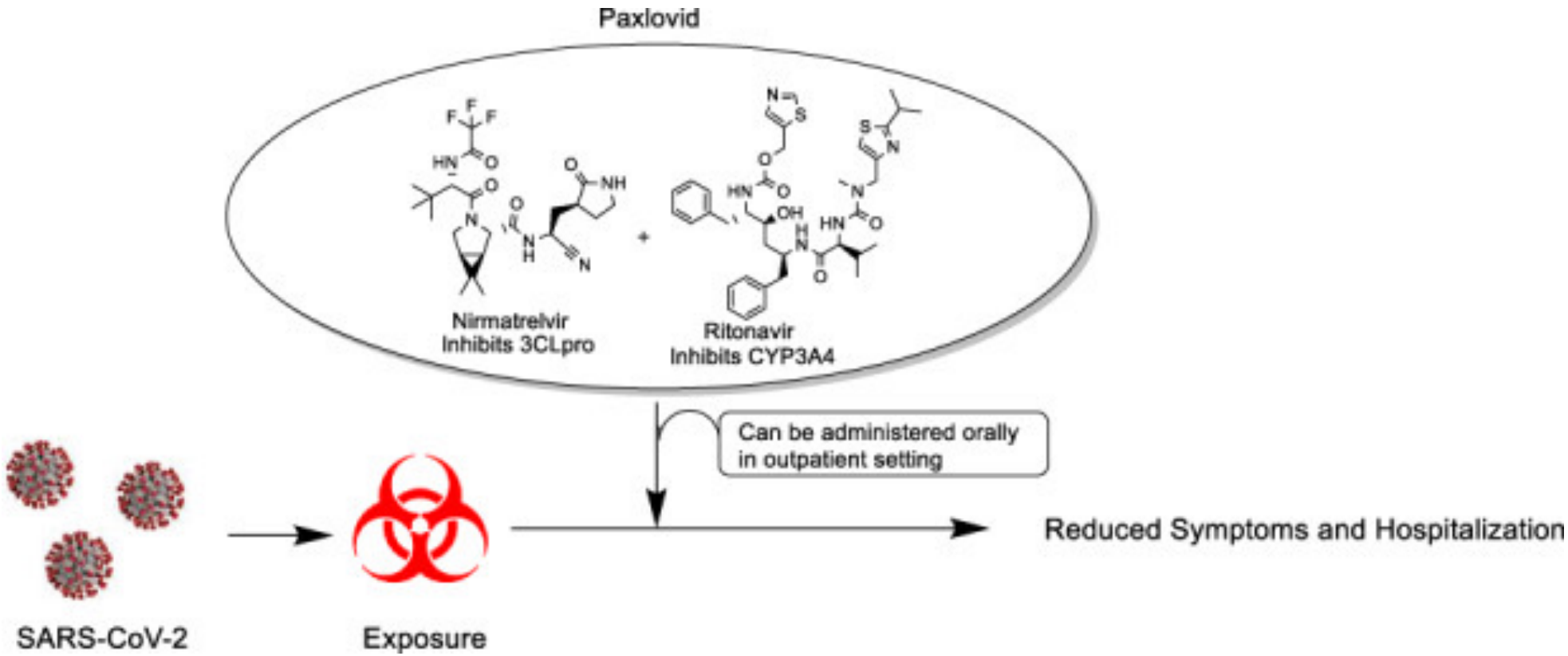


NIRMATRELVIR/RITONAVIR (PAXLOVID)

- Nirmatrelvir (PF-07321332) is an orally bioavailable M^{pro} (also called $3CL^{pro}$) inhibitor developed by Pfizer.
- It is administered in combination with ritonavir, a potent CYP3A4 inhibitor that decreases the metabolism of nirmatrelvir

Mechanism of Action:

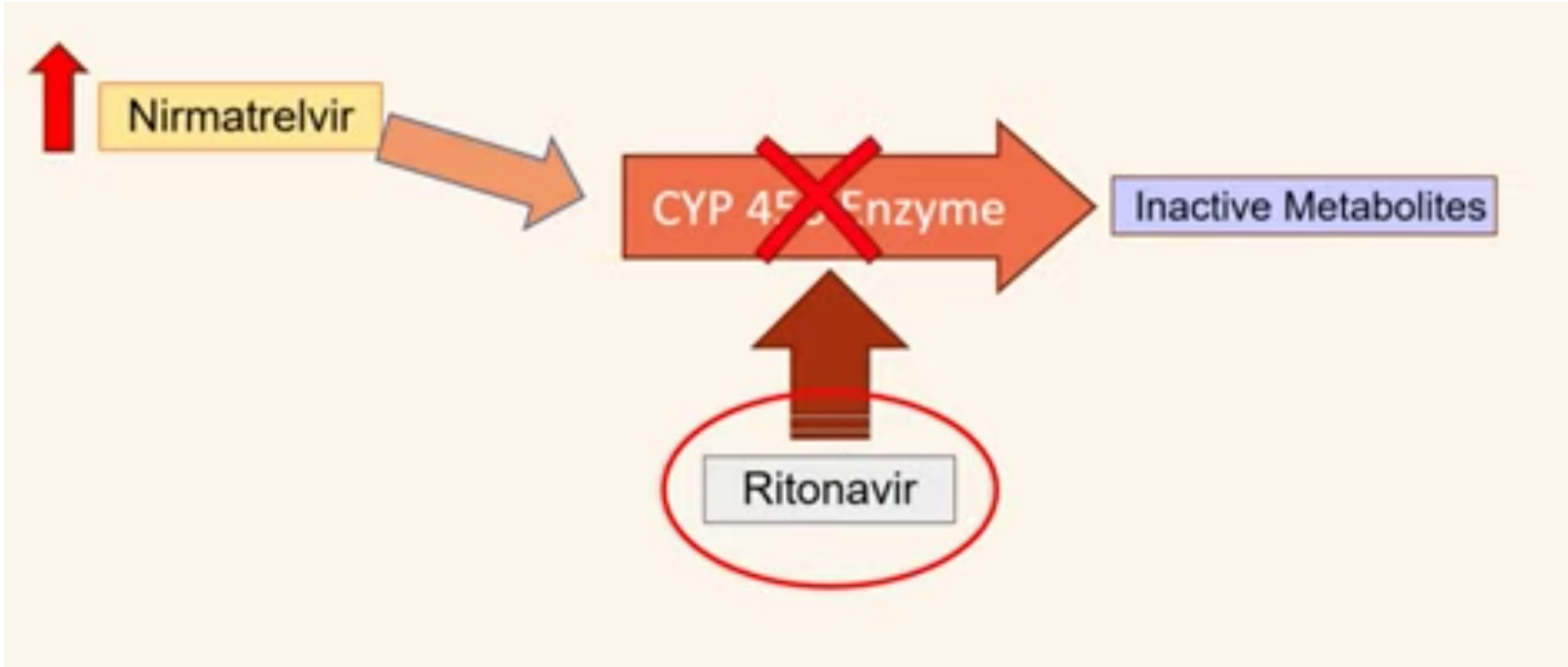
- Paxlovid® is a combination of two drugs: nirmatrelvir and ritonavir.
- Nirmatrelvir is a **protease inhibitor** of the SARS-CoV-2 main protease (Mpro).
    - The SARS-CoV-2 main protease (Mpro), is also referred to as 3C-like protease (3CLpro) or nsp5 protease.
- Inhibition of SARS-CoV-2 Mpro renders the virus incapable of processing polyprotein precursors, thus preventing viral replication.



Joyce RP, Hu VW, Wang J. The history, mechanism, and perspectives of nirmatrelvir (PF-07321332): an orally bioavailable main protease inhibitor used in combination with ritonavir to reduce COVID-19-related hospitalizations. Med Chem Res. 2022

Paxlovid®

- Nirmatrelvir functions primarily as the main antiviral.
  - It blocks a key enzyme that viruses need to multiply in the human body.
- Ritonavir is used to boost the effectiveness of nirmatrelvir.
  - Ritonavir is administered with nirmatrelvir as a “pharmacokinetic enhancer” resulting in higher systemic concentrations and longer half-life of nirmatrelvir, thereby supporting a twice daily administration regimen.
  - Ritonavir slows down nirmatrelvir’s breakdown to help it remain in the body for a longer period at higher concentrations.


Nirmatrelvir
CYP 45 Enzyme
Inactive Metabolites
Ritonavir

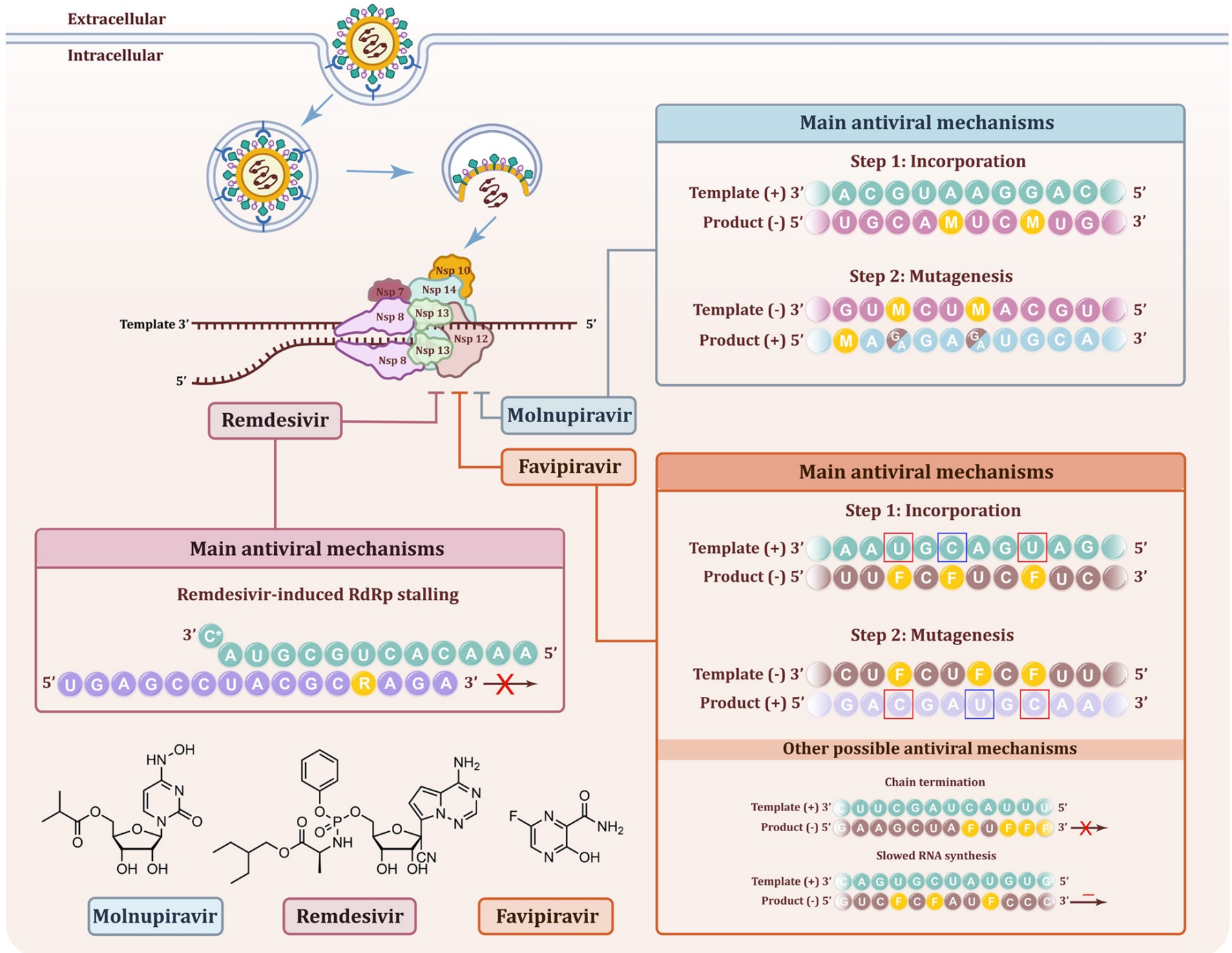
Molnupiravir

- Farmaco antivirale ad ampio spettro sviluppato da Merck e Ridgeback Biotherapeutics per il trattamento della COVID-19.
- Ha ricevuto la prima approvazione il 4 novembre 2021 nel Regno Unito
- Approvato per l'uso in adulti con COVID-19 da lieve a moderata.

In sintesi

- È un profarmaco del derivato nucleosidico sintetico N4-idrossicitidina, ed esplica la sua azione antivirale attraverso l'introduzione di errori di copiatura durante la replicazione dell'RNA virale.

Syed, Y. Y. Drugs. 2022. https://doi.org/10.1007/s40265-022-01684-5


Extracellular
Intracellular
Nsp 10
Nsp 7
Nsp 14
Nsp 8
Nsp 13
Template 3'
5'
Nsp 12
Nsp 13
Nsp 8
5'
Remdesivir
Molnupiravir
Favipiravir
Main antiviral mechanisms
Step 1: Incorporation
Template (+) 3'
Product (-) 5'
Step 2: Mutagenesis
Template (-) 3'
Product (+) 5'
Main antiviral mechanisms
Remdesivir-induced RdRp stalling
Main antiviral mechanisms
Step 1: Incorporation
Step 2: Mutagenesis
Other possible antiviral mechanisms
Chain termination
Slowed RNA synthesis
Molnupiravir
Remdesivir
Favipiravir

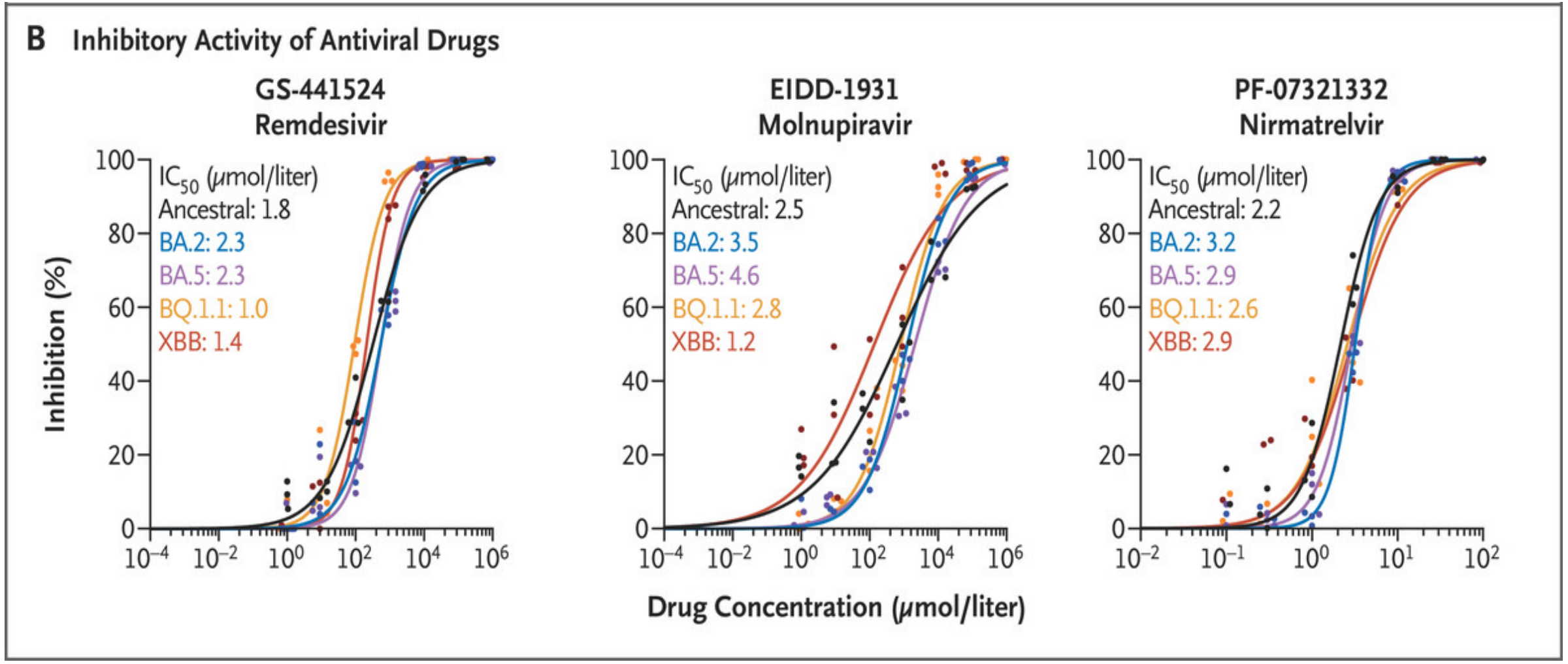
AGENZIA ITALIANA DEL FARMACO

In che tipologia di pazienti si possono usare gli antivirali?

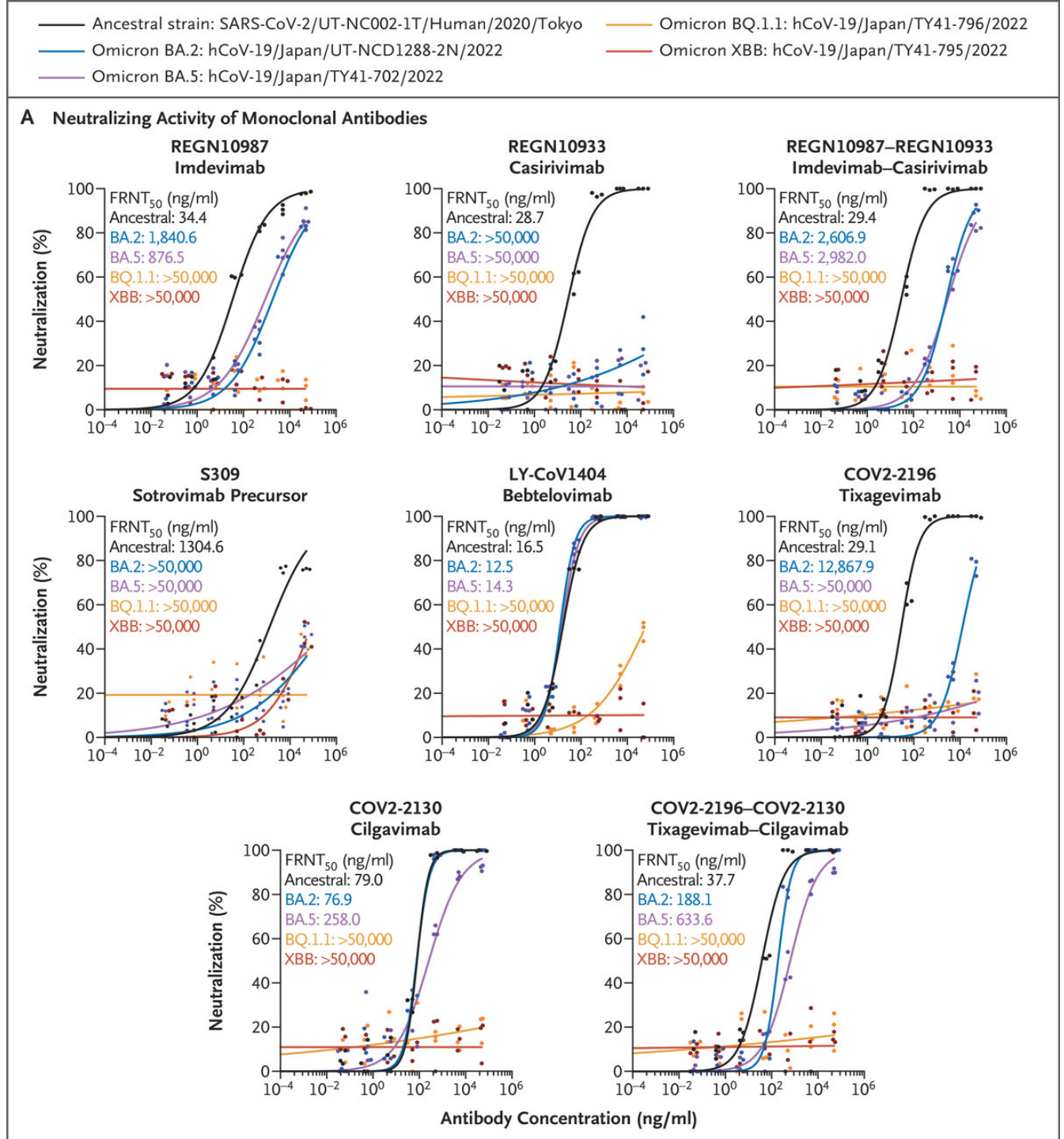
Il paziente **non deve essere ospedalizzato** a causa di COVID-19, deve presentare una forma di **grado lieve-moderato** e almeno uno fra i seguenti fattori di rischio associati all'evoluzione in malattia severa:

- Patologia oncologica/oncoematologica in fase attiva
- Insufficienza renale cronica
- Broncopneuomopatia cronica ostruttiva e/o altra malattia
- Malattia respiratoria cronica (ad es. soggetti affetti da asma, fibrosi polmonare o che necessitano di ossigenoterapia per ragioni differenti da SARS-CoV-2)
- Immunodeficienza primaria o acquisita
- Obesità (BMI >30)
- Malattia cardio-cerebrovascolare (scompenso cardiaco, malattia coronarica, cardiomiopatia, ipertensione con concomitante danno d'organo, ictus)
- Diabete mellito non compensato (HbA1c>9.0% 75 mmol/mol) o con complicanze croniche
- Età >65 anni
- Epatopatia cronica
- Emoglobinopatie
- Patologie del neurosviluppo e patologie neurodegenerative

In Vitro Efficacy of Therapeutic Monoclonal Antibodies and Antiviral Drugs against Omicron Subvariants.

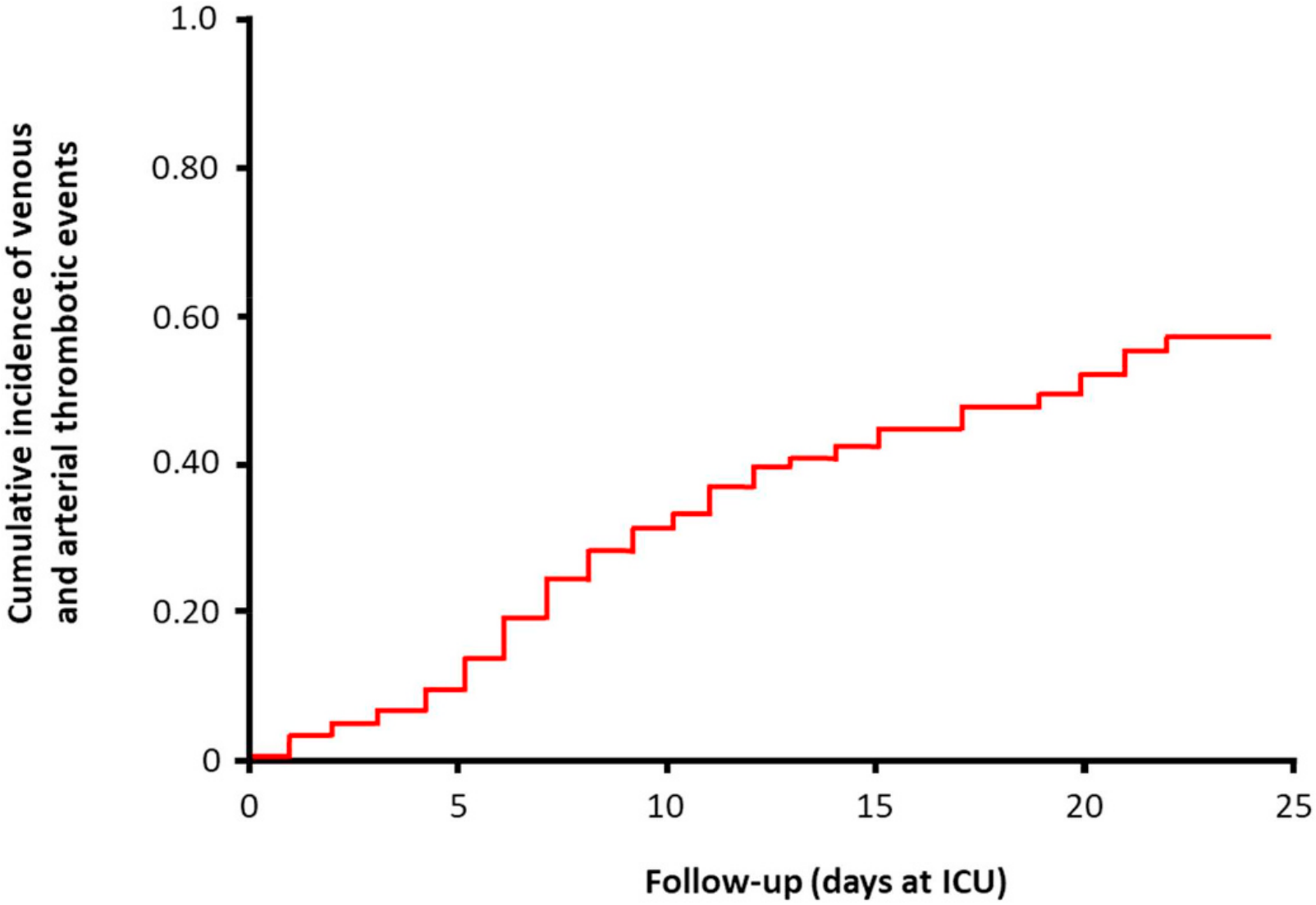


M Imai et al. N Engl J Med 2022.


Ancestral strain: SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo
Omicron BA.2: hCoV-19/Japan/UT-NCD1288-2N/2022
Omicron BA.5: hCoV-19/Japan/TY41-702/2022
Omicron BQ.1.1: hCoV-19/Japan/TY41-796/2022
Omicron XBB: hCoV-19/Japan/TY41-795/2022
A Neutralizing Activity of Monoclonal Antibodies
REGN10987
Imdevimab
FRNT50 (ng/ml)
Ancestral: 34.4
BA.2: 1,840.6
BA.5: 876.5
BQ.1.1: >50,000
XBB: >50,000
REGN10933
Casirivimab
FRNT50 (ng/ml)
Ancestral: 28.7
BA.2: >50,000
BA.5: >50,000
BQ.1.1: >50,000
XBB: >50,000
REGN10987–REGN10933
Imdevimab–Casirivimab
FRNT50 (ng/ml)
Ancestral: 29.4
BA.2: 2,606.9
BA.5: 2,982.0
BQ.1.1: >50,000
XBB: >50,000
S309
Sotrovimab Precursor
FRNT50 (ng/ml)
Ancestral: 1304.6
BA.2: >50,000
BA.5: >50,000
BQ.1.1: >50,000
XBB: >50,000
LY-CoV1404
Bebtelovimab
FRNT50 (ng/ml)
Ancestral: 16.5
BA.2: 12.5
BA.5: 14.3
BQ.1.1: >50,000
XBB: >50,000
COV2-2196
Tixagevimab
FRNT50 (ng/ml)
Ancestral: 29.1
BA.2: 12,867.9
BA.5: >50,000
BQ.1.1: >50,000
XBB: >50,000
COV2-2130
Cilgavimab
FRNT50 (ng/ml)
Ancestral: 79.0
BA.2: 76.9
BA.5: 258.0
BQ.1.1: >50,000
XBB: >50,000
COV2-2196–COV2-2130
Tixagevimab–Cilgavimab
FRNT50 (ng/ml)
Ancestral: 37.7
BA.2: 188.1
BA.5: 633.6
BQ.1.1: >50,000
XBB: >50,000
Neutralization (%)
Antibody Concentration (ng/ml)

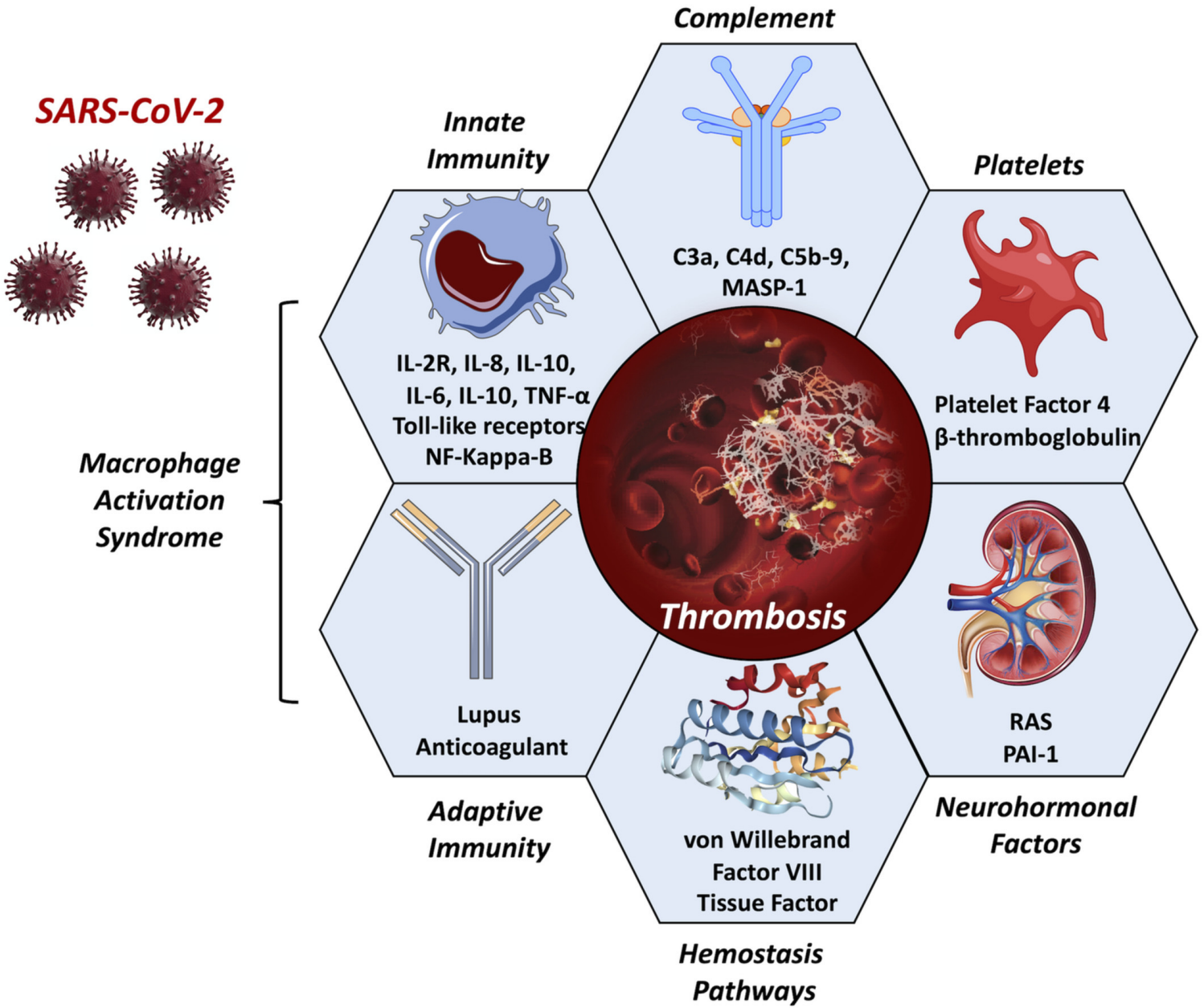
Eparine

Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.



Klok FA, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020 Jul;191:148-150.

Eparine



Hanff, TC, et al. Thrombosis in COVID-19. *Am J Hematol*. 2020; 95: 1578– 1589.

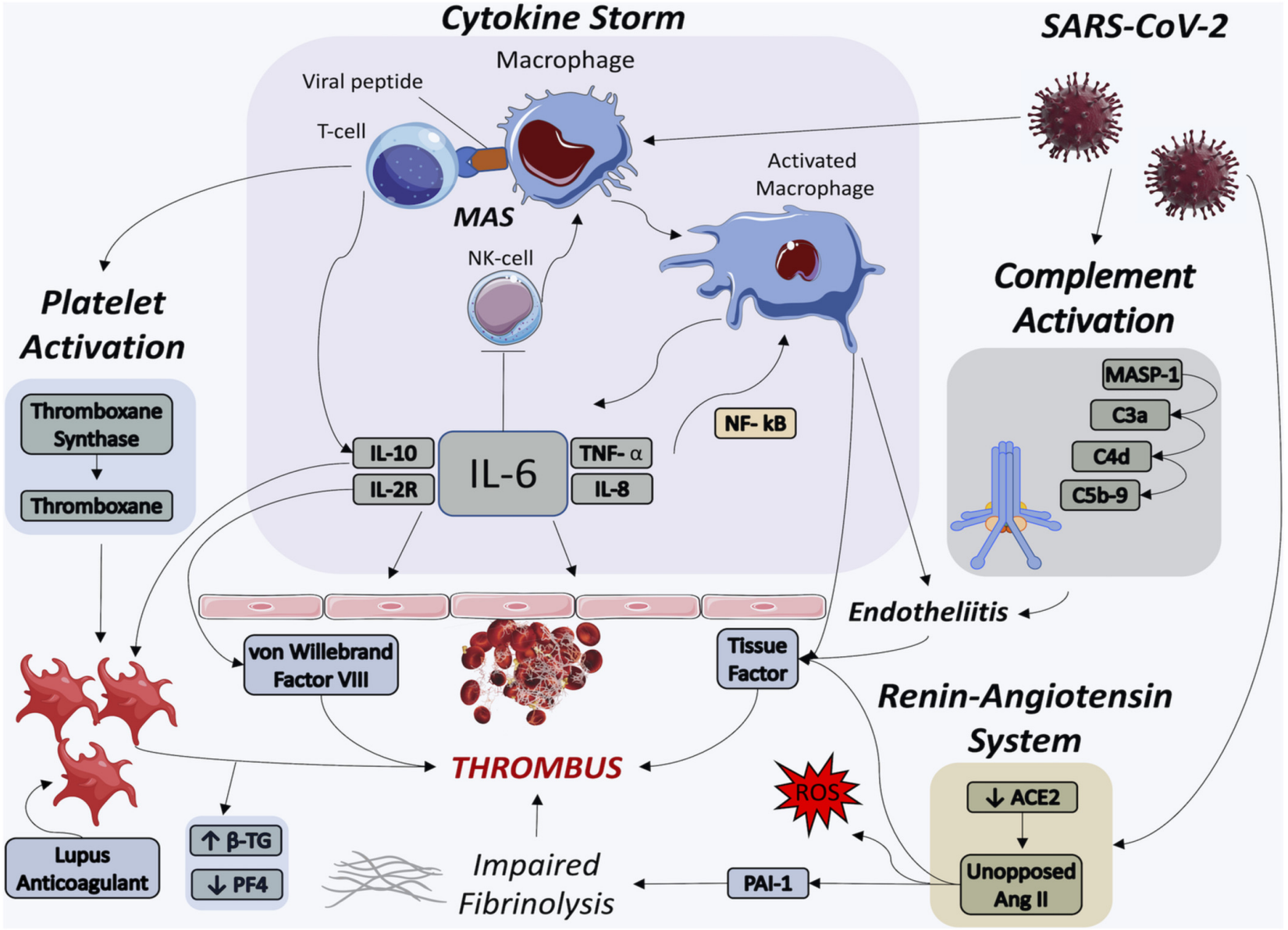
Eparine

Biomarkers of inflammation, coagulopathy, and renin-angiotensin system activity of interest in COVID-19

Inflammation	Coagulopathy	Renin angiotensin system activity
IL-2R	Prothrombin time	Angiotensin II
IL-6	Activated partial-thromboplastin time	Angiotensin converting enzyme 2
IL-8	D-dimer	
IL-10	Plasminogen activator inhibitor 1	
TNF-α	Platelet count	
Ferritin	Fibrinogen (↑ or ↓)[a]	
Transforming growth factor-β	Fibrin degradation products	
Erythrocyte sedimentation rate	von Willebrand factor	
C-reactive protein	Factor VIII	

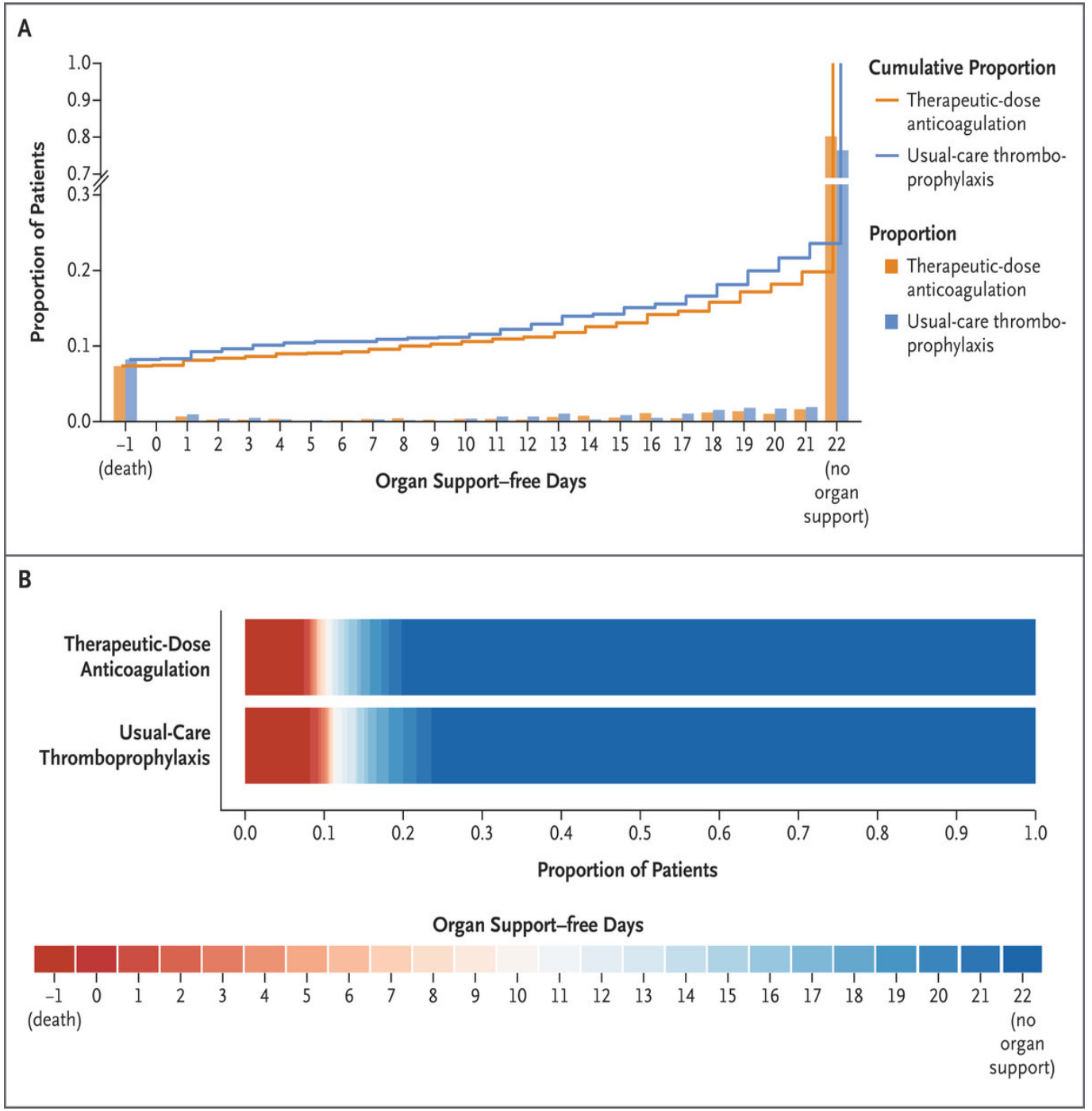
Hanff, TC, et al. Thrombosis in COVID-19. *Am J Hematol*. 2020; 95: 1578– 1589.

Eparine



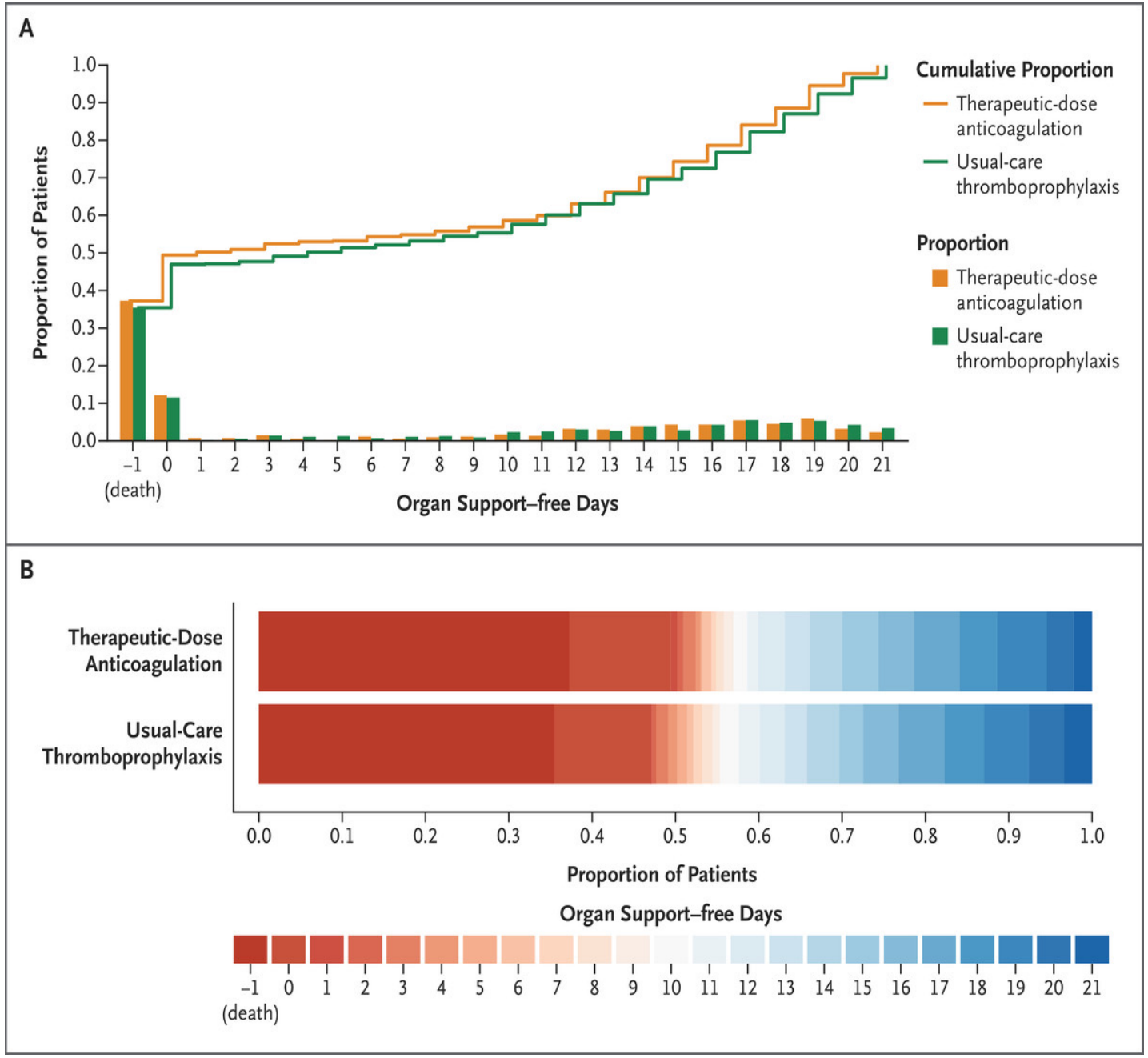
Hanff, TC, et al. Thrombosis in COVID-19. *Am J Hematol*. 2020; 95: 1578– 1589.

Days without Organ Support among All the Patients with Moderate Disease.



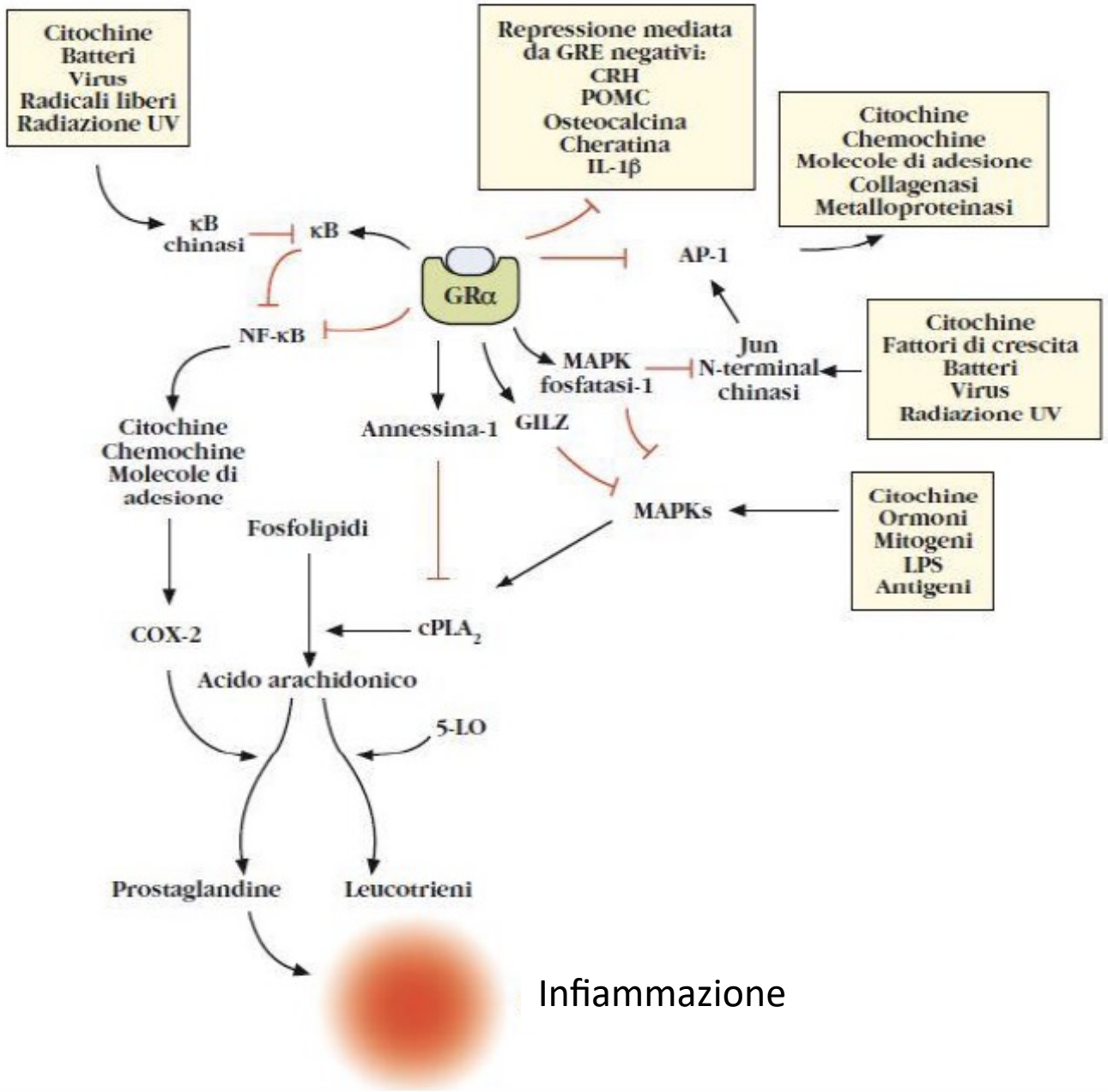
ATTACC Investigators et al., Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 26;385(9):790-802.

Organ Support–free Days Up to Day 21 in Critically Ill Patients with Covid-19.



REMAP-CAP Investigators et al., Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 26;385(9):777-789.

Corticosteroidi:



⊥ Inibizione

↓ Stimolazione

RECOVERY

Randomised Evaluation of COVID-19 Therapy

HAVE YOU BEEN ADMITTED TO HOSPITAL WITH SUSPECTED OR CONFIRMED COVID-19?

Are you interested in research?

We still have so much to learn about effective treatments for COVID-19.

Oxford University is running the **RECOVERY** Trial which will enable reliable assessment of the effects of multiple different treatments on major outcomes among people with suspected or confirmed COVID-19.

Some of the treatments will be drugs used for other conditions, other new drugs may become available during the trial.

All patients participating in the trial will receive usual standard of care.

We need your help

If you are interested in joining the **RECOVERY** Trial, please ask your medical team for information about the trial.

UNIVERSITY OF OXFORD

RECOVERY Poster

V3.0 11-Nov-2020

- Aspirin
- Azithromycin
- Colchicine
- Convalescent Plasma
- Dexamethasone
- Hydroxychloroquine
- Lopinavir-Ritonavir
- Regeneron's Monoclonal Antibody Combination
- Tocilizumab

www.recoverytrial.net

GLOBAL CUMULATIVE TOTALS

43988 Participants

187 Active sites

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexamethasone in Hospitalized Patients with Covid-19

BACKGROUND Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

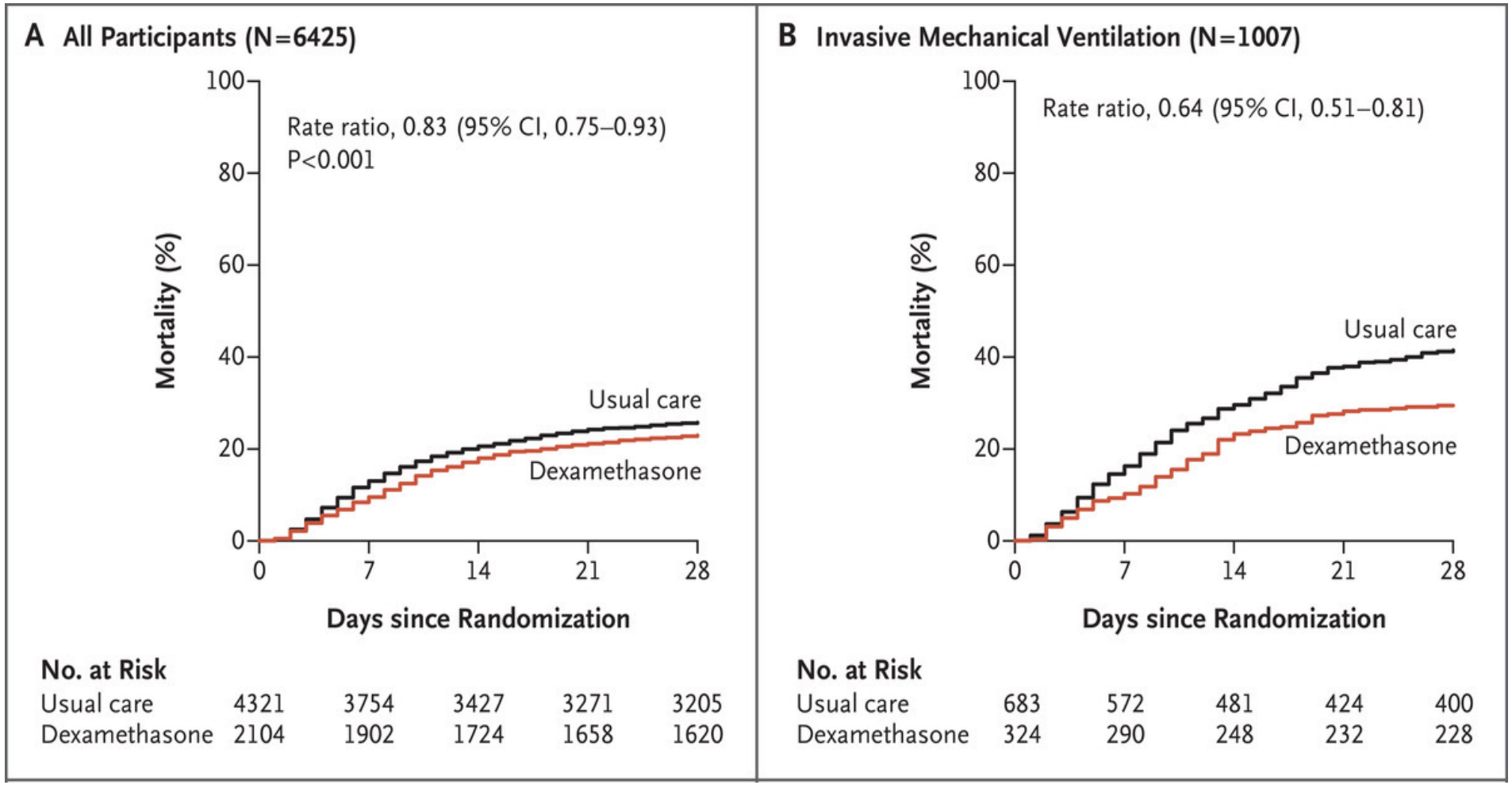
METHODS In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality.

RESULTS A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55).

CONCLUSIONS

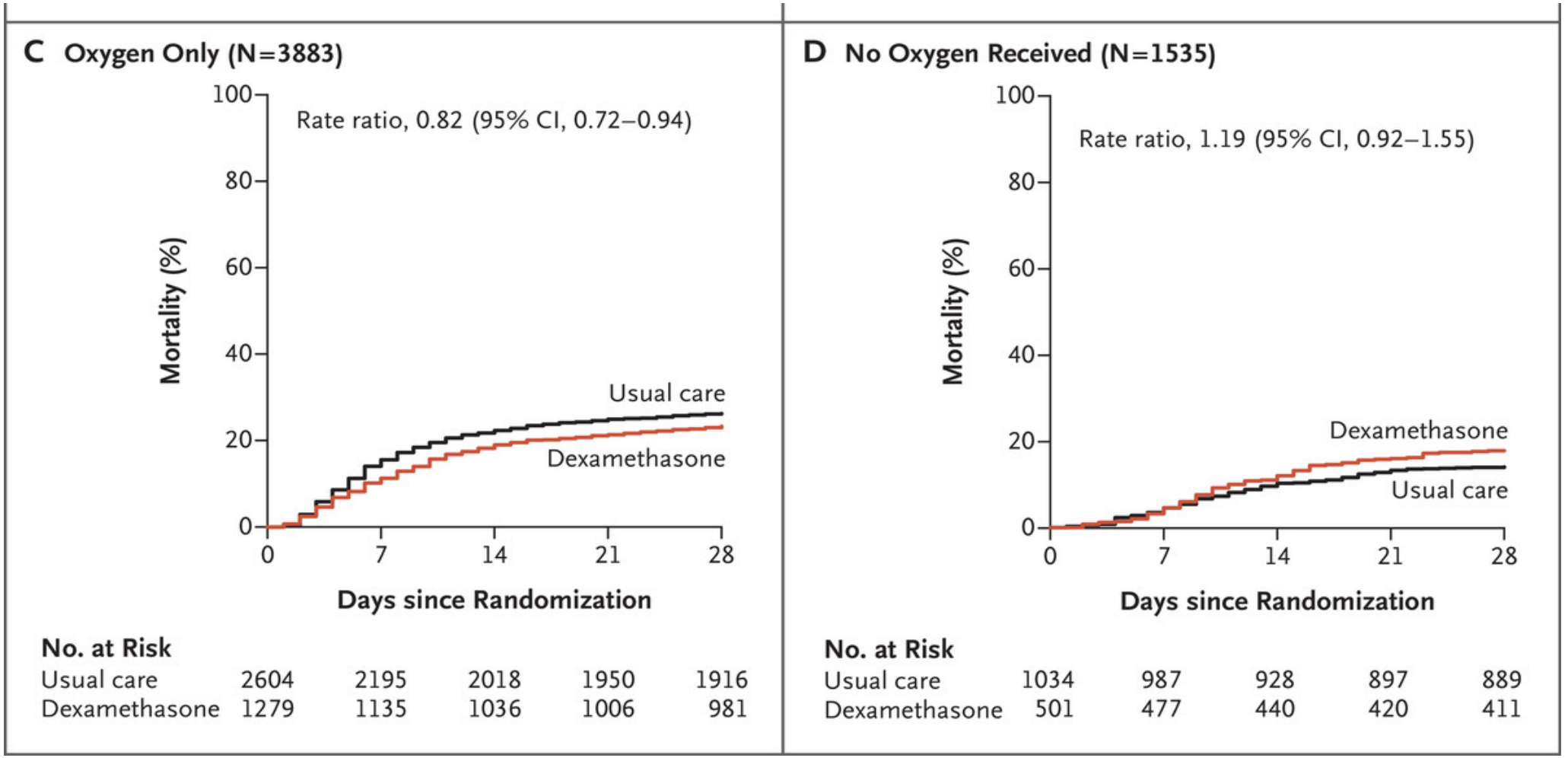
In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support

Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.



The RECOVERY Collaborative Group. N Engl J Med 2021;384:693-704.

Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

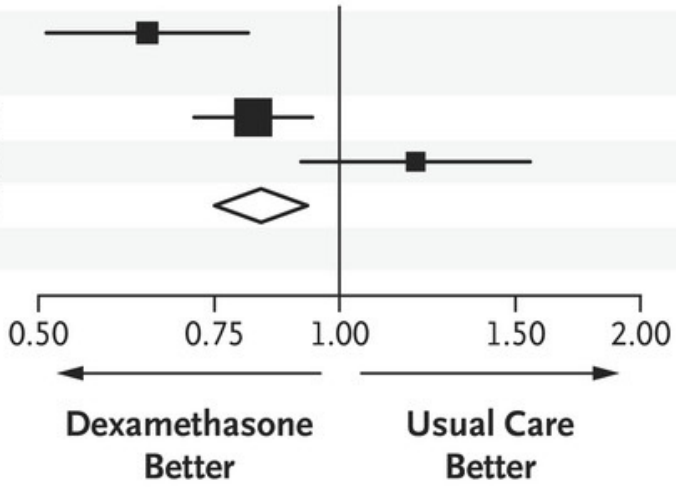


The RECOVERY Collaborative Group. N Engl J Med 2021;384:693-704.

Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.92–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.6



The RECOVERY Collaborative Group. N Engl J Med 2021;384:693-704.

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Objective To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality.

Design, Setting, and Participants Prospective meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The trials were conducted in 12 countries from February 26, 2020, to June 9, 2020, and the date of final follow-up was July 6, 2020. Pooled data were aggregated from the individual trials, overall, and in predefined subgroups. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool. Inconsistency among trial results was assessed using the I^2 statistic. The primary analysis was an inverse variance–weighted fixed-effect meta-analysis of overall mortality, with the association between the intervention and mortality quantified using odds ratios (ORs). Random-effects meta-analyses also were conducted (with the Paule-Mandel estimate of heterogeneity and the Hartung-Knapp adjustment) and an inverse variance–weighted fixed-effect analysis using risk ratios.

Exposures Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients).

Main Outcomes and Measures The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events.

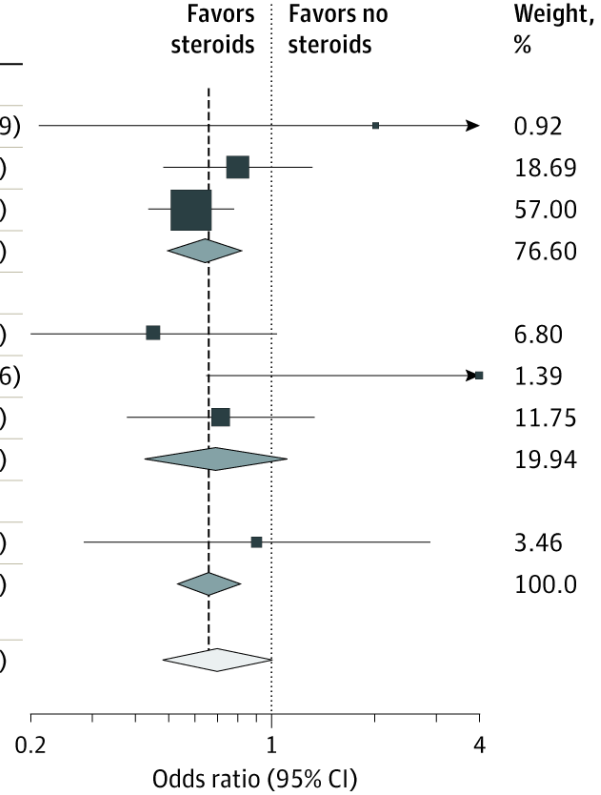
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Results A total of 1703 patients (median age, 60 years [interquartile range, 52-68 years]; 488 [29%] women) were included in the analysis. Risk of bias was assessed as "low" for 6 of the 7 mortality results and as "some concerns" in 1 trial because of the randomization method. Five trials reported mortality at 28 days, 1 trial at 21 days, and 1 trial at 30 days. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; $P < .001$ based on a fixed-effect meta-analysis). There was little inconsistency between the trial results ($I^2 = 15.6\%$; $P = .31$ for heterogeneity) and the summary OR was 0.70 (95% CI, 0.48-1.01; $P = .053$) based on the random-effects meta-analysis. The fixed-effect summary OR for the association with mortality was 0.64 (95% CI, 0.50-0.82; $P < .001$) for dexamethasone compared with usual care or placebo (3 trials, 1282 patients, and 527 deaths), the OR was 0.69 (95% CI, 0.43-1.12; $P = .13$) for hydrocortisone (3 trials, 374 patients, and 94 deaths), and the OR was 0.91 (95% CI, 0.29-2.87; $P = .87$) for methylprednisolone (1 trial, 47 patients, and 26 deaths). Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.

Conclusions and Relevance In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients		Odds ratio (95% CI)	Weight, %
			Steroids	No steroids		
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

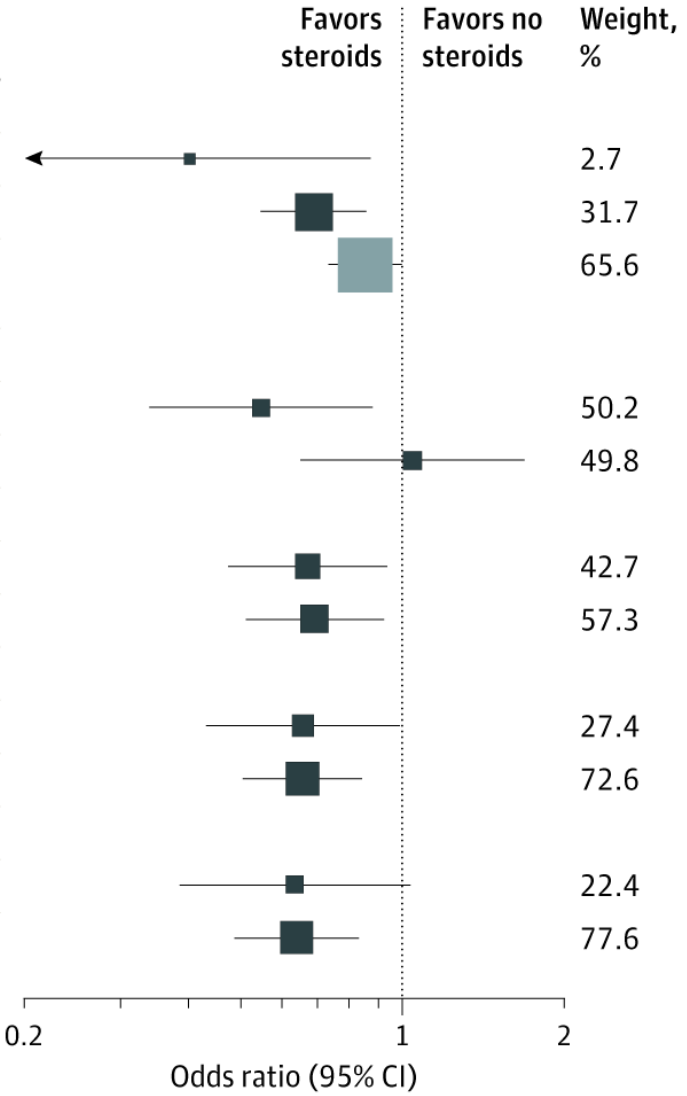


Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid DrugThe area of the data marker for each trial is proportional to its weight in the fixed-effect meta-analysis. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial result is for patients who were receiving invasive mechanical ventilation at randomization. CAPE COVID indicates Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

JAMA. 2020;324(13):1330-1341.

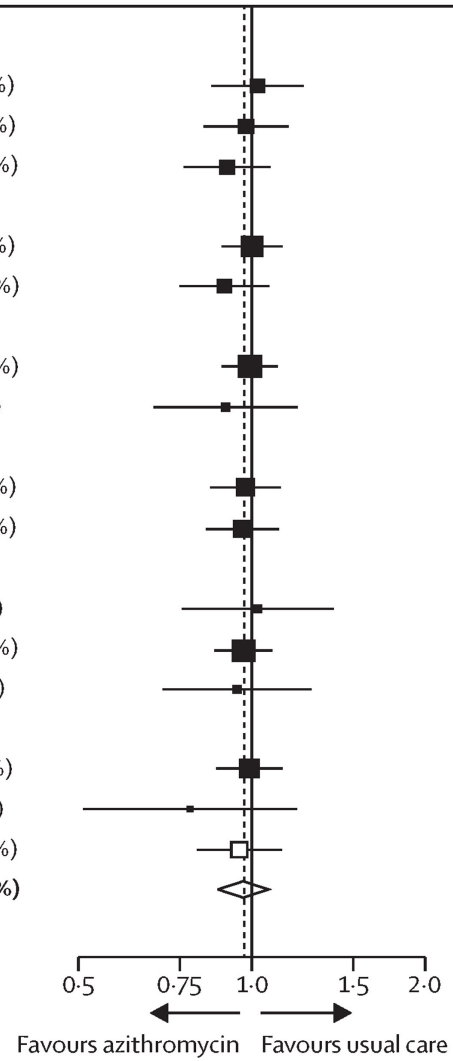
Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization. The area of the data markers is proportional to their weight in the meta-analysis. The estimated odds ratios were derived using fixed-effect meta-analyses across all trials for which data on the specified subgroup were available. The results for patients in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization is shown in a light blue box because these data were not otherwise included in this prospective meta-analysis

Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No (I^2 = 0%)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes (I^2 = 44.1%)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No (I^2 = 0%)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes (I^2 = 0%)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 (I^2 = 0%)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 (I^2 = 49.7%)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female (I^2 = 0%)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male (I^2 = 14.7%)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 (I^2 = 69.1%)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 (I^2 = 0%)	139/418	293/693	0.64 (0.49-0.83)	77.6



JAMA. 2020;324(13):1330-1341.

	Azithromycin group	Usual care group	Rate ratio (95% CI)
Age, years (χ^2_1=0·9; p=0·34)			
<70	173/1508 (11%)	341/3014 (11%)	1·02 (0·85–1·23)
≥70 to <80	206/615 (33%)	399/1167 (34%)	0·98 (0·83–1·16)
≥80	182/459 (40%)	422/1000 (42%)	0·91 (0·76–1·08)
Sex (χ^2_1=1·0; p=0·32)			
Men	391/1604 (24%)	782/3215 (24%)	1·00 (0·89–1·13)
Women	170/978 (17%)	380/1966 (19%)	0·90 (0·75–1·07)
Ethnicity (χ^2_1=0·4; p=0·54)			
White	458/1961 (23%)	936/3978 (24%)	0·99 (0·89–1·11)
Black, Asian, and minority ethnic	66/372 (18%)	145/737 (20%)	0·90 (0·68–1·20)
Days since symptom onset (χ^2_1=0·0; p=0·91)			
≤7	289/1163 (25%)	599/2354 (25%)	0·98 (0·85–1·12)
>7	272/1418 (19%)	558/2812 (20%)	0·96 (0·83–1·11)
Respiratory support at randomisation (χ^2_1=0·1; p=0·70)			
No oxygen received	66/490 (13%)	120/918 (13%)	1·02 (0·76–1·39)
Oxygen only*	430/1940 (22%)	908/3963 (23%)	0·97 (0·86–1·09)
Invasive mechanical ventilation	65/152 (43%)	134/300 (45%)	0·94 (0·70–1·27)
Use of corticosteroids (χ^2_1=1·1; p=0·30)			
Yes	332/1567 (21%)	682/3171 (22%)	0·99 (0·87–1·13)
No	26/182 (14%)	72/397 (18%)	0·78 (0·51–1·20)
Not recorded	202/828 (24%)	404/1600 (25%)	0·95 (0·80–1·13)
All participants	**561/2582 (22%)**	**1162/5181 (22%)**	**0·97 (0·87–1·07)**
			p=0·50



RECOVERY Collaborative Group. Lancet. 2021 Feb 13;397(10274):605-612.

PRINCIPLE

Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

UNIVERSITY OF OXFORD

Help find treatments for COVID-19 from home

PRINCIPLE is a UK-wide clinical study from the University of Oxford to find COVID-19 treatments for recovery at home.

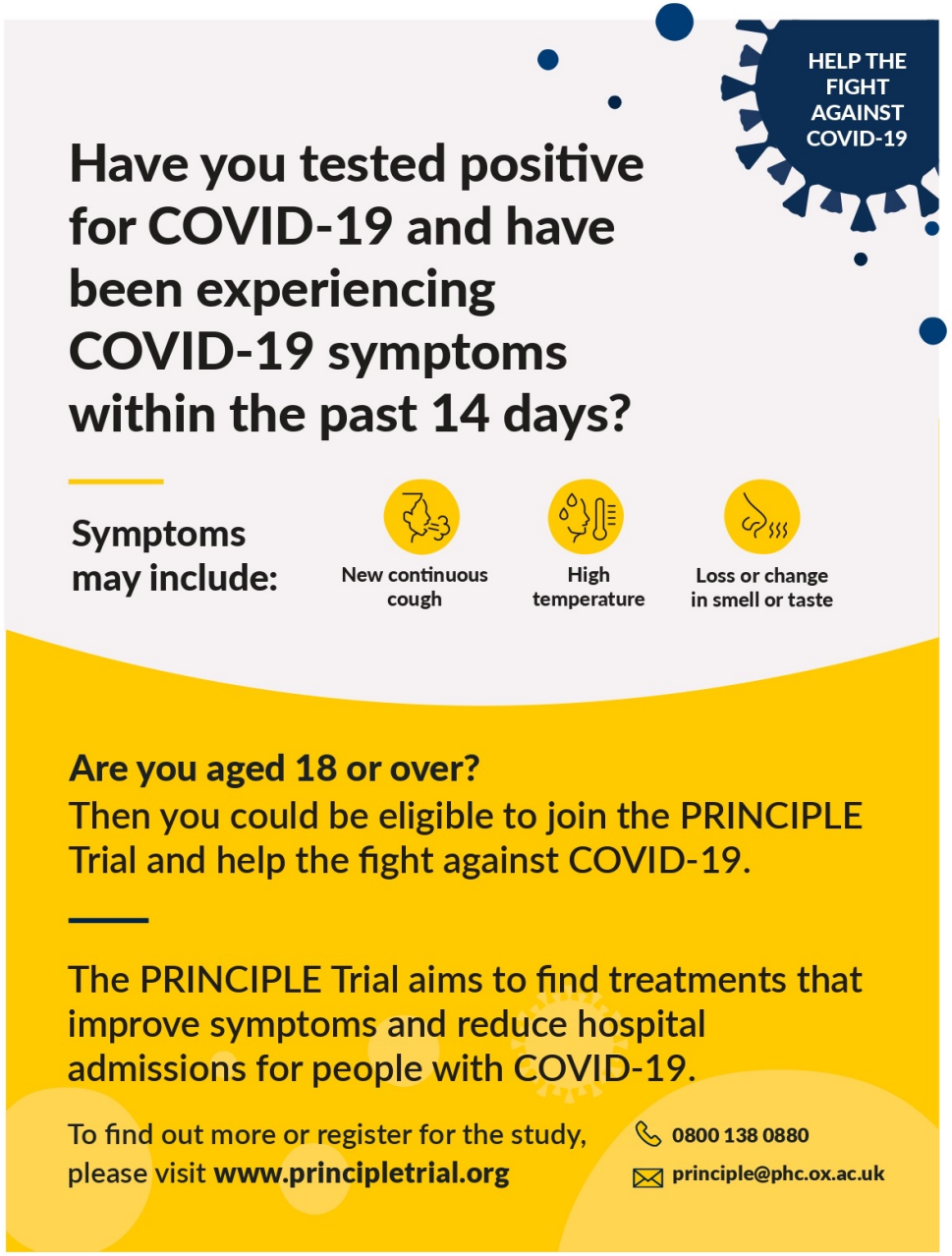
We are looking for medicines that can help people with COVID-19 symptoms get better quickly and stop them needing to go to hospital. PRINCIPLE is recruiting participants through this website and also through GP practices across the UK.

PRINCIPLE is open to all with ongoing symptoms of COVID-19, regardless of vaccination status.

7,006

PARTICIPANTS RECRUITED

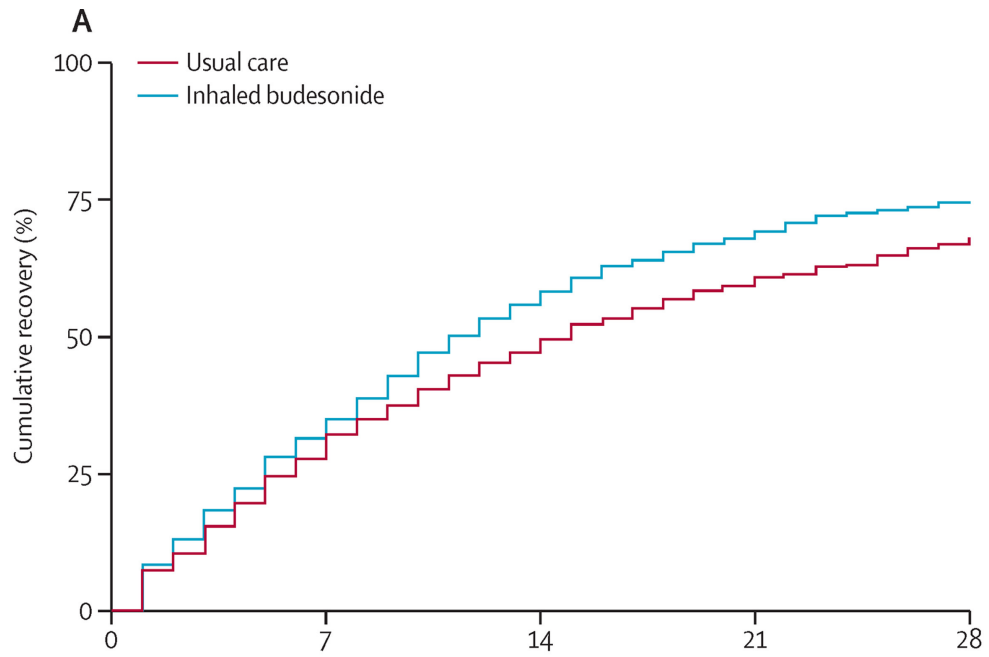
https://www.principletrial.org



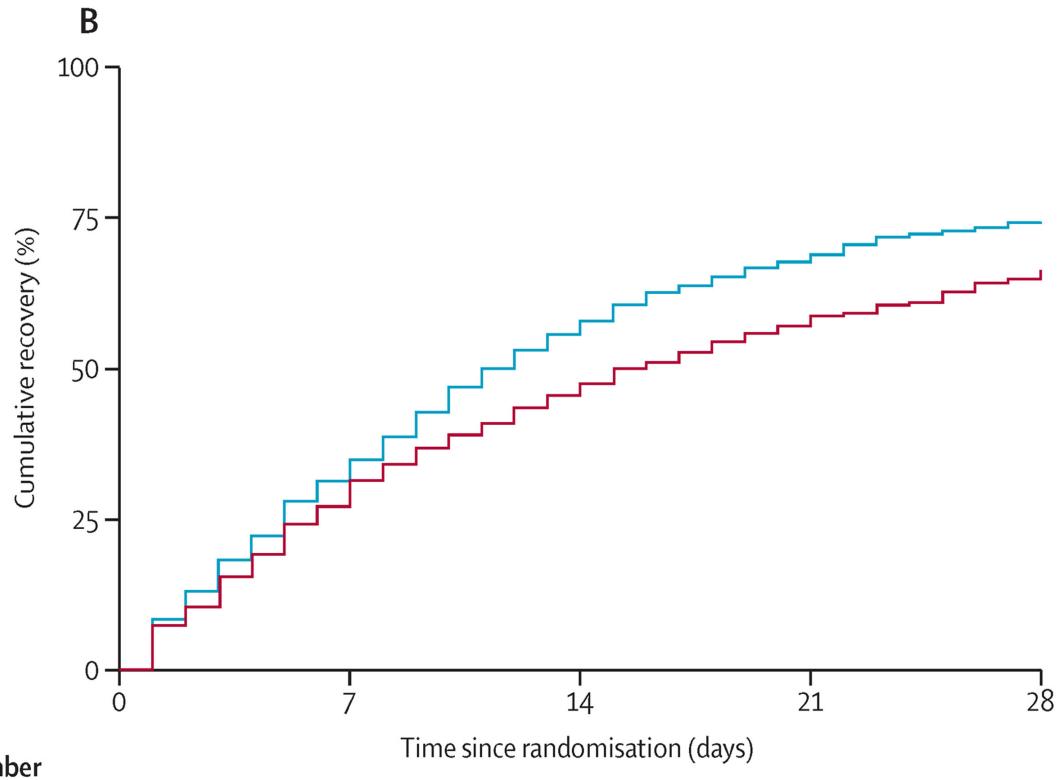
- Inhaled budesonide
- Colchicine
- Azithromycin
- Doxycycline
- Favipiravir (an antiviral drug)
- Ivermectin (used to treat several types of parasitic infections)
- The usual standard of NHS care

https://www.principletrial.org

Inhalated budesonide: PRINCIPLE trial



Cumulative number not yet recovered (recovered)					
Inhaled budesonide	787 (0)	529 (272)	328 (446)	235 (526)	186 (566)
Usual care	1069 (0)	762 (341)	550 (522)	416 (637)	334 (710)

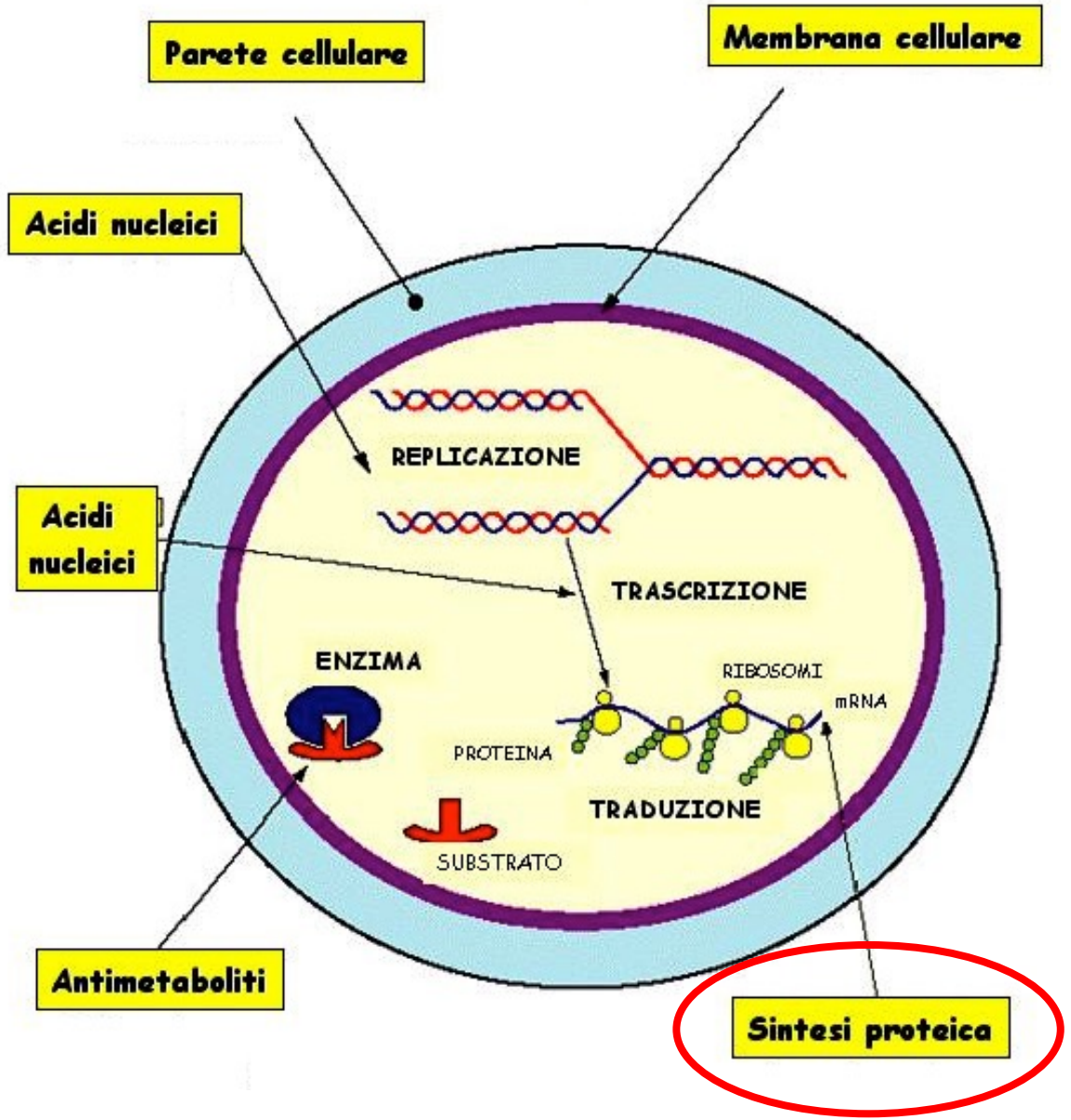


Cumulative number not yet recovered (recovered)					
Inhaled budesonide	787 (0)	529 (272)	328 (446)	235 (526)	186 (566)
Usual care	838 (0)	601 (262)	442 (394)	342 (483)	275 (544)

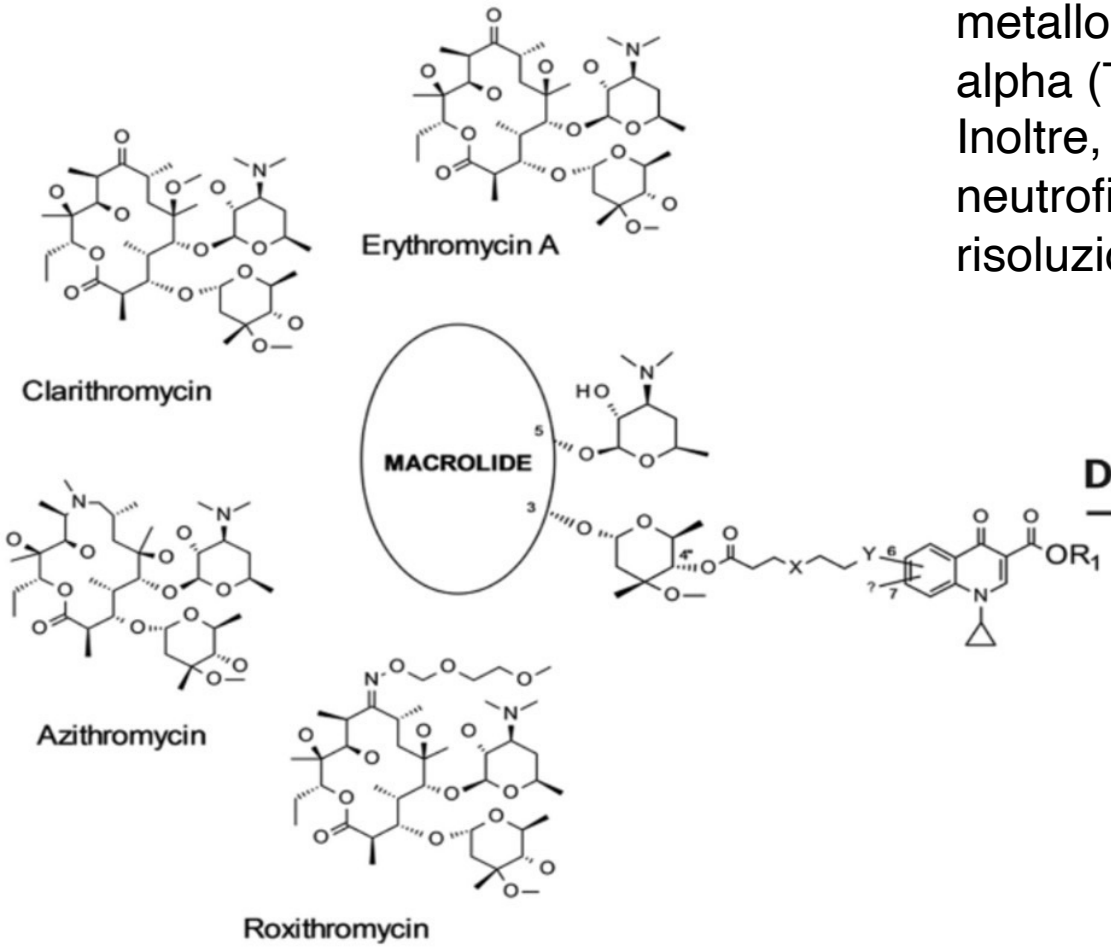
Yu et al., Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021 Sep 4;398(10303):843-855.

Azitromicina: qual è il razionale per la terapia nel COVID-19?

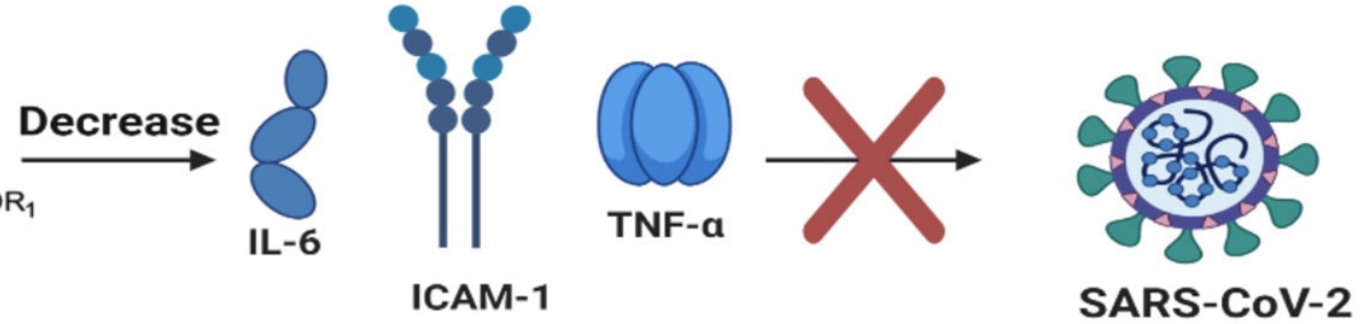
Esistono prove che gli antibiotici macrolidi esercitino effetti benefici nei pazienti con malattie polmonari infiammatorie oltre alla loro capacità di inibire la replicazione dei batteri patogeni.
Studi in vitro e in vivo hanno dimostrato che i macrolidi mitigano l'infiammazione e modulano il sistema immunitario; in particolare essi si sono mostrati in grado di causare la down-regulation delle molecole di adesione della superficie cellulare, ridurre la produzione di citochine pro-infiammatorie, stimolare la fagocitosi da parte dei macrofagi alveolari e inibire l'attivazione e la mobilizzazione dei neutrofili. Il meccanismo con cui i macrolidi esercitano questi effetti antinfiammatori e immunomodulatori non è ben noto.



Effetti antivirali dei macrolidi



È stata studiata la capacità dei macrolidi di ridurre la produzione di metalloproteasi della matrice (MMPs), del tumor necrosis factor-alpha (TNF-a), interleukin (IL)-6 e IL-8.
Inoltre, i macrolidi hanno mostrato di aumentare l'apoptosi dei neutrofili e lo stress ossidativo legato all'infiammazione nella fase di risoluzione di un'infezione.



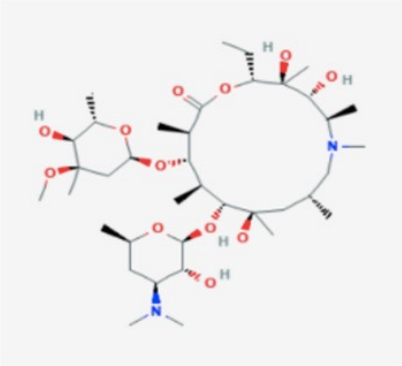
Batiha G-S, et al., (2021). Management of SARS-CoV-2 Infection: Key Focus in Macrolides Efficacy for COVID-19. Front. Med. 8:642313.

Effetti antivirali dell'azitromicina

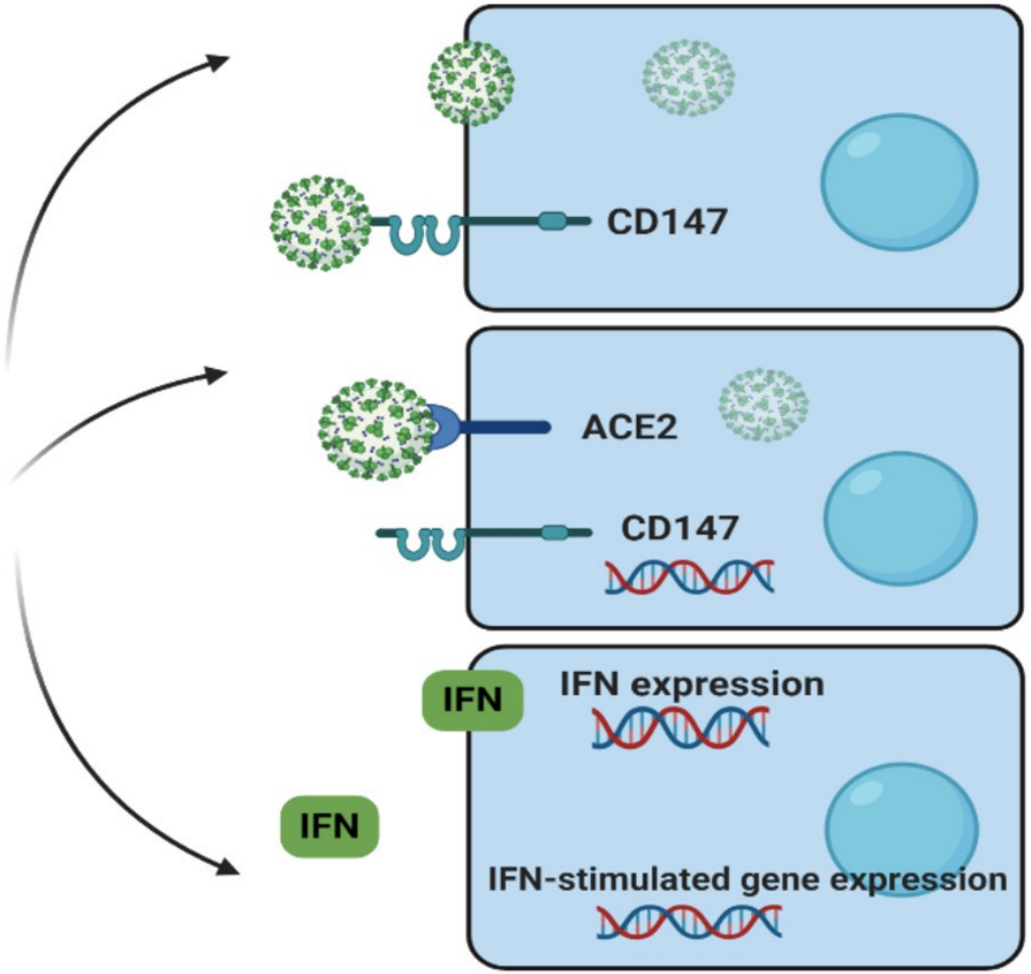
Angiotensin-converting enzyme 2 (ACE2) e cluster differentiation 147 (CD147) (anche noto come EMMPRIN or Basigin) sono recettori dell'ospite e vie per l'invasione da parte di SARS-CoV-2 .

Nelle cellule ospiti, ACE2 o CD147 si legano alla proteina virale spike (S-protein), causando la disseminazione del virus e mediando l'invasione virale all'interno di altre cellule.

Il trattamento con azitromicina causa un significativo incremento nella produzione dell'interferone e dei geni da esso espressi.



Azithromycin



Batiha G-S, et al., (2021). Management of SARS-CoV-2 Infection: Key Focus in Macrolides Efficacy for COVID-19. Front. Med. 8:642313.

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

RECOVERY Collaborative Group*

Lancet 2021; 397: 605–12

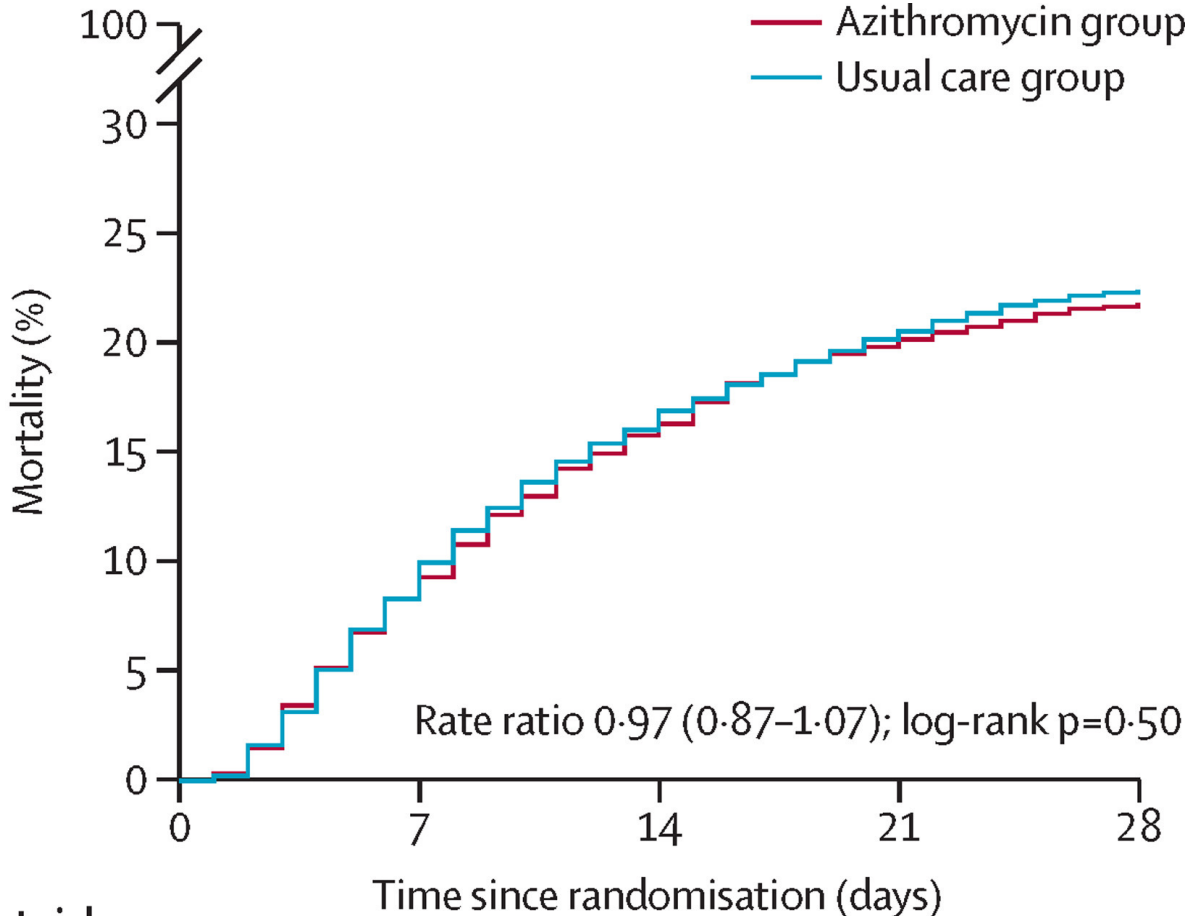
Published Online
February 2, 2021

Background Azithromycin has been proposed as a treatment for COVID-19 on the basis of its immunomodulatory actions. We aimed to evaluate the safety and efficacy of azithromycin in patients admitted to hospital with COVID-19.

Methods In this randomised, controlled, open-label, adaptive platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), several possible treatments were compared with usual care **in patients admitted to hospital** with COVID-19 in the UK. The trial is underway at 176 hospitals in the UK. Eligible and consenting patients were randomly allocated to either usual standard of care alone or usual standard of care plus azithromycin 500 mg once per day by mouth or intravenously **for 10 days or until discharge** (or allocation to one of the other RECOVERY treatment groups). Patients were assigned via unstratified randomisation with allocation concealment and were twice as likely to be randomly assigned to usual care than to any of the active treatment groups. Participants and local study staff were not masked to the allocated treatment, but all others involved in the trial were masked to the outcome data during the trial. The primary outcome was 28-day all-cause mortality, assessed in the intention-to-treat population.

Findings Between April 7 and Nov 27, 2020, of 16 442 patients enrolled in the RECOVERY trial, 9433 (57%) were eligible and 7763 were included in the assessment of azithromycin. The mean age of these study participants was 65·3 years (SD 15·7) and approximately a third were women (2944 [38%] of 7763). 2582 patients were randomly allocated to receive azithromycin and 5181 patients were randomly allocated to usual care alone. Overall, 561 (22%) patients allocated to azithromycin and 1162 (22%) patients allocated to usual care died within 28 days (rate ratio 0·97, 95% CI 0·87–1·07; p=0·50). No significant difference was seen in duration of hospital stay (median 10 days [IQR 5 to >28] *vs* 11 days [5 to >28]) or the proportion of patients discharged from hospital alive within 28 days (rate ratio 1·04, 95% CI 0·98–1·10; p=0·19). Among those not on invasive mechanical ventilation at baseline, no significant difference was seen in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (risk ratio 0·95, 95% CI 0·87–1·03; p=0·24).

Interpretation In patients admitted to hospital with COVID-19, azithromycin did not improve survival or other prespecified clinical outcomes. Azithromycin use in patients admitted to hospital with COVID-19 should be restricted to patients in whom there is a clear antimicrobial indication.



Number at risk					
Azithromycin group	2582	2337	2155	2056	2014
Usual care group	5181	4658	4298	4108	4010

RECOVERY Collaborative Group. Lancet. 2021 Feb 13;397(10274):605-612.

Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

*PRINCIPLE Trial Collaborative Group**

Lancet 2021; 397: 1063–74

Published Online
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Background

Azithromycin, an antibiotic with potential antiviral and anti-inflammatory properties, has been used to treat COVID-19, but evidence from community randomised trials is lacking. We aimed to assess the effectiveness of azithromycin to treat suspected COVID-19 among **people in the community** who had an increased risk of complications.

Methods

In this UK-based, primary care, open-label, multi-arm, adaptive platform randomised trial of interventions against COVID-19 in people at increased risk of an adverse clinical course (PRINCIPLE), we randomly assigned people aged 65 years and older, or 50 years and older with at least one comorbidity, who had been unwell for 14 days or less with suspected COVID-19, to usual care plus azithromycin 500 mg daily for three days, usual care plus other interventions, or usual care alone. The trial had two coprimary endpoints measured within 28 days from randomisation: time to first self-reported recovery, analysed using a Bayesian piecewise exponential, and hospital admission or death related to COVID-19, analysed using a Bayesian logistic regression model. Eligible participants with outcome data were included in the primary analysis, and those who received the allocated treatment were included in the safety analysis.

Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

PRINCIPLE Trial Collaborative Group*

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Published Online
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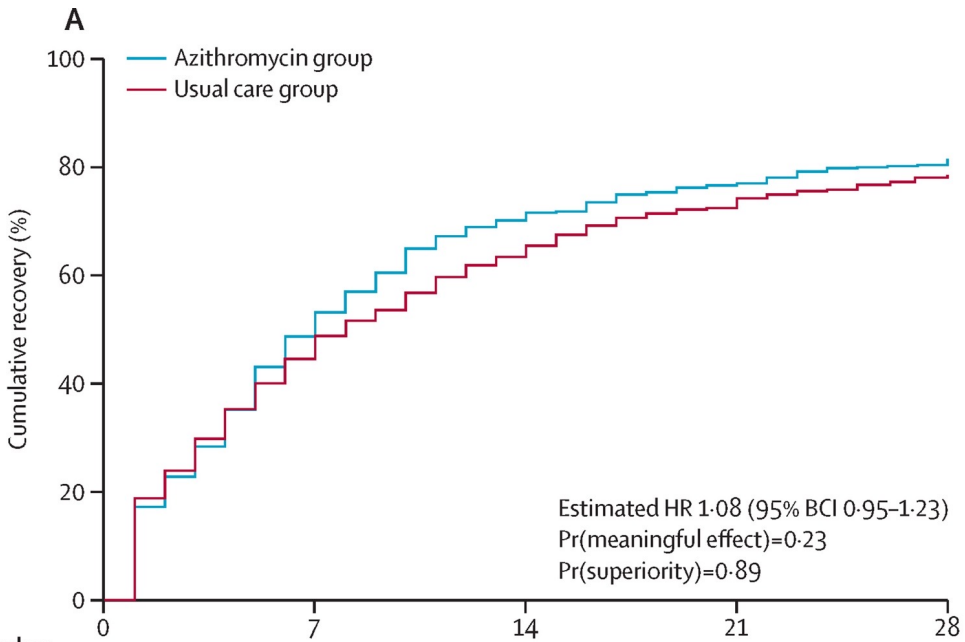
Findings

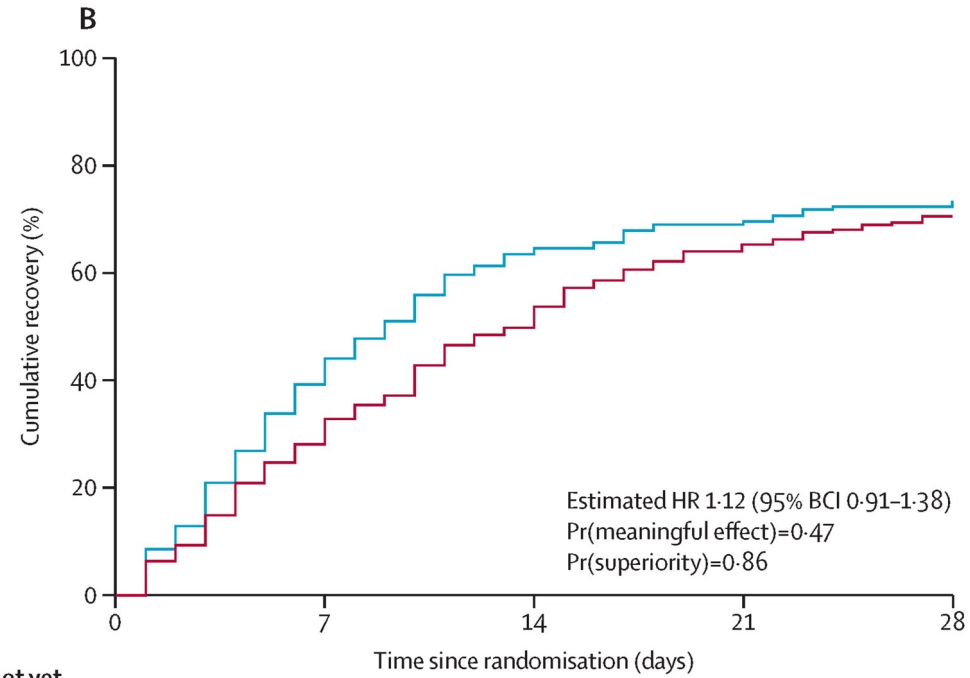
The first participant was recruited to PRINCIPLE on April 2, 2020. The azithromycin group enrolled participants between May 22 and Nov 30, 2020, by which time 2265 participants had been randomly assigned, 540 to azithromycin plus usual care, 875 to usual care alone, and 850 to other interventions. 2120 (94%) of 2265 participants provided follow-up data and were included in the Bayesian primary analysis, 500 participants in the azithromycin plus usual care group, 823 in the usual care alone group, and 797 in other intervention groups. 402 (80%) of 500 participants in the azithromycin plus usual care group and 631 (77%) of 823 participants in the usual care alone group reported feeling recovered within 28 days. We found little evidence of a meaningful benefit in the azithromycin plus usual care group in time to first reported recovery versus usual care alone (hazard ratio 1·08, 95% Bayesian credibility interval [BCI] 0·95 to 1·23), equating to an estimated benefit in median time to first recovery of 0·94 days (95% BCI –0·56 to 2·43). The probability that there was a clinically meaningful benefit of at least 1·5 days in time to recovery was 0·23. 16 (3%) of 500 participants in the azithromycin plus usual care group and 28 (3%) of 823 participants in the usual care alone group were hospitalised (absolute benefit in percentage 0·3%, 95% BCI –1·7 to 2·2). There were no deaths in either study group. Safety outcomes were similar in both groups. Two (1%) of 455 participants in the azothromycin plus usual care group and four (1%) of 668 participants in the usual care alone group reported admission to hospital during the trial, not related to COVID-19.

Interpretation

Our findings do not justify the routine use of azithromycin for reducing time to recovery or risk of hospitalisation for people with suspected COVID-19 in the community. These findings have important antibiotic stewardship implications during this pandemic, as inappropriate use of antibiotics leads to increased antimicrobial resistance, and there is evidence that azithromycin use increased during the pandemic in the UK.

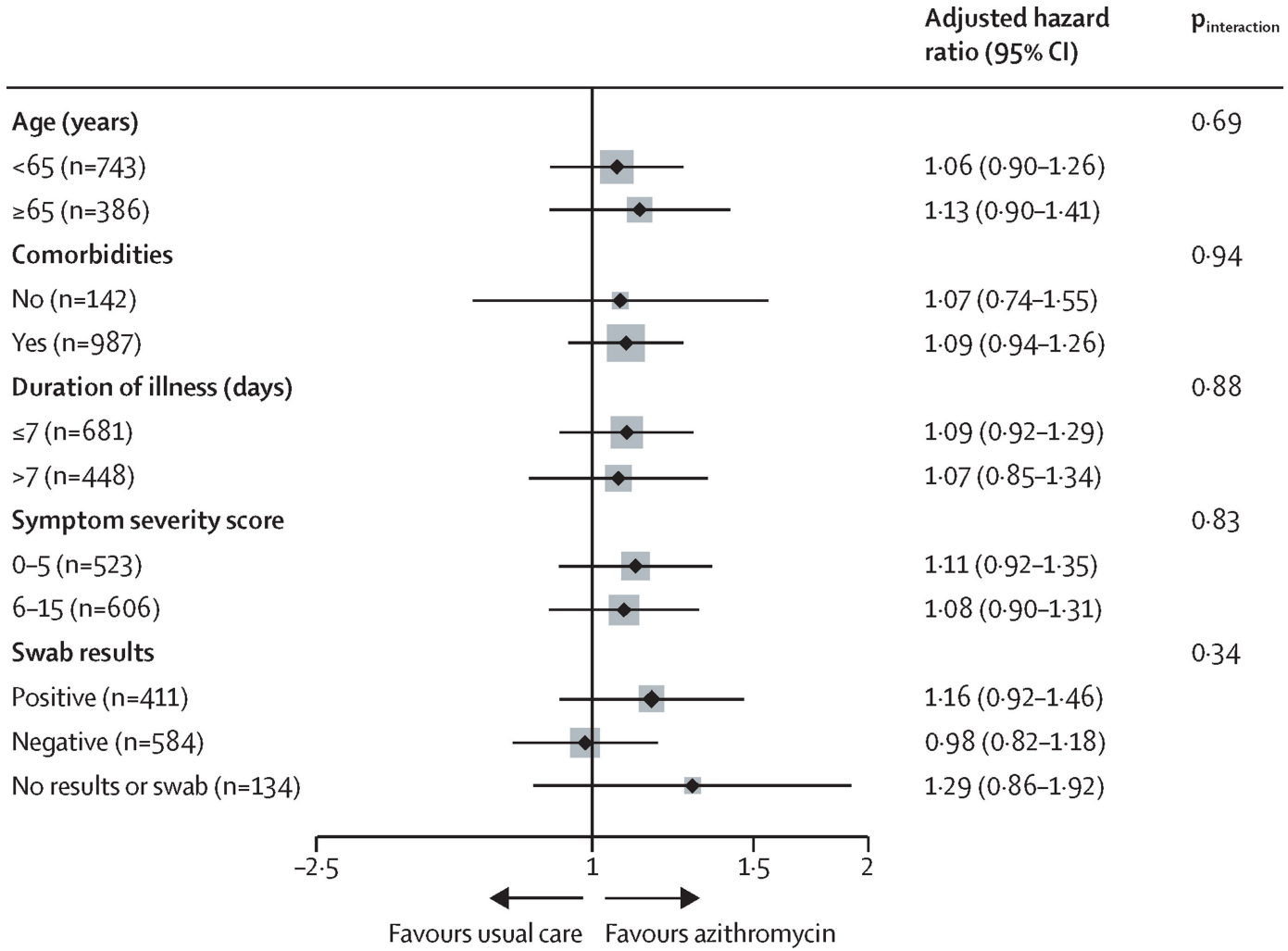


Cumulative number not yet recovered (recovered)					
Azithromycin group	500 (0)	254 (265)	144 (355)	111 (381)	93 (402)
Usual care group	823 (0)	451 (400)	288 (534)	210 (600)	167 (631)



Number not yet recovered (recovered)					
Azithromycin group	186 (0)	113 (82)	67 (120)	56 (129)	50 (136)
Usual care group	236 (0)	168 (77)	115 (125)	80 (151)	65 (163)

PRINCIPLE Trial Collaborative Group. Lancet. 2021 Mar 20;397(10279):1063-1074.



PRINCIPLE Trial Collaborative Group. Lancet. 2021 Mar 20;397(10279):1063-1074.

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

BACKGROUND Hydroxychloroquine and chloroquine have been proposed as treatments for coronavirus disease 2019 (Covid-19) on the basis of in vitro activity and data from uncontrolled studies and small, randomized trials.

METHODS In this randomized, controlled, open-label platform trial comparing a range of possible treatments with usual care in patients hospitalized with Covid-19, we randomly assigned 1561 patients to receive hydroxychloroquine and 3155 to receive usual care. The primary outcome was 28-day mortality.

RESULTS The enrollment of patients in the hydroxychloroquine group was closed on June 5, 2020, after an interim analysis determined that there was a lack of efficacy. Death within 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% confidence interval [CI], 0.97 to 1.23; P=0.15). Consistent results were seen in all prespecified subgroups of patients. The results suggest that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98). Among the patients who were not undergoing mechanical ventilation at baseline, those in the hydroxychloroquine group had a higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; risk ratio, 1.14; 95% CI, 1.03 to 1.27). There was a small numerical excess of cardiac deaths (0.4 percentage points) but no difference in the incidence of new major cardiac arrhythmia among the patients who received hydroxychloroquine.

CONCLUSIONS Among patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care.

Grazie per l’attenzione!

Dott. Daniele Pala