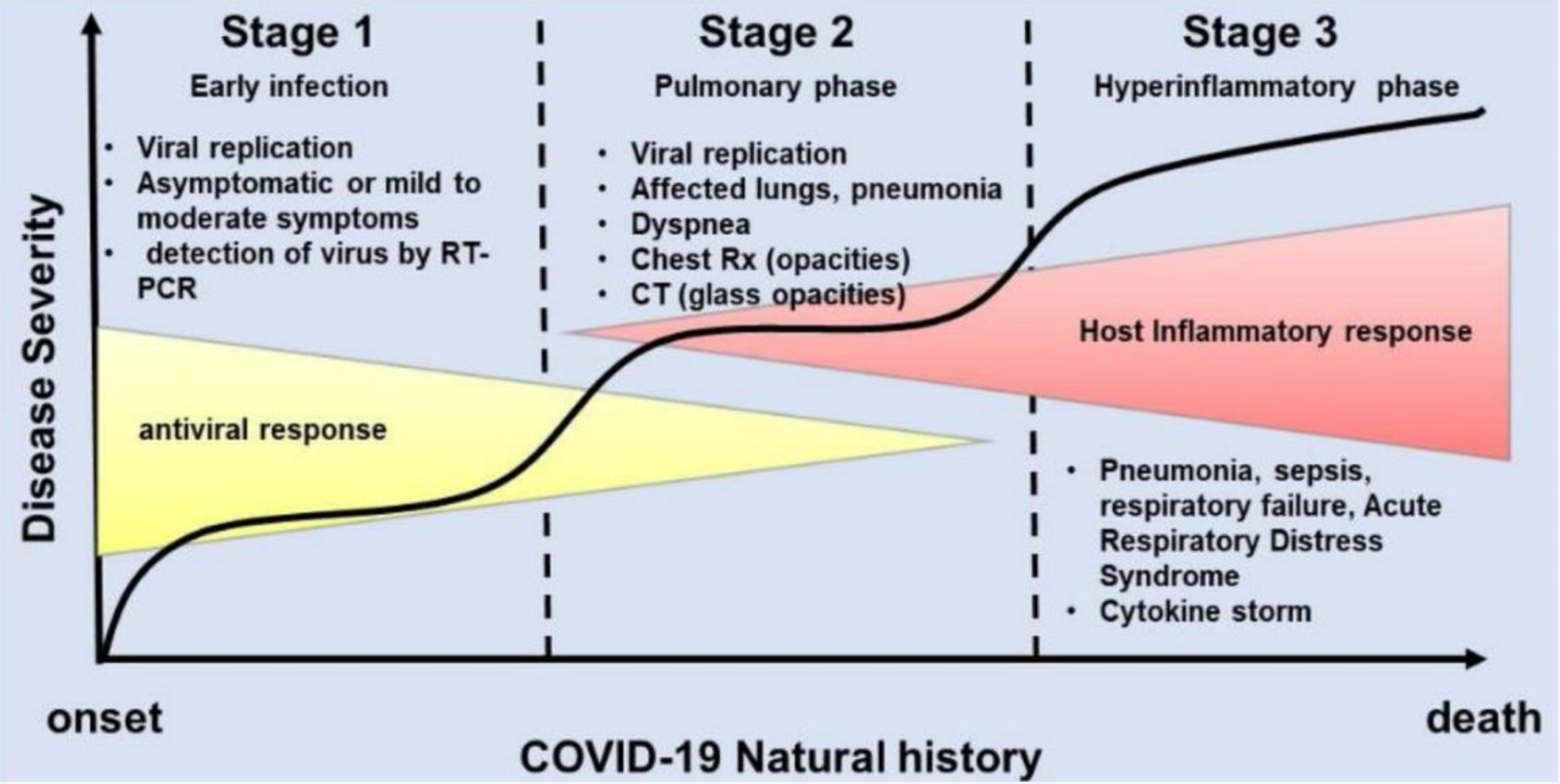
Update of COVID-19 Treatment

전남대학교병원 호흡기 내과

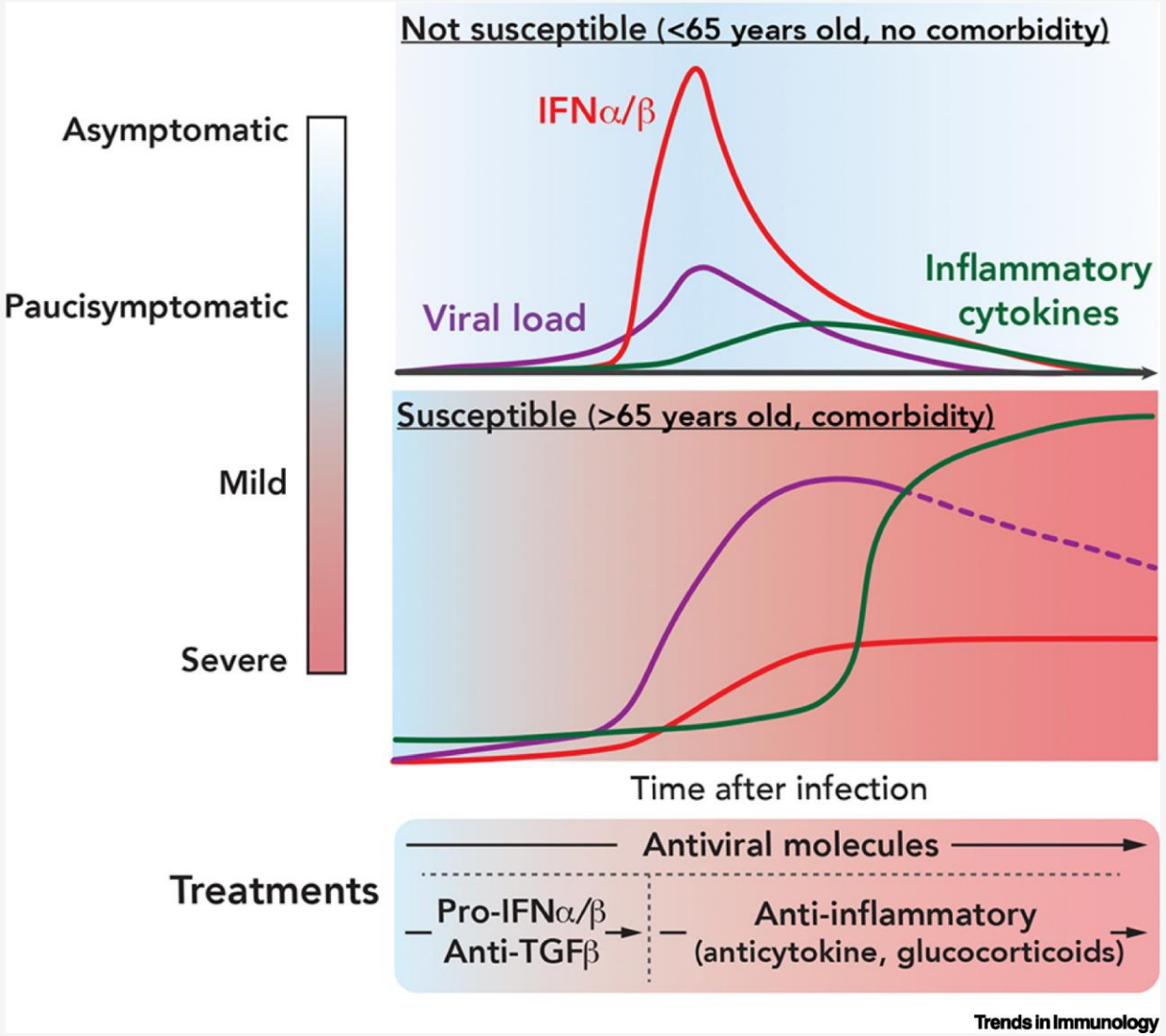
김태옥

Natural history of COVID-19



Biomed Pharmacother. 2020 Sep;129:110493.

Kinetics of COVID-19



Trends Immunol . 2021 Jan;42(1):31-44.

Inhibition of Viral response

- Anti-viral agent
  - Nirmatrelvir/Ritonavir
  - Remdesivir
  - Molnupiravir
- Convalescent plasma
- Monoclonal antibody

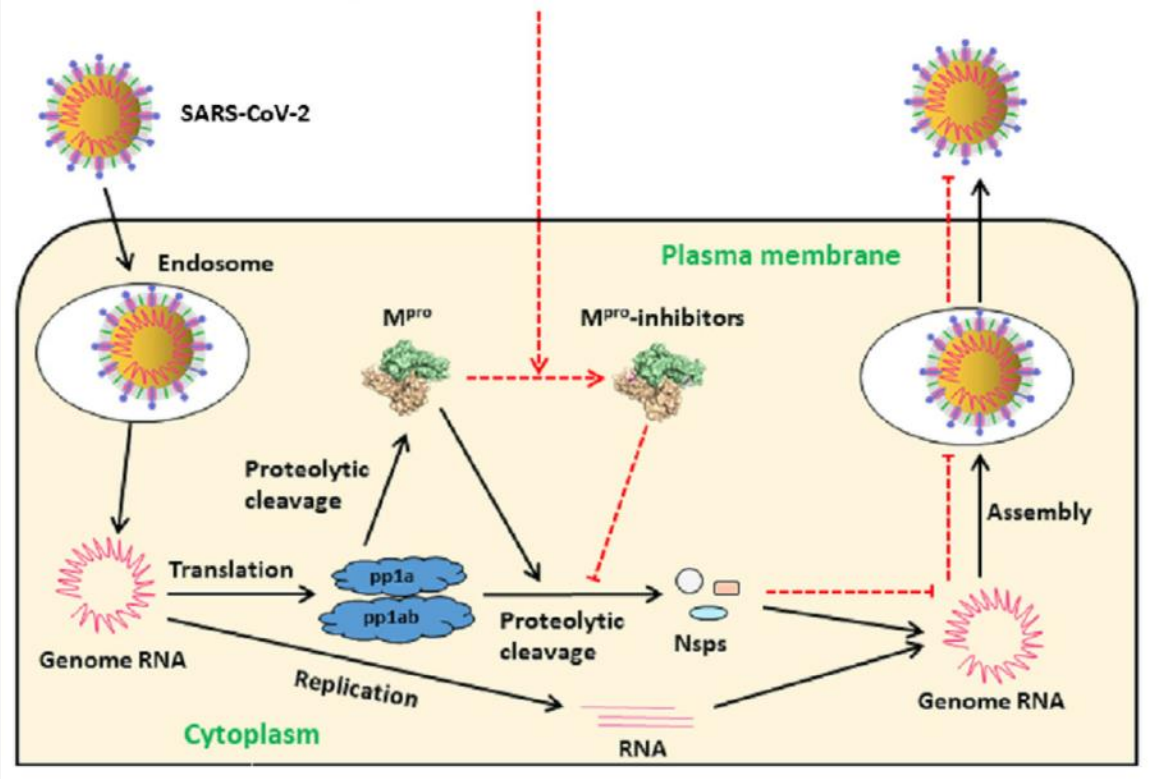
Anti-viral agents

Drug	Recommend	Adverse events	drug-drug interaction
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	FDA, EUA Mild to moderate High risk+≥12yr+≥40kg	Dysgeusia, myalgia Diarrhea, HTN	Carefully review
Remdesivir	FDA High risk+≥12yr+≥40kg	Nausea, AST/ALT, Hypersensitivity	Has not been established
Molnupiravir	FDA, EUA Mild to moderate High risk + ≥18yr	Diarrhea, nausea, dizziness	Has not been established
Interferon alfa/beta	Not approved Not recommended		
Ivermectin	Not approved Not recommended		
Nitazoxanide	Not approved Not recommended		

Last Updated: February 24, 2022; https://www.covid19treatmentguidelines.nih.gov/tables/antiviral-characteristics/

Nirmatrelvir/Ritonavir

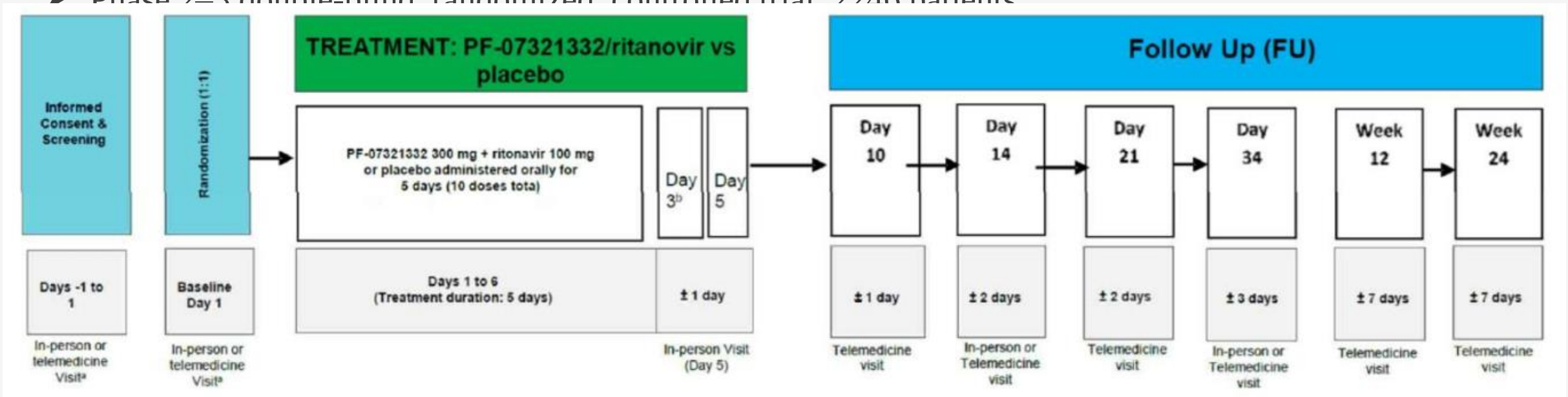
- Orally active form
- Nirmatrelvir
  - SARS-CoV-2 main protease inhibitor
  - Incapable of processing polyprotein precursor
- Ritonavir
  - HIV-1 protease inhibitor and CYP3A inhibitor
  - Increase the level of nirmatrelvir
  - No activity against SARS-CoV-2 Mpro



ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

- Phase 2–3 double-blind, randomized, controlled trial, 2246 patients



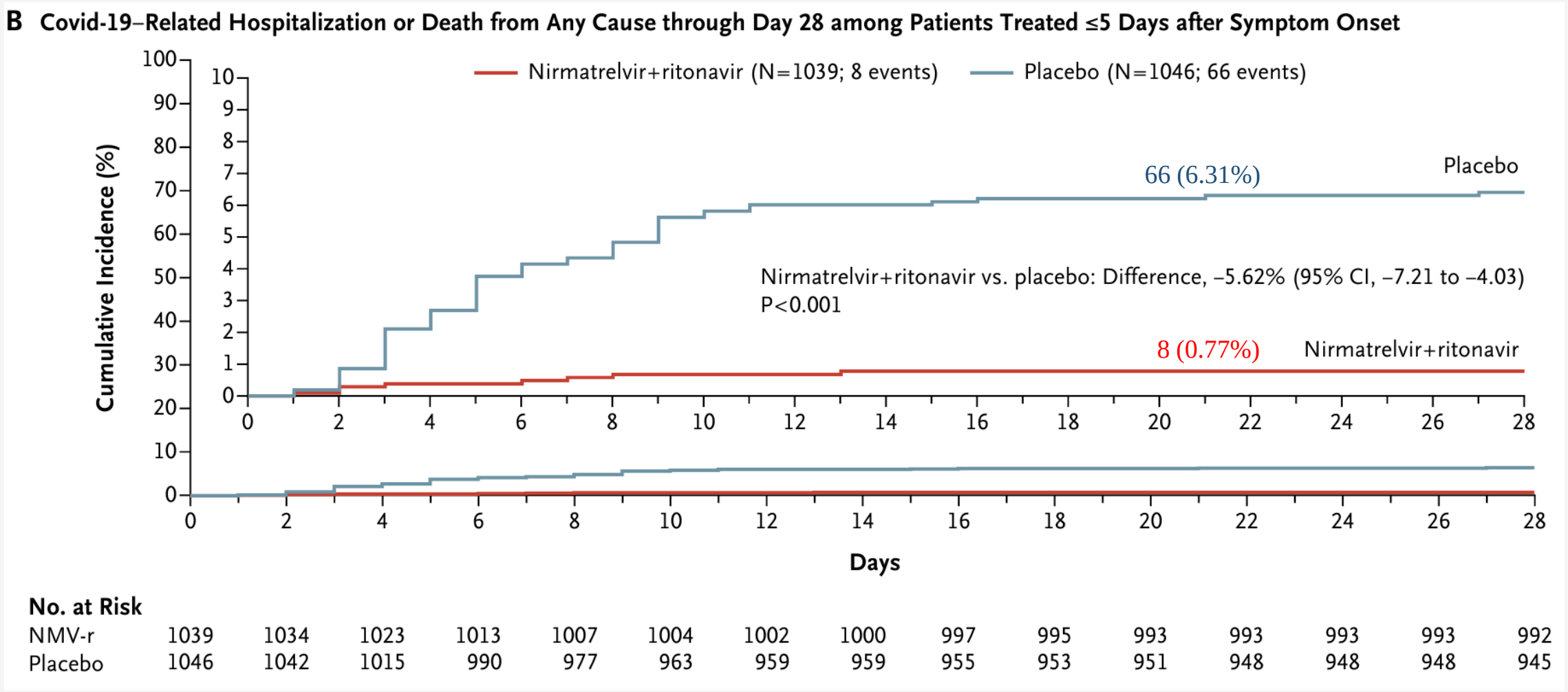
N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542.

Risk factor for progression

- ≥ 60 years of age
- BMI > 25
- Current smoker and history of at least 100 lifetime cigarettes;
- Immunosuppressive disease (eg, bone marrow or organ transplantation or primary immune deficiencies) or prolonged use of immune-weakening medications:
  - Has received corticosteroids equivalent to prednisone ≥ 20 mg daily for at least 14 consecutive days within 30 days prior to study
  - Biologics (eg, infliximab, ustekinumab), immunomodulators (eg, methotrexate, 6MP, azathioprine) or cancer chemotherapy within 90 days prior to study
  - HIV infection with CD4 cell count < 200 mm^3 and a viral load less than 400 copies/mL
- Chronic lung disease (if asthma, requires daily prescribed therapy);
- Known diagnosis of hypertension;
- CVD, defined as history of any of the following: myocardial infarction, stroke, TIA, HF, angina with prescribed nitroglycerin, CABG, PCI, carotid endarterectomy, and aortic bypass;
- Type 1 or Type 2 diabetes mellitus;
- CKD, Sickle cell disease
- Active cancer, other than localized skin cancer, including those requiring treatment as long as the treatment is not among the prohibited medications that must be administered/continued during the trial period;

N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542.

COVID-19 related hospitalization or death

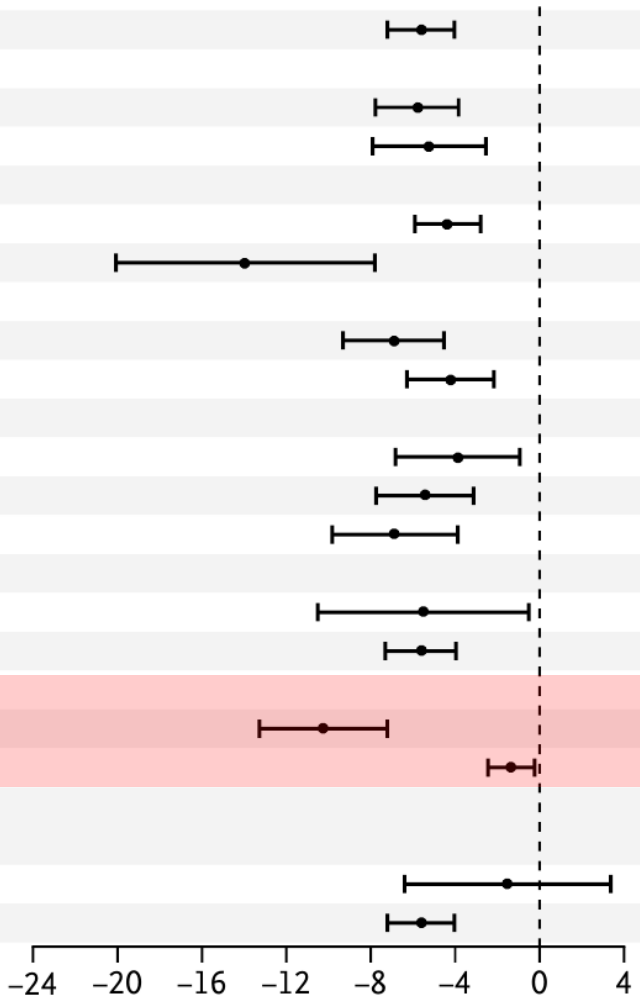


Reduced risk of hospitalization or death by 87.8%

N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542.

C Subgroup Analysis

Subgroup	Nirmatrelvir+Ritonavir	Placebo	Difference from Placebo (95% CI)
	no. of events/total no.		*percentage points*
Overall	8/1039	66/1046	−5.62 (−7.21 to −4.03)
Time since symptom onset			
≤3 days	5/697	44/682	−5.81 (−7.78 to −3.84)
>3 days	3/342	22/364	−5.23 (−7.91 to −2.55)
Age			
<65 yr	7/908	46/909	−4.35 (−5.91 to −2.79)
≥65 yr	1/131	20/137	−13.93 (−20.07 to −7.80)
Sex			
Male	4/520	41/540	−6.93 (−9.32 to −4.53)
Female	4/519	25/506	−4.23 (−6.29 to −2.17)
Body-mass index			
<25	1/209	9/207	−3.88 (−6.83 to −0.94)
25 to <30	3/458	28/466	−5.44 (−7.75 to −3.13)
≥30	4/371	29/373	−6.85 (−9.82 to −3.87)
Diabetes mellitus			
Yes	2/125	9/127	−5.51 (−10.51 to −0.52)
No	6/913	57/919	−5.63 (−7.30 to −3.96)
Baseline SARS-CoV-2 serology status			
Negative	7/487	58/505	−10.25 (−13.28 to −7.21)
Positive	1/540	8/528	−1.34 (−2.45 to −0.23)
Received or expected to receive Covid-19 monoclonal antibody treatment			
Yes	1/70	2/69	−1.51 (−6.40 to 3.37)
No	8/1039	66/1046	−5.62 (−7.21 to −4.03)



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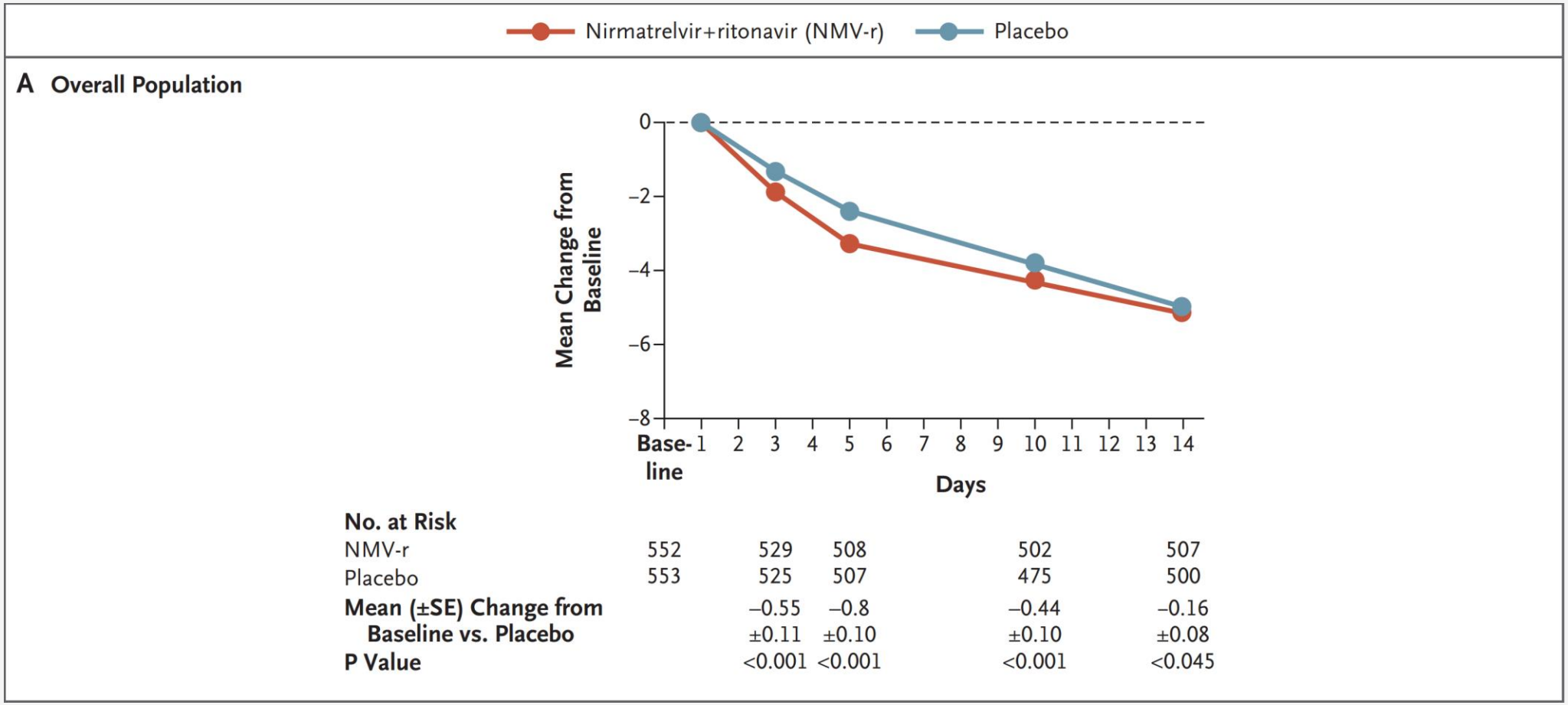
Change from Baseline in Log_{10}- Transformed Viral Load over Time (Modified Intention-to-Treat Population)



No. at Risk					
NMV-r	552	529	508	502	507
Placebo	553	525	507	475	500
Mean (±SE) Change from Baseline vs. Placebo		−0.55 ±0.11	−0.8 ±0.10	−0.44 ±0.10	−0.16 ±0.08
P Value		<0.001	<0.001	<0.001	<0.045

N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542.

Table 2. Summary of Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation through Day 34 (Safety Analysis Population).*

Adverse Event Category	Nirmatrelvir plus Ritonavir (N=1109)	Placebo (N=1115)
Events that emerged during treatment period		
No. of adverse events	476	525
Patients with adverse events — no. (%)		
Any adverse event	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13† (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)
Events considered to be related to drug or placebo		
No. of adverse events	123	52
Patients with adverse events — no. (%)		
Any adverse event	86 (7.8)	42 (3.8)
Serious adverse event	1 (<0.1)	0
Maximum grade 3 or 4 adverse event	5 (0.5)	5 (0.4)
Maximum grade 5 adverse event	0	0
Discontinued drug or placebo because of adverse event	9 (0.8)	7 (0.6)
Had dose reduction or temporary discontinuation owing to adverse event	2 (0.2)	3 (0.3)

- Dysgeusia (m/c 5.6%)
- diarrhea (3.1%)
- fibrin D-dimer increase
- alanine aminotransferase increase
- headache
- creatinine renal clearance decrease
- nausea and vomiting

N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542.

[표1] 팍스로비드 병용금기
(니르마트렐비르+리토나비르)

연번	성분명
1	아미오다론
2	에르고타민
3	피모자이드
4	실데나필
5	심바스타틴
6	세인트존스워트
7	플레카이니드
8	로바스타틴
9	알푸조신
10	페티딘
11	피록시캄
12	라놀라진
13	드로네다론
14	콜키신
15	클로자핀
16	트리아졸람
17	카르바마제핀
18	페노바르비탈
19	페니토인
20	리팜피신
21	아팔루타마이드
22	프로파페논
23	메틸에르고노빈 (메틸에르고메트린)
24	디히드로에르고타민
25	미다졸람(경구)
26	퀴니딘
27	프로폭시펜
28	루라시돈
합계	28개 성분

[표2] 국내 허가품목 현황(복합제 포함) 총 23개 성분

■ 17종 : 현재 복용중일 경우, 해당 약제 복용 중단 후 또는 대체약품 처방 가능한 경우 팍스로비드 투여 가능

연번	성분명	효능、효과
1	아미오다론	부정맥
2	에르고타민	편두통
3	피모자이드	정신분열증
4	실데나필	발기부전, 폐동맥고혈압
5	심바스타틴	고지혈증
6	플레카이니드	빈맥
7	로바스타틴	고지혈증
8	알푸조신	전립선 비대증
9	페티딘	통증
10	피록시캄	류마티스관절염
11	라놀라진	협심증
12	드로네다론	심방세동
13	콜키신	통풍
14	클로자핀	조현병
15	트리아졸람	불면증
16	프로파페논	부정빈맥
17	메틸에르고노빈 (메틸에르고메트린)	자궁수축 (출혈방지 및 치료)
합계	17개성분	

CYP450 3A4 strong inducer

연번	성분명	효능、효과
1	세인트존스워트	불안, 우울증상
2	카르바마제핀	간질
3	페노바르비탈	간질
4	페니토인	간질
5	리팜피신	결핵
6	아팔루타마이드	전립선암
합계	6개성분	

연번	품목명	업체명
1	노이로민정	(주)유유제약
2	마인트롤정	동국제약(주)
3	미시업정-골드	정우신약(주)
4	심미안정	에이치엘비제약(주)
5	에버컨정	태극제약(주)
6	에스미정	(주)비보존제약
7	예스큐정	(주)테라젠이텍스
8	지노플러스정	진양제약(주)
9	훼라민큐정	동국제약(주)
10	히페린정	동성제약(주)
11	명원정	(주)한국신약
12	센스업정	(주)아이월드제약
13	시메신-플러스정	영풍제약(주)
14	아름정	미래제약(주)
15	에스몬플러스정	삼익제약(주)
16	제일세라민큐정	(주)한국파비스제약
17	페리시정	(주)서울제약
18	페미센스정	광동제약(주)
19	페미영정	부광약품(주)
20	헤라큐정	(주)서흥
21	헤피리온정	(주)동구바이오제약
22	훼민업정	일양약품(주)

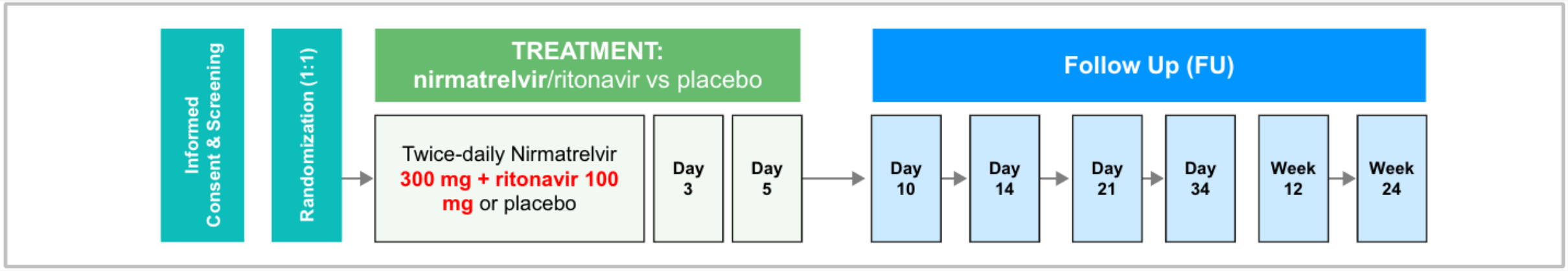
Clinical Trials for Nirmatrelvir/Ritonavir

Protocol	Population	Primary endpoint	Major eligibility
EPIC-HR NCT04960202 (final n=2246)	Non-hospitalized symptomatic SARS-CoV-2 positive* **(High risk population)**	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28	• ≥ 18 years of age • At least one risk factor for severe COVID-19 infection • No previous SARS-CoV-2 infection or hospitalization to treat COVID-19 infection • No prior or planned convalescent COVID-19 plasma • No prior or planned SARS-CoV-2 vaccine before study the Day 34 visit • Oxygen saturation of ≥ 92% on room air within 24 hours prior to randomization • Adequate liver function
EPIC-SR NCT05011513 (N=1140)	Non-hospitalized symptomatic SARS-CoV-2 positive* **(Standard risk population)**	Time (days) to sustained alleviation of all targeted COVID-19 sign / symptoms through Day 28	• ≥ 18 years of age • No risk factors for severe COVID-19 infection; or with risk factors plus vaccinated • No previous SARS-CoV-2 infection or hospitalization to treat COVID-19 infection • No prior or planned convalescent COVID-19 plasma or monoclonal antibodies • Oxygen saturation of ≥ 92% on room air within 24 hours prior to randomization • Adequate renal and liver function
EPIC-PEP NCT05047601 (N=2634)	**Household contacts** of individuals infected with SARS-CoV-2	Proportion of participants who symptomatic, RT-PCR confirmed SARS-CoV-2 infection (Day 1–14)	• ≥18 years of age • Asymptomatic household contacts with exposure to an individual who is symptomatic and recently tested positive for SARS-CoV-2 (index case) • Randomized within 96 hours of collection of the index case's first positive SARS-CoV-2 test • No prior laboratory-confirmed SARS-CoV-2 infection • No measured fever or signs or symptoms consistent with COVID-19 • No known exposure to individual with positive SARS-CoV-2 or suspected COVID-19 infection, except for the index case, within 1 month before screening

EPIC-SR

- Double-blind, randomized, placebo-controlled trial, from September 2020 to April 2021, 584 patients
- Unvaccinated patients without conditions indicative for progression to severe disease or patients who are at high risk for progression to severe disease and are fully vaccinated.
- Onset of symptoms and confirmation of SARS-CoV-2 infection as determined by RT-PCR or RAT

  - Within 5 days prior to randomization
- At least 1 COVID-19 signs/symptoms
- Primary outcome
  - Time to sustained alleviation of all targeted COVID-19 sign/symptoms through day 28 in the mITT cohort (≤ 3 days since symptom onset)



Pfizer

EPIC-SR: Analysis of Time to Symptom Alleviation

	Median (95% confidence interval) Time to Event (Days)		
	PAX	PBO	p-value
EPIC-SR mITT (N=367)	13.0 (12-15)	13.0 (11-15)	0.335
EPIC-SR mITT1 (N=662)	13.0 (12-15)	13.0 (11-14)	0.469

Abbreviations: PAX = PAXLOVID; PBO = placebo
mITT = Modified Intent to Treat Population (≤3 days since symptom onset)
mITT1 = Modified Intent to Treat Population (≤5 days since symptom onset)

EPIC-SR: Hospitalization and Death through Day 28 mITT1 Population (≤5 days since symptom onset)

	EPIC-SR Interim Analysis	
	PAX	PBO
Hospitalization or death by Day 28 (n/N, %)	3/428 (0.70)	10/426 (2.35)
RRR	70%	
p-value	0.051	
Death by Day 28 (n/N, %)	0/428 (0.0)	0/426 (0.0)

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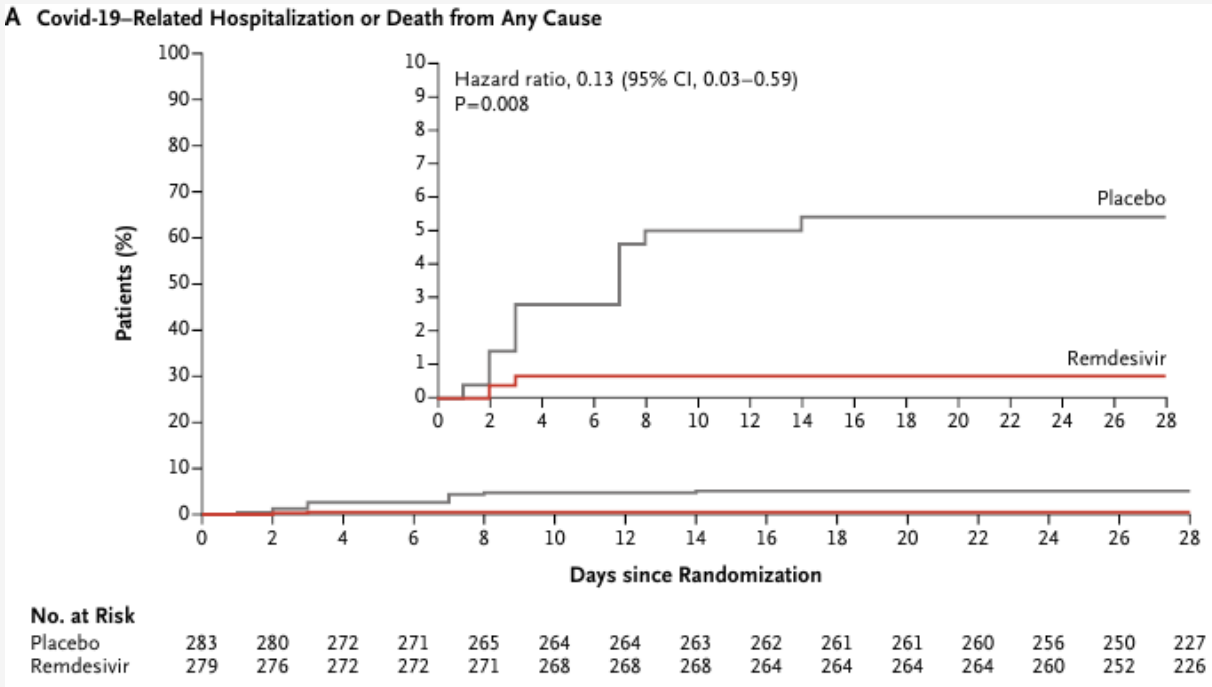
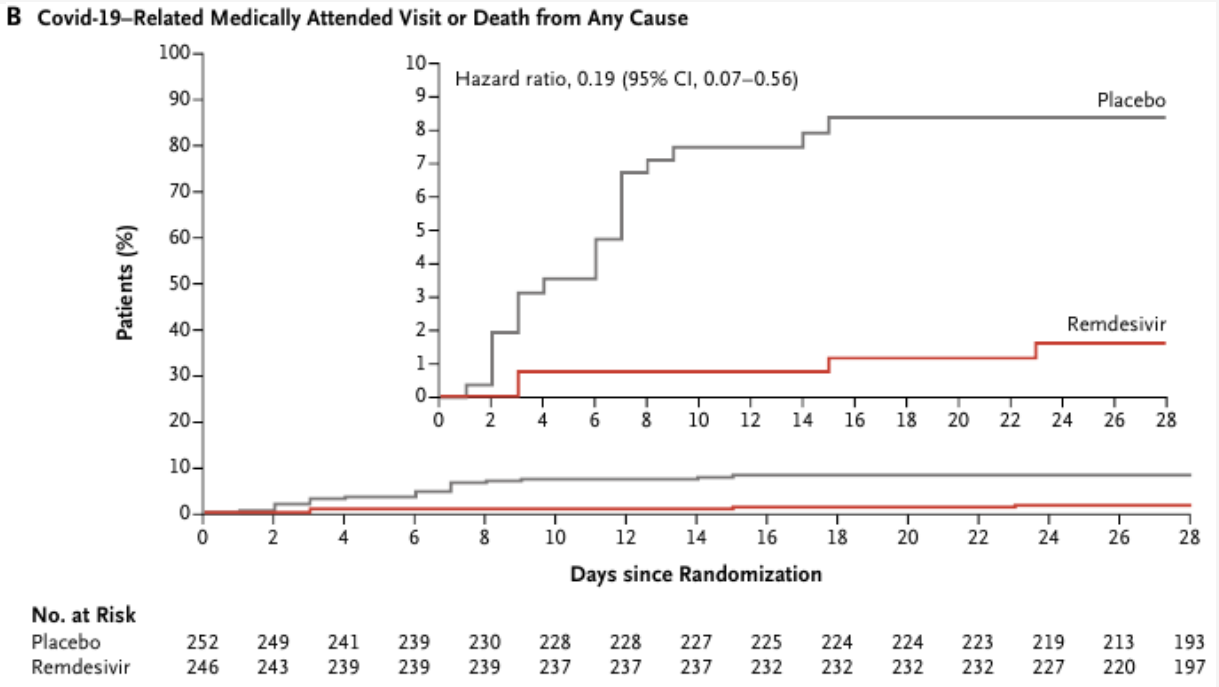
Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

- Double-blind, randomized, placebo-controlled trial, from September 2020 to April 2021, 584 patients
- Non-hospitalized and risk factor ≥ 1 for severe Covid-19
- Treatment started within 7 days after the onset of sings and symptoms
- Remdesivir (200mg on day 1 followed by 100mg on days 2 and 3) vs. placebo for 3 days
- Primary outcome
  - Incidence hospitalization or death at day 29

N Engl J Med 2022; 386:305-315.

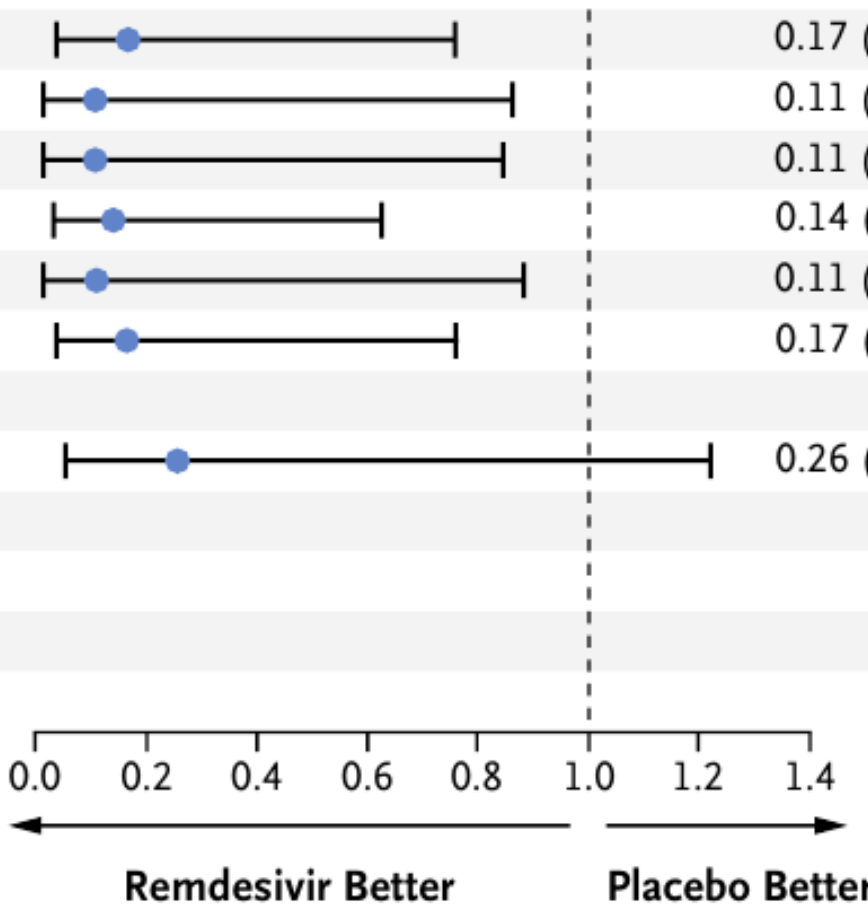
Covid 19 related hospitalization or death





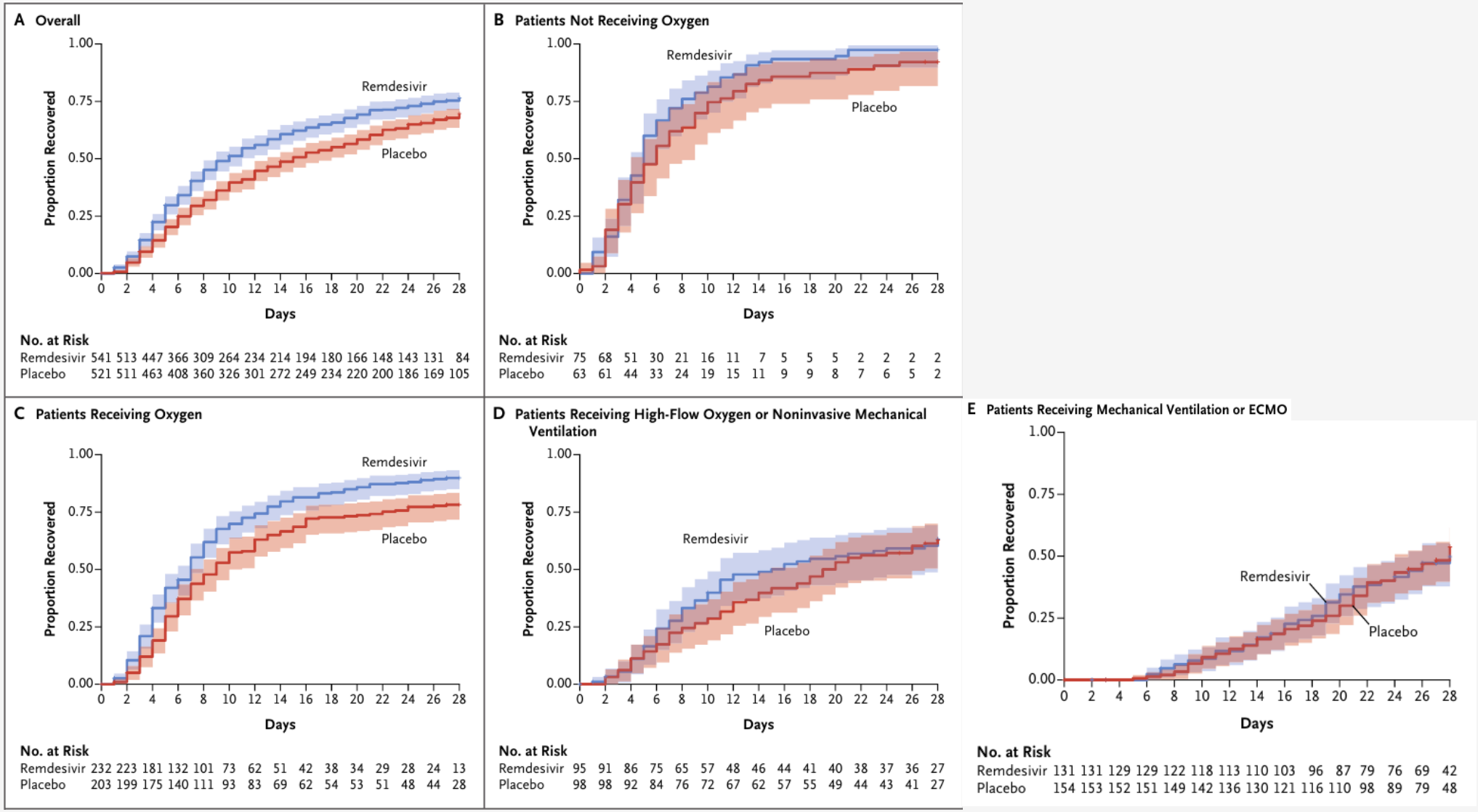
N Engl J Med 2022; 386:305-315.

Subgroup	Remdesivir	Placebo	Hazard Ratio (95% CI)
	no./total no. of patients (%)		
Residence in the United States	2/264 (0.8)	12/267 (4.5)	0.17 (0.04–0.76)
Age ≥60 yr	1/83 (1.2)	9/87 (10.3)	0.11 (0.01–0.86)
Male sex	1/148 (0.7)	9/145 (6.2)	0.11 (0.01–0.84)
Diabetes mellitus	2/173 (1.2)	14/173 (8.1)	0.14 (0.03–0.63)
Obesity	1/154 (0.6)	9/156 (5.8)	0.11 (0.01–0.88)
Hypertension	2/138 (1.4)	10/130 (7.7)	0.17 (0.04–0.76)
Ethnic group			
Not Hispanic or Latinx	2/146 (1.4)	8/158 (5.1)	0.26 (0.06–1.22)
Hispanic or Latinx	0/123	6/112 (5.4)	—
Chronic lung disease	0/67	4/68 (5.9)	—
Cardiovascular or cerebrovascular disease	0/20	2/24 (8.3)	—
Current cancer	0/12	2/18 (11.1)	—



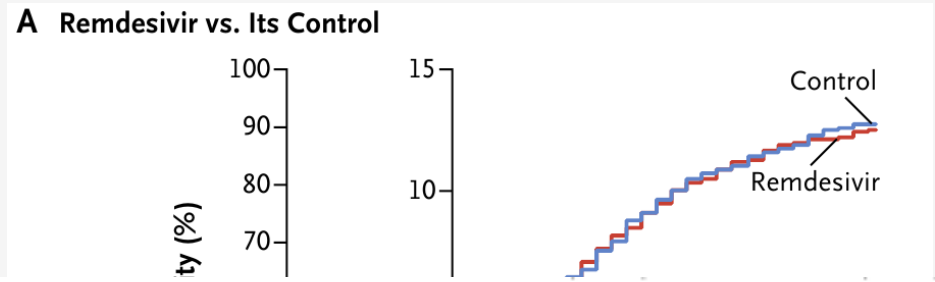
N Engl J Med 2022; 386:305-315.

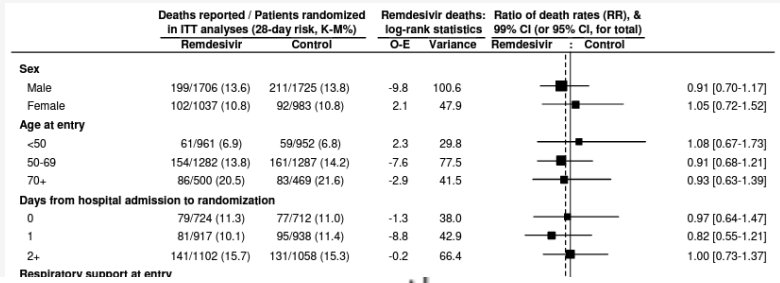
Remdesivir : ACTT-1 study



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

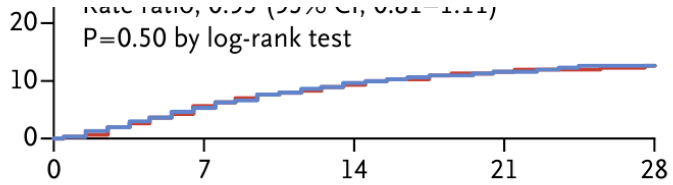
WHO Solidarity Trial Consortium*





Respiratory support at entry

No O_2	11/661 (2.0)	13/664 (2.1)	-0.6	6.0	0.90 [0.31-2.58]
Low-flow or hi-flow O_2	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]

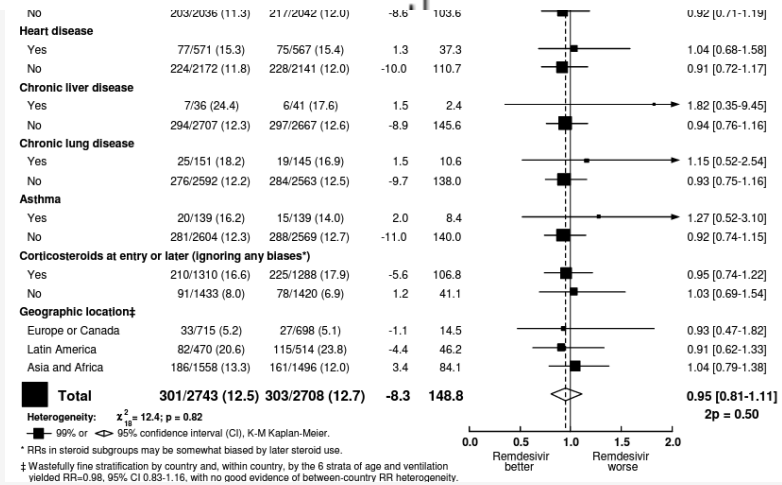


Denominator

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



N Engl J Med 2021;384:497-511.

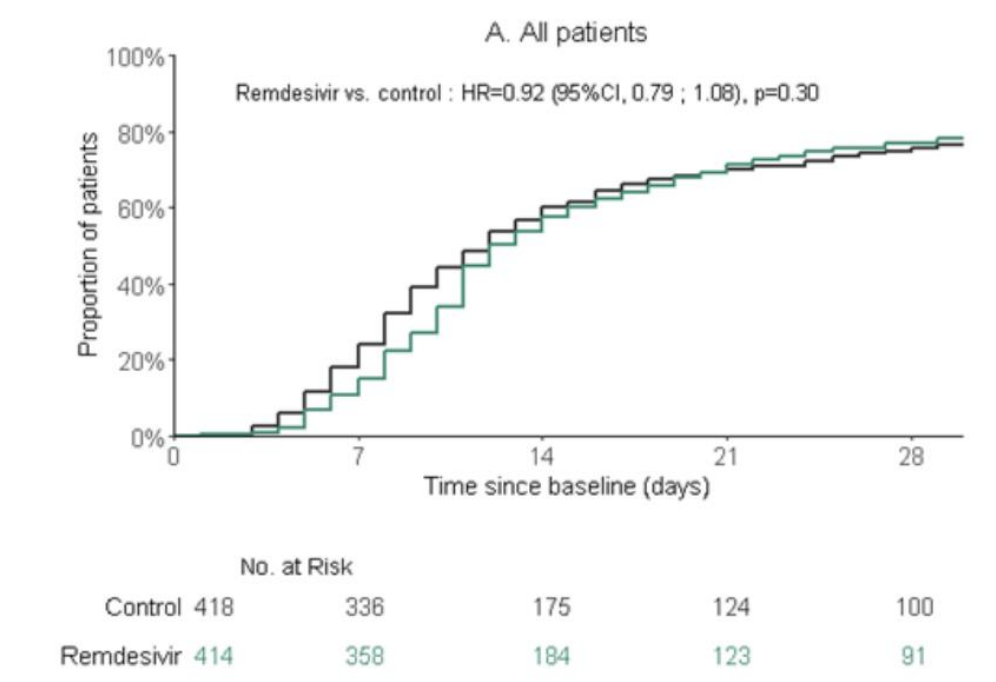
Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

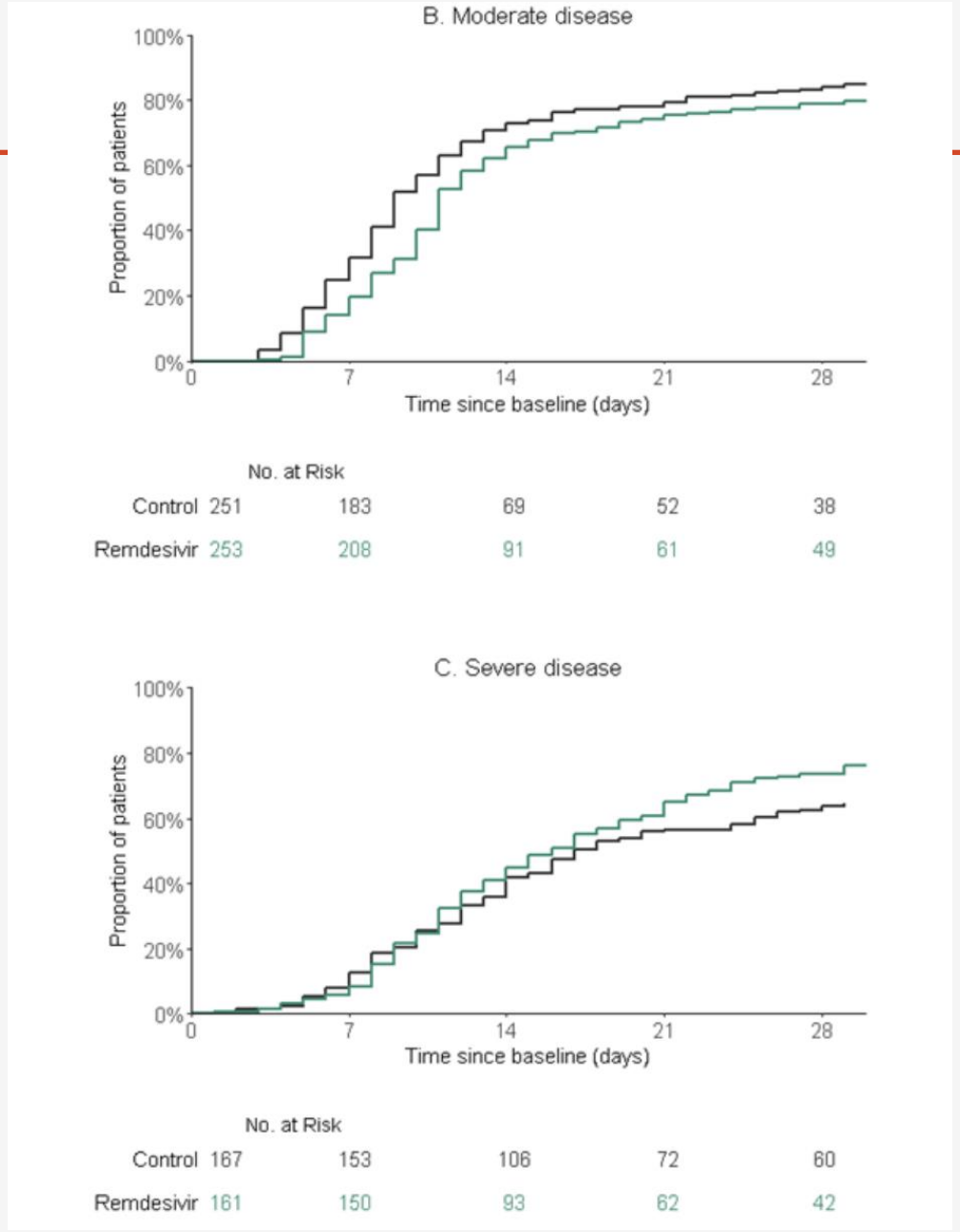
- phase 3, open-label, adaptive, multicenter RCT, from March 2020 to Jan 2021, 857 patients
- Hospitalized, SpO2 < 94%, requirement of supplemental oxygen, HFOT, NIV or MV
- Remdesivir (n=429) vs. placebo (n=428) up to 10 days
- Primary outcome
  - Clinical status at day 15 as measured on the seven-point ordinal scale of the WHO Master Protocol

Lancet Infect Dis 2022;22: 209–21

Time to Recovery

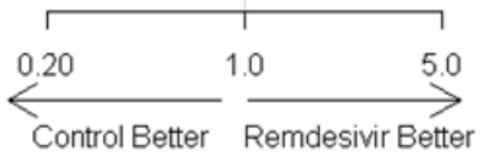
- Days to improvement of 2 catergories of the 7-point ordinal scale or hospital discharge within day 29





Lancet Infect Dis 2022;22: 209–21

Subgroups	Number of patients	OR (95%CI)	P-value
Age			
< 50	135	1.24 (0.67 to 2.29)	0.50
[50;70[	418	0.94 (0.67 to 1.33)	0.75
≥ 70	279	0.96 (0.64 to 1.46)	0.85
Sex			
Men	579	0.91 (0.68 to 1.22)	0.53
Women	253	1.26 (0.81 to 1.95)	0.31
Duration of symptoms prior to randomization			
≤ 7 days	264	1.14 (0.75 to 1.75)	0.54
8-14 days	480	1.01 (0.73 to 1.39)	0.97
>14 days	66	0.44 (0.18 to 1.07)	0.07
Severity at randomization			
Moderate	504	0.85 (0.62 to 1.16)	0.31
Severe	328	1.20 (0.82 to 1.77)	0.35
Country			
France	708	1.06 (0.82 to 1.38)	0.66
Austria	28	1.03 (0.27 to 4.02)	0.96
Portugal	32	1.04 (0.29 to 3.73)	0.95
Belgium/Luxembourg	64	0.43 (0.17 to 1.05)	0.07
All patients	**832**	**0.98 (0.77 to 1.25)**	**0.85**

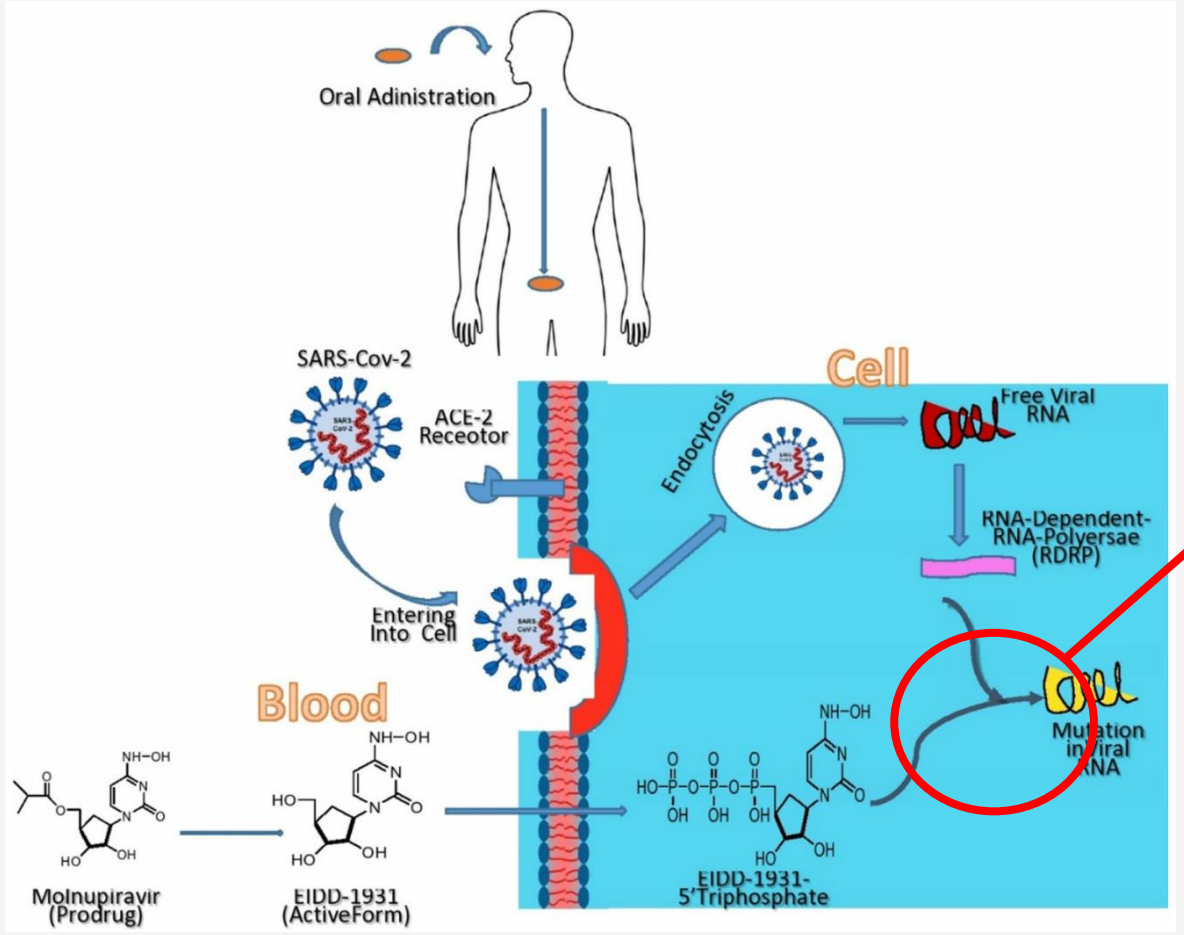


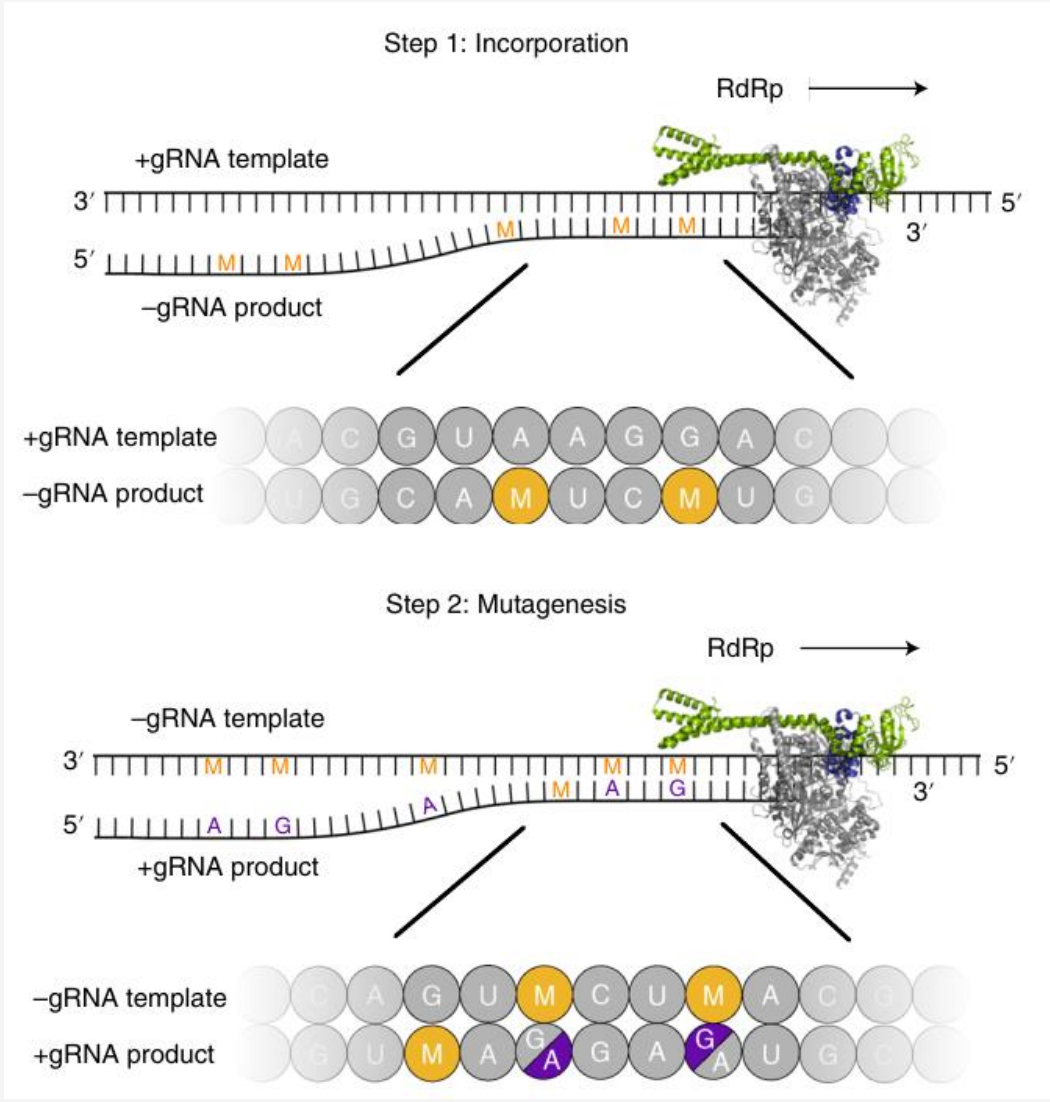
Lancet Infect Dis 2022;22: 209–21

Molnupiravir

- Orally active form
- A prodrug of β-d-N4-hydroxycytidine(NHC)
- Developed to treat hepatitis and influenza
- Introduce copying errors during viral RNA replication
- No dose adjustment in renal and liver dysfuction
- No drug interaction

Mechanism of Molnupiravir





Nat Struct Mol Biol. 2021 Sep;28(9):740-746.

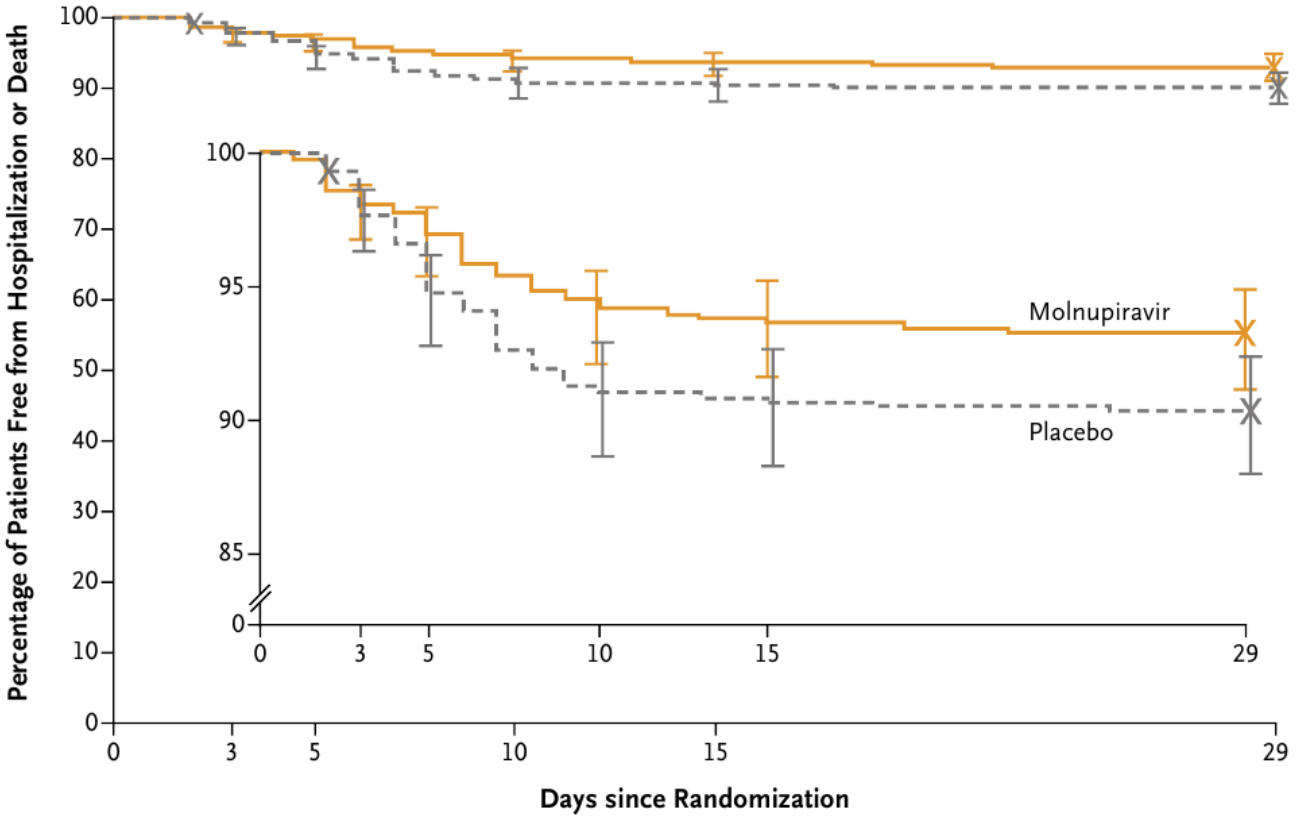
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2022 VOL. 386 NO. 6

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

- Phase 3, double-blind, randomized, placebo-controlled trial
- Non-hospitalized, unvaccinated adults with mild to moderate and risk factor ≥ 1 for severe Covid-19
- Treatment started within 5 days after the onset of sings and symptoms
- Molnupiravir (800mg) vs. placebo twice daily for 5 days
- Primary outcome
  - incidence hospitalization or death at day 29

N Engl J Med 2022;386:509-20.



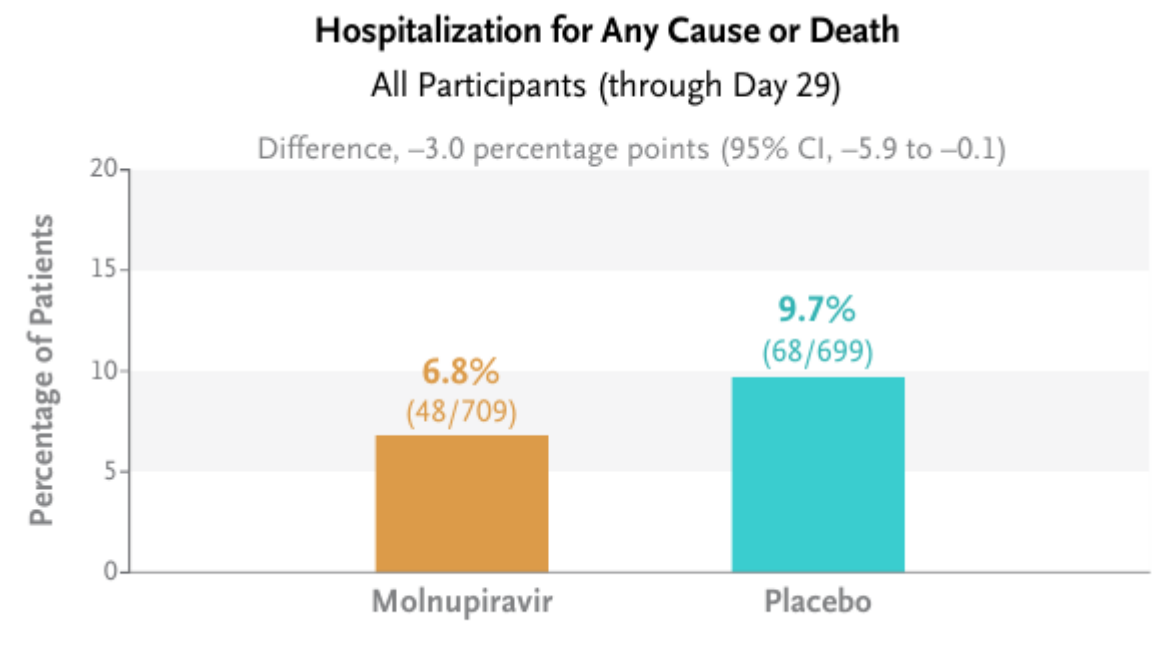
No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

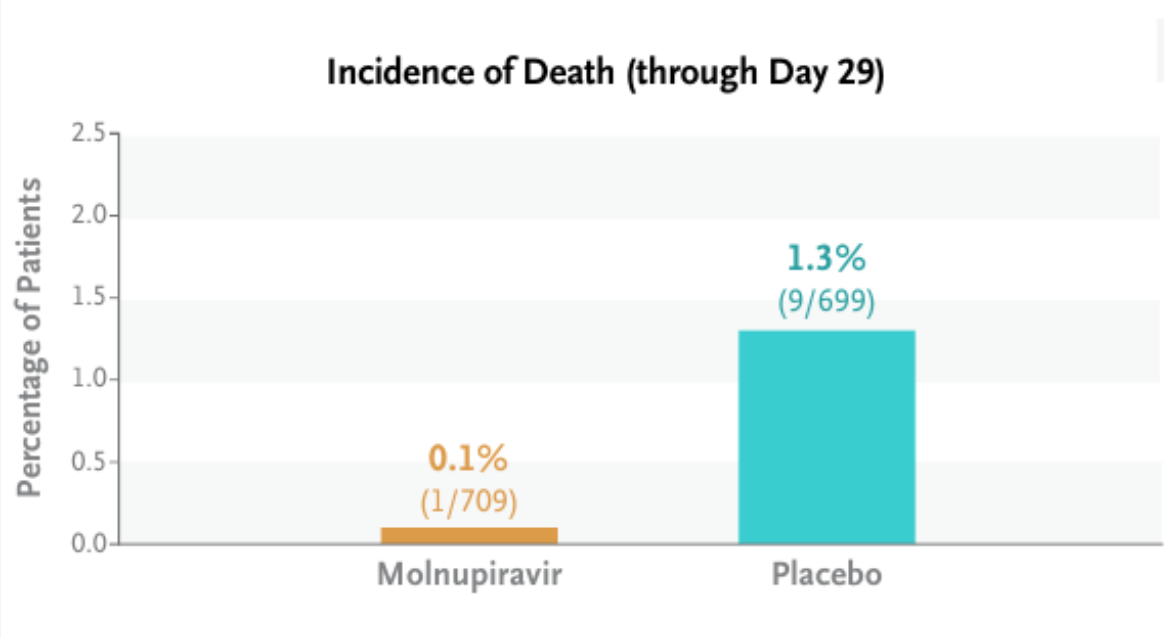
6.8%

9.7%

(hazard ratio, 0.69; 95% CI, 0.48 to 1.01)

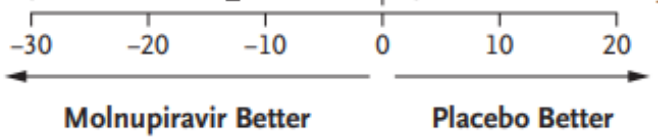
N Engl J Med 2022;386:509-20.





N Engl J Med 2022;386:509-20.

Subgroup	Molnupiravir	Placebo	Absolute Risk Reduction (95% CI)
	no. of events/no. of participants		*percentage points*
Sex			
Female	16/379	27/344	−3.6 (−7.4 to −0.2)
Male	32/330	41/355	−1.9 (−6.5 to 2.8)
Days since onset of symptoms			
≤3	25/339	28/335	−1.0 (−5.2 to 3.2)
>3	23/370	40/364	−4.8 (−9.0 to −0.7)
Baseline Covid-19 severity			
Mild	19/395	27/376	−2.4 (−5.9 to 1.0)
Moderate	29/311	40/321	−3.1 (−8.1 to 1.8)
Baseline SARS-CoV-2 nucleocapsid antibody status			
Positive	5/136	2/146	2.3 (−1.7 to 7.1)
Negative	39/541	64/520	−5.1 (−8.8 to −1.6)
Risk factors for severe Covid-19			
>60 yr of age	12/118	16/127	−2.4 (−10.6 to 5.8)
Obese	29/535	46/507	−3.7 (−6.9 to −0.5)
Diabetes mellitus	17/107	17/117	1.4 (−8.2 to 11.1)
Serious heart condition	8/86	9/78	−2.2 (−12.4 to 7.5)
Race			
American Indian or Native American	18/207	21/199	−1.9 (−7.8 to 4.0)
Asian	7/25	7/23	−2.4 (not calculated)
Black	10/157	15/142	−4.2 (−11.1 to 2.2)
White	29/556	54/573	−4.2 (−7.3 to −1.2)
Baseline SARS-CoV-2 qualitative assay			
Detectable	45/614	61/613	−2.6 (−5.8 to 0.5)
Undetectable	0/54	0/51	0.0 (−7.1 to 6.7)
Unknown	3/41	7/35	−12.7 (−29.9 to 2.9)



N Engl J Med 2022;386:509-20.

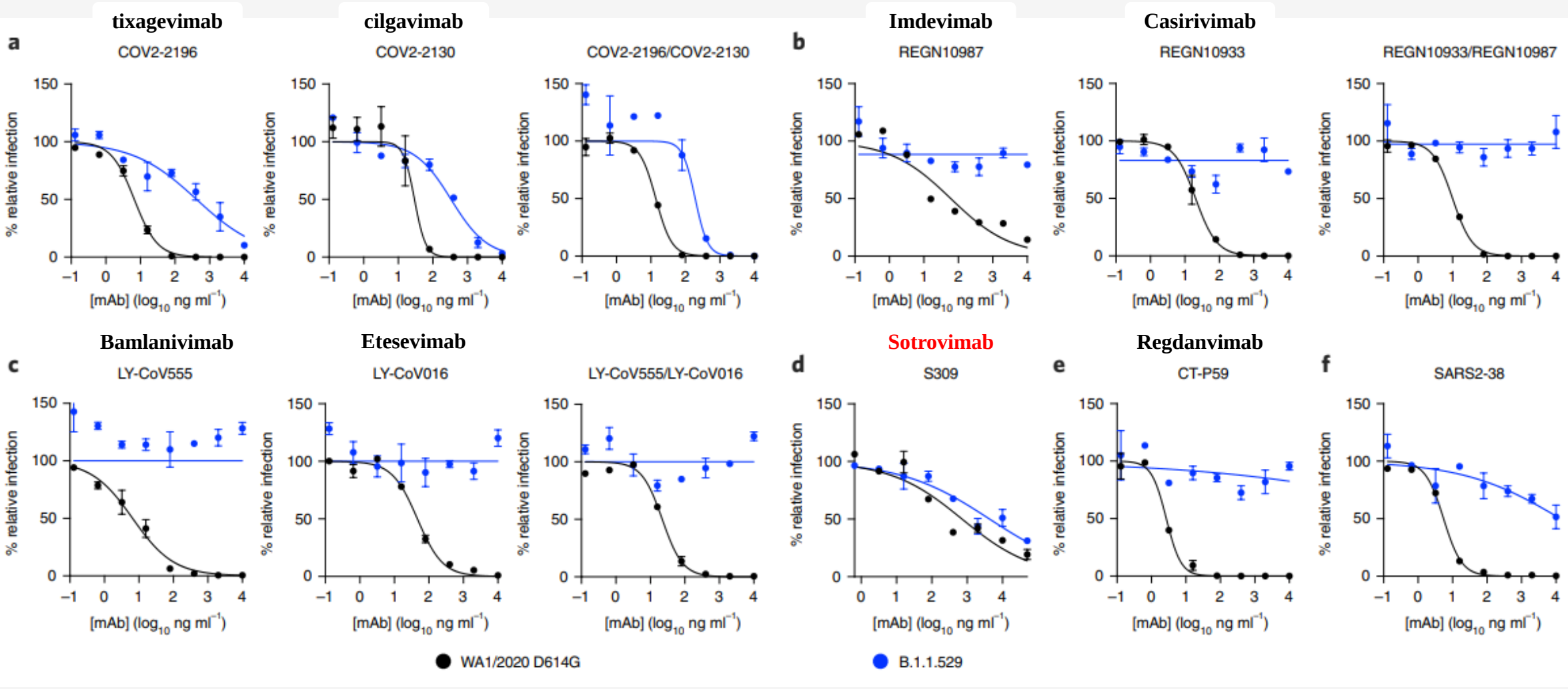
Summary of Antiviral drug

	Remdesivir	Molnupiravir	Nirmatrelvir
Target	Inhibitor of RNA dependent RNA polymerase	Mutagenesis of RNA replication	M^{PRO} protease inhibitor
Vaccination history	No vaccination	No vaccination	No vaccination
Duration of Symptoms	7 days	5 days	5 days
Age > 60 yrs	30%	17.2%	13%
Risk factors	DM (61.6%) Obesity (55.2%) Hypertension (47.7%)	Obesity (75.1%) Age > 60 yr (17.2%) DM (15.9%)	Obesity (BMI > 25) (80.5%) Current smoking (39.0%) Hypertension (32.9%)
Hospitalization or death	0.77% vs. 7.01%	6.3% vs. 9.2%	0.72% vs. 6.53%
Drug interaction	-	-	+

Monoclonal Antibodies in mild or moderate COVID-19

Study	Patients	Intervention	outcomes
BLAZE-1	• Aged ≥12 years • Within 3 days after SARS-CoV-2 diagnosis • At high risk for severe COVID-19 or hospitalization	• Bamlanivimab 2800mg + etesevimab 2800mg single infusion vs. placebo	• COVID-19-related hospitalizations or all-cause deaths by Day 29: 11 (2.1%) in BAM plus ETE arm vs. 36 (7.0%) in placebo arm; relative risk difference: 70% (P < 0.001). • All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 10 (1.9%) in placebo arm.
REGN-COV2	• Aged ≥18 years • Within 7 days after symptom onset • At high risk for severe COVID-19 or hospitalization	• Casirivimab 600mg + Imdevimab 600mg (n=736) vs. placebo (n=748) • Casirivimab 1200mg + Imdevimab 1200 (n=1355) vs. placebo(n=1341)	• COVID-19-related hospitalizations or all-cause deaths through Day 29: • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm (P = 0.002). • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm (P < 0.001)
COMET-ICE	• Aged ≥18 years with ≥ 1 comorbidity or aged ≥ 55 years • Symptom onset ≤ 5 days before enrollment	• SOT 500 mg IV (n = 291) vs. placebo (n = 292)	• Hospitalizations or all-cause deaths by Day 29 • 3 (1%) in SOT arm vs. 21 (7%) in placebo arm (P = 0.002).

Neutralization of Omicron VOC by monoclonal antibodies



Nat Med. 2022 Mar;28(3):490-495.

Neutralization of Omicron/BA.2 by monoclonal antibodies

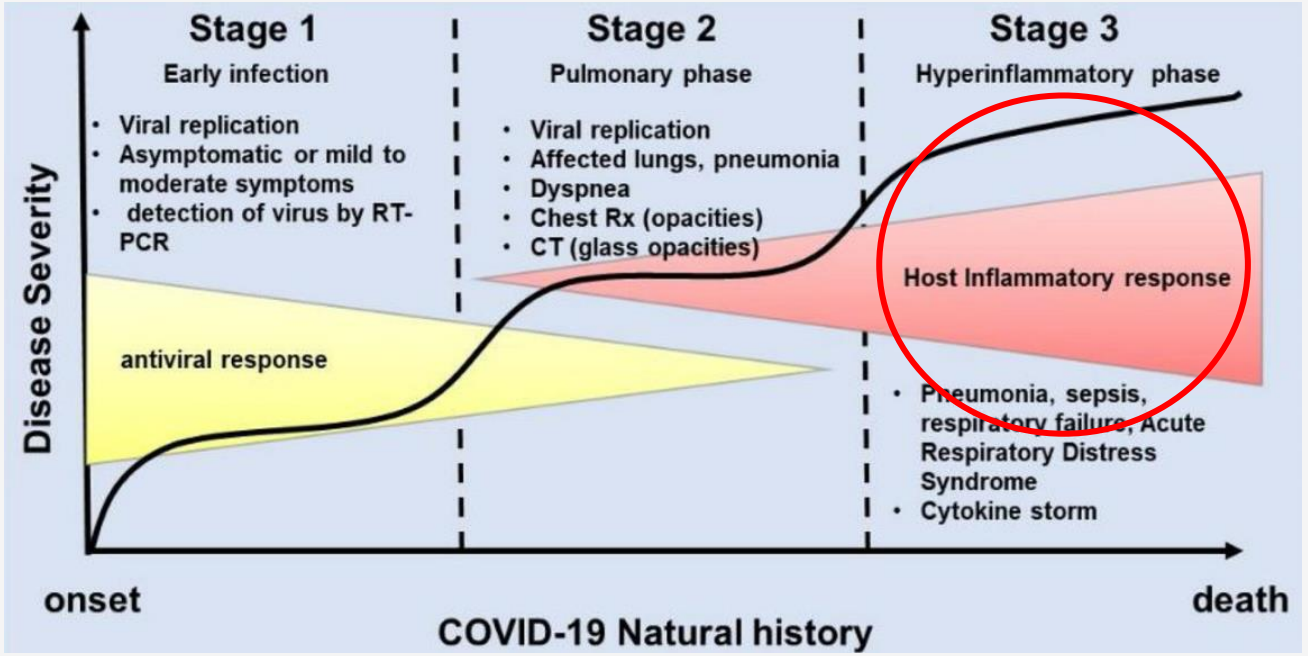
Table S2. Efficacy of Monoclonal Antibodies and Antiviral Drugs against SARS-CoV-2 Variants in Vitro.*

Monoclonal Antibody or Antiviral Drug	SARS-CoV-2 Variant							
	SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo (An ancestral strain/A)	SARS-CoV-2/UT-HP127-1Nf/Human/2021/Tokyo (Alpha/B.1.1.7)	hCoV-19/USA/MD-HP01542/2021 (Beta/B.1.351)	hCoV-19/Japan/TY7-503/2021 (Gamma/P.1)	hCoV-19/USA/WI-UW-5250/2021 (Delta/B.1.617.2)	hCoV-19/Japan/NC928-2N/2021 (Omicron/BA.1)	hCoV-19/Japan/NC929-1N/2021 (Omicron/BA.1.1)	hCoV-19/Japan/UT-NCD1288-2N/2022 (Omicron/BA.2)
Neutralization activity of monoclonal antibody — ng/ml†								
LY-CoV016, etesevimab	18.19 ± 9.10	150.38 ± 83.51	>50,000	>50,000	15.37 ± 9.78	>50,000	>50,000	>50,000
LY-CoV555, bamlanivimab	4.69 ± 1.43	2.65 ± 1.30	9554.88 ± 926.53	1601.65 ± 896.02	641.73 ± 324.79	>50,000	>50,000	>50,000
REGN10987, imdevimab	3.05 ± 0.93	1.87 ± 1.60	2.17 ± 1.30	1.04 ± 0.68	3.95 ± 1.78	>50,000	>50,000	68.65 ± 8.84
REGN10933, casirivimab	2.79 ± 1.87	2.74 ± 1.84	757.13 ± 287.91	187.69 ± 128.88	2.89 ± 1.78	14110.70 ± 1782.13	11998.94 ± 2604.70	1666.19 ± 771.77
COV2-2196, tixagevimab	1.92 ± 0.28	1.34 ± 0.67	18.98 ± 1.42	6.56 ± 1.56	4.05 ± 2.60	1299.94 ± 406.58	880.47 ± 68.08	395.78 ± 62.37
COV2-2130, cilgavimab	7.70 ± 2.20	3.60 ± 1.62	10.03 ± 3.05	4.00 ± 2.70	12.76 ± 2.93	443.87 ± 167.96	13558.20 ± 4646.95	4.44 ± 2.72
S309, sotrovimab precursor	27.33 ± 3.24	44.91 ± 22.76	100.98 ± 22.27	28.38 ± 1.86	111.43 ± 58.22	373.47 ± 159.49	384.52 ± 65.98	1359.05 ± 269.23
LY-CoV016 plus LY-CoV555	12.60 ± 1.91	15.26 ± 3.98	>10,000	2545.04 ± 625.72	10.28 ± 3.33	>10,000	>10,000	>10,000
REGN10987 plus REGN10933	3.53 ± 0.66	1.55 ± 0.78	5.18 ± 1.45	2.11 ± 0.48	1.91 ± 0.79	>10,000	>10,000	222.59 ± 64.47
COV2-2196 plus COV2-2130	3.42 ± 0.92	1.94 ± 0.34	10.30 ± 1.17	1.79 ± 0.87	5.50 ± 2.75	255.86 ± 45.31	1374.90 ± 14.47	14.48 ± 2.04
Viral susceptibility to drug — μM‡								
GS-441524§	1.04 ± 0.32	0.83 ± 0.19	0.63 ± 0.20	0.91 ± 0.33	1.12 ± 0.20	1.28 ± 0.42	1.63 ± 0.30	2.85 ± 0.31
EIDD-1931¶	0.51 ± 0.14	0.95 ± 0.17	0.60 ± 0.21	0.41 ± 0.13	0.83 ± 0.41	0.43 ± 0.08	1.09 ± 0.13	0.67 ± 0.22
PF-07321332‖	3.59 ± 0.96	4.23 ± 1.04	2.03 ± 0.96	4.57 ± 1.14	3.90 ± 0.50	4.26 ± 0.36	3.63 ± 0.42	6.76 ± 0.69

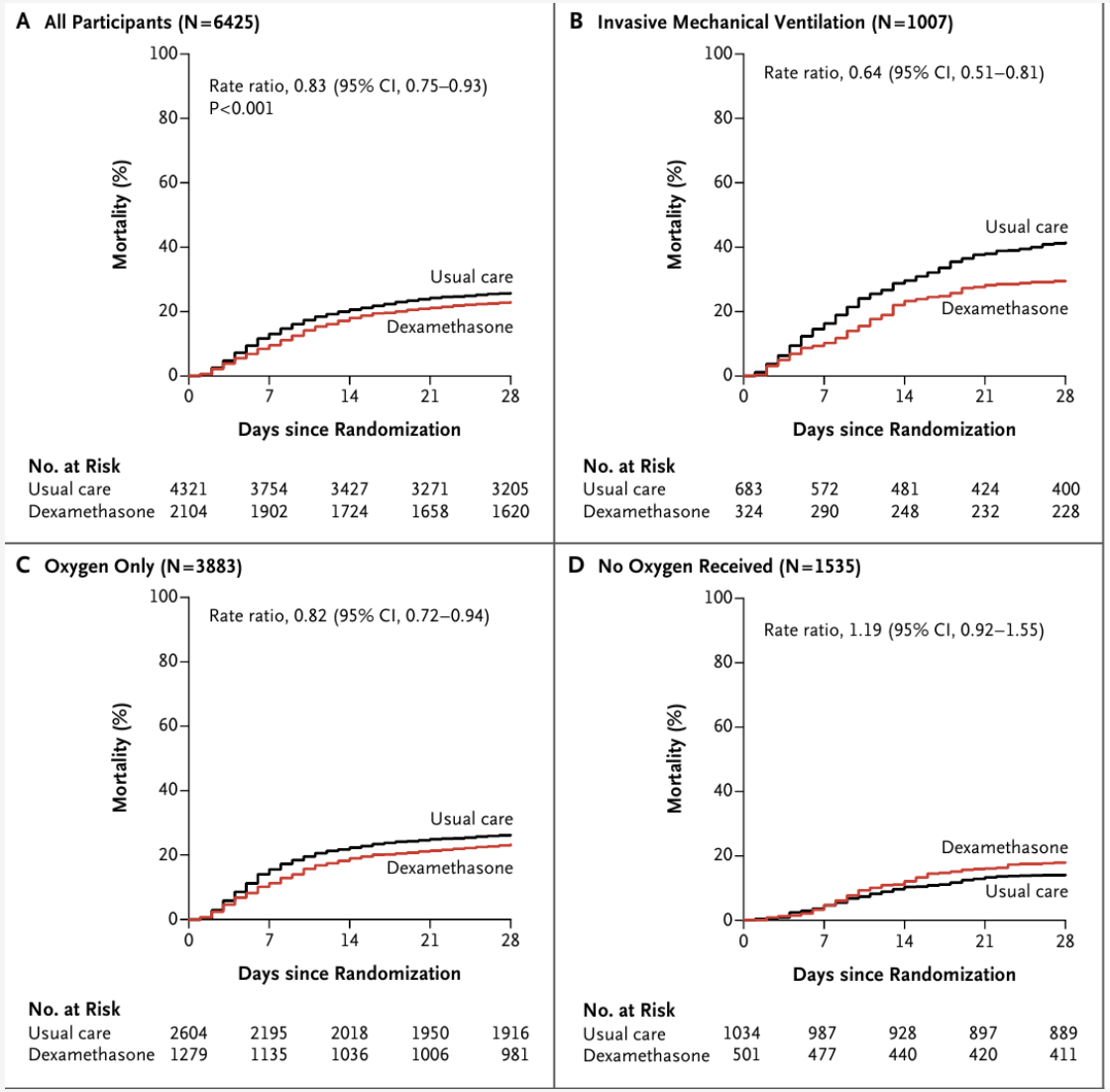
NEJM DOI: 10.1056/NEJMc2201933

Immunomodulators in COVID-19

- Immunotherapies targeting immune mediators of host defense.
  - Corticosteroids
  - Kinase inhibitors – JAK inhibitor
  - Anti-cytokine treatment – Anti-IL-6 Antibody
  - Anti-complement therapies
  - Stimulators of antiviral defense

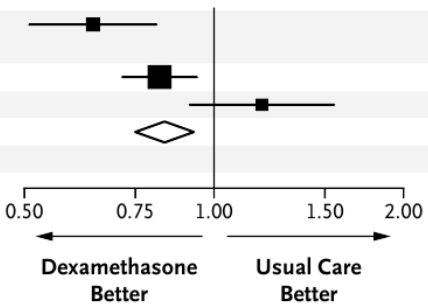


RECOVERY trial



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



N Engl J Med 2021;384:693-704.

Table 2. Primary and Secondary Outcomes and Prespecified Subsidiary Clinical Outcomes.

Outcome	Dexamethasone (N = 2104)	Usual Care (N = 4321)	Rate or Risk Ratio (95% CI)*
		no./total no. of patients (%)	
Primary outcome			
Death at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1416/2104 (67.3)	2748/4321 (63.6)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	462/1780 (26.0)	1003/3638 (27.6)	0.93 (0.85–1.01)
Invasive mechanical ventilation	110/1780 (6.2)	298/3638 (8.2)	0.79 (0.64–0.97)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)
Subsidiary clinical outcomes			
Use of ventilation‡	25/501 (5.0)	65/1034 (6.3)	0.84 (0.54–1.32)
Noninvasive ventilation	20/501 (4.0)	57/1034 (5.5)	0.77 (0.47–1.26)
Invasive mechanical ventilation	9/501 (1.8)	19/1034 (1.8)	1.07 (0.49–2.34)
Successful cessation of invasive mechanical ventilation§	160/324 (49.4)	268/683 (39.2)	1.47 (1.20–1.78)
Renal-replacement therapy¶	89/2034 (4.4)	314/4194 (7.5)	0.61 (0.48–0.76)

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

The COVID STEROID 2 Trial Group

- Multicenter, blinded, randomized clinical trial
- 1000 patients requiring at least 10 L/min of oxygen, NIV, MV
- 12mg/d of IV dexamethasone (n=503) vs. 6mg/d of IV dexamethasone (n=497) for up to 10 days
- Primary outcome
  - the number of days alive without life support at 28 days

JAMA. 2021;326(18):1807-1817.

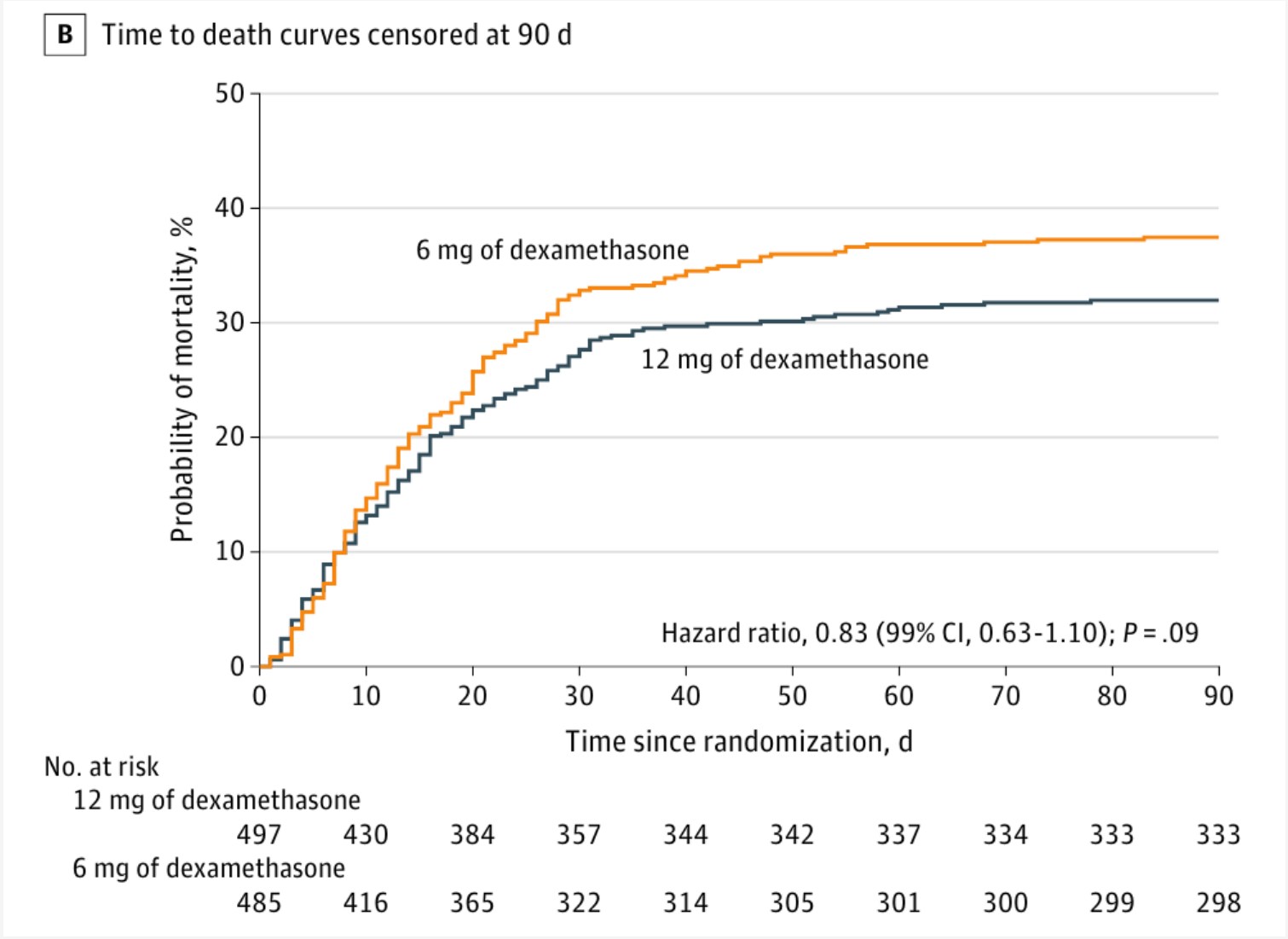
Number of days alive without life support at 28 days

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. 2021;326(18):1807-1817.

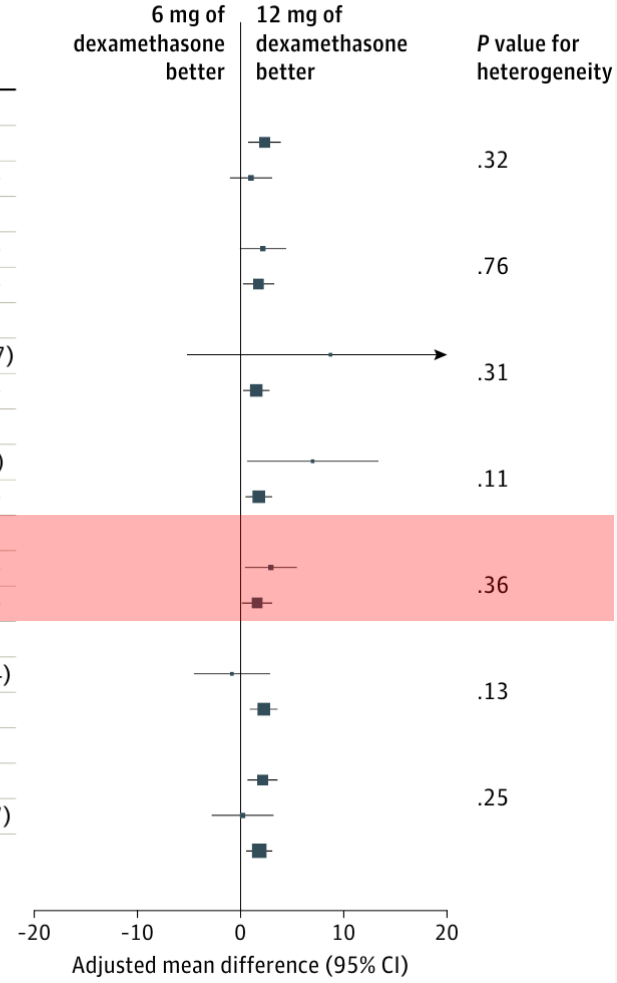
All cause mortality at 90 d



JAMA. 2021;326(18):1807-1817.

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)		Adjusted mean difference (95% CI)[a]	*P* value for heterogeneity
	12 mg	6 mg		
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)	.32
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)	.76
<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)	.31
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)	.11
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)	.36
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)	.13
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)	.25
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)	



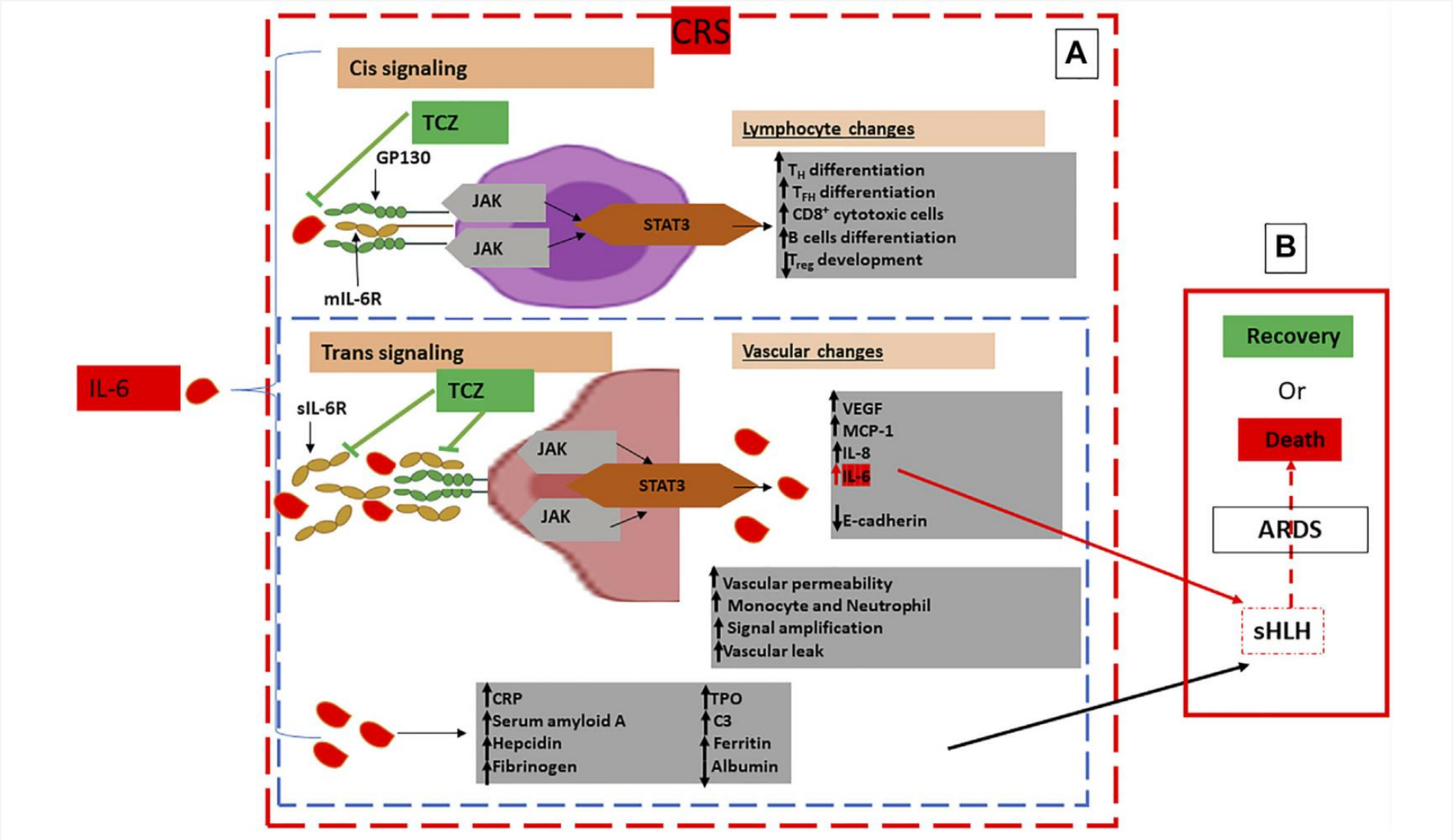
Effect of dexamethasone in patients with ARDS and COVID-19 - prospective, multi-centre, open-label, parallel-group, randomised controlled trial (REMED trial): A structured summary of a study protocol for a randomised controlled trial.

Maláska, Jan; Stasek, Jan; Duska, Frantisek; Balík, Martin; Máca, Jan; Hruda, Jan; Vymazal, Tomás; Klementová, Olga; Zatloukal, Jan; Gabrhelík, Tomás; Novotný, Pavel; Demlová, Regina; Kubátová, Jana; Vinklerová, Jana; Svobodník, Adam; Kratochvíl, Milan; Klucka, Jozef; Gál, Roman; Singer, Mervyn.

Trials ; 22(1): 172, 2021 Mar 01.

Article in English | MEDLINE | ID: covidwho-1622253

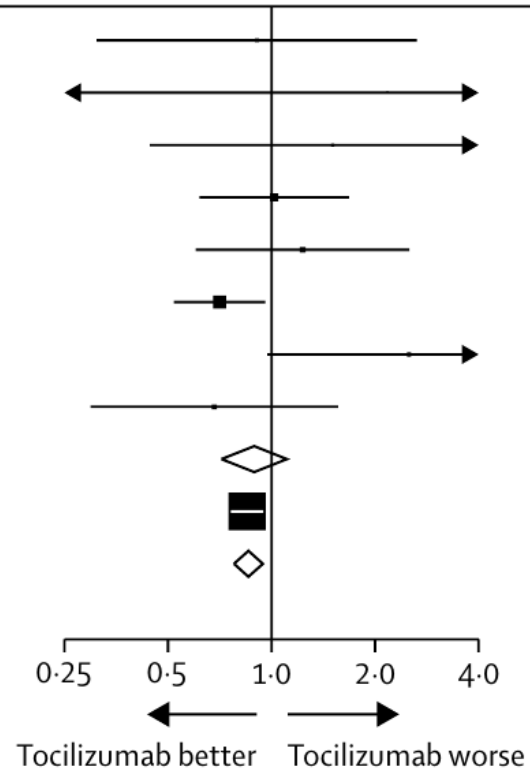
Pathogenic Host Response to SARS-CoV-2 and Pathways to Cytokine Release Syndrome (CRS)



Front. Pharmacol. 13:825749.

Meta-analysis of mortality in randomised, controlled trials of tocilizumab in patients hospitalised with COVID-19

	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO–TOCI[10]	7/64 (11%)	8/67 (12%)	–0·3	3·3	0·91 (0·31–2·65)
RCT–TCZ–COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP–CAP[15]	98/353 (28%)	142/402 (35%)	–14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	–2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**–9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	–54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**–63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017



Lancet 2021; 397: 1637-45

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

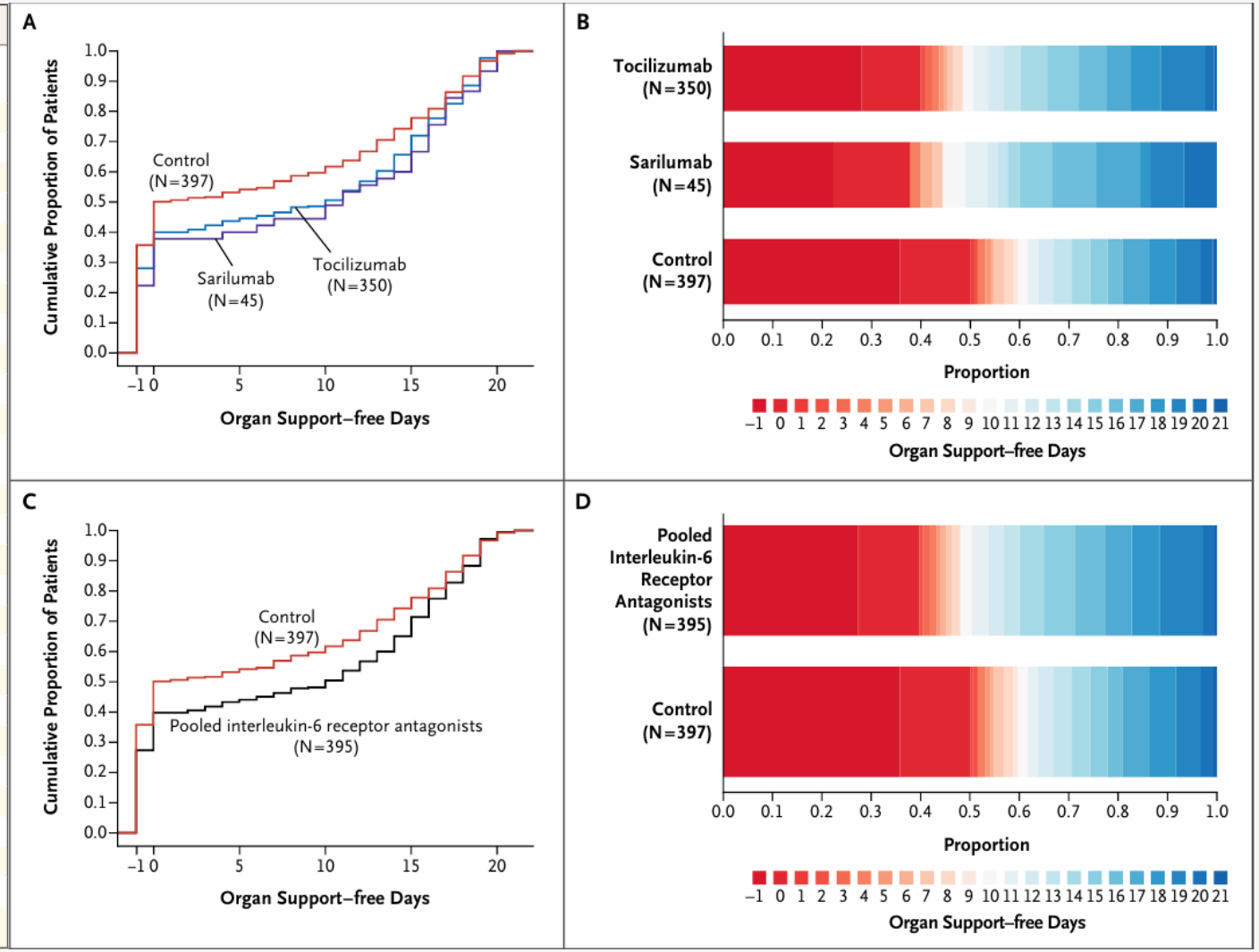
- Multifactorial, adaptive platform trial
- Within 24 hours after starting organ support in ICU
  - Respiratory organ support : invasive MV or NIV or HFNC (≥ 30L/min and ≥ 0.4)
  - Cardiovascular organ support : IV infusion of any vasopressor or inotrope
- HFNC(29%), NIV(42%), IMV(29%)
- IV tocilizumab (8mg/kg) or Sarilumab (400mg) vs. Placebo
- Primary outcome
  - The number of respiratory and cardiovascular organ support–free days up to 21 days

N Engl J Med 2021;384:1491-502.

The number of organ support free days

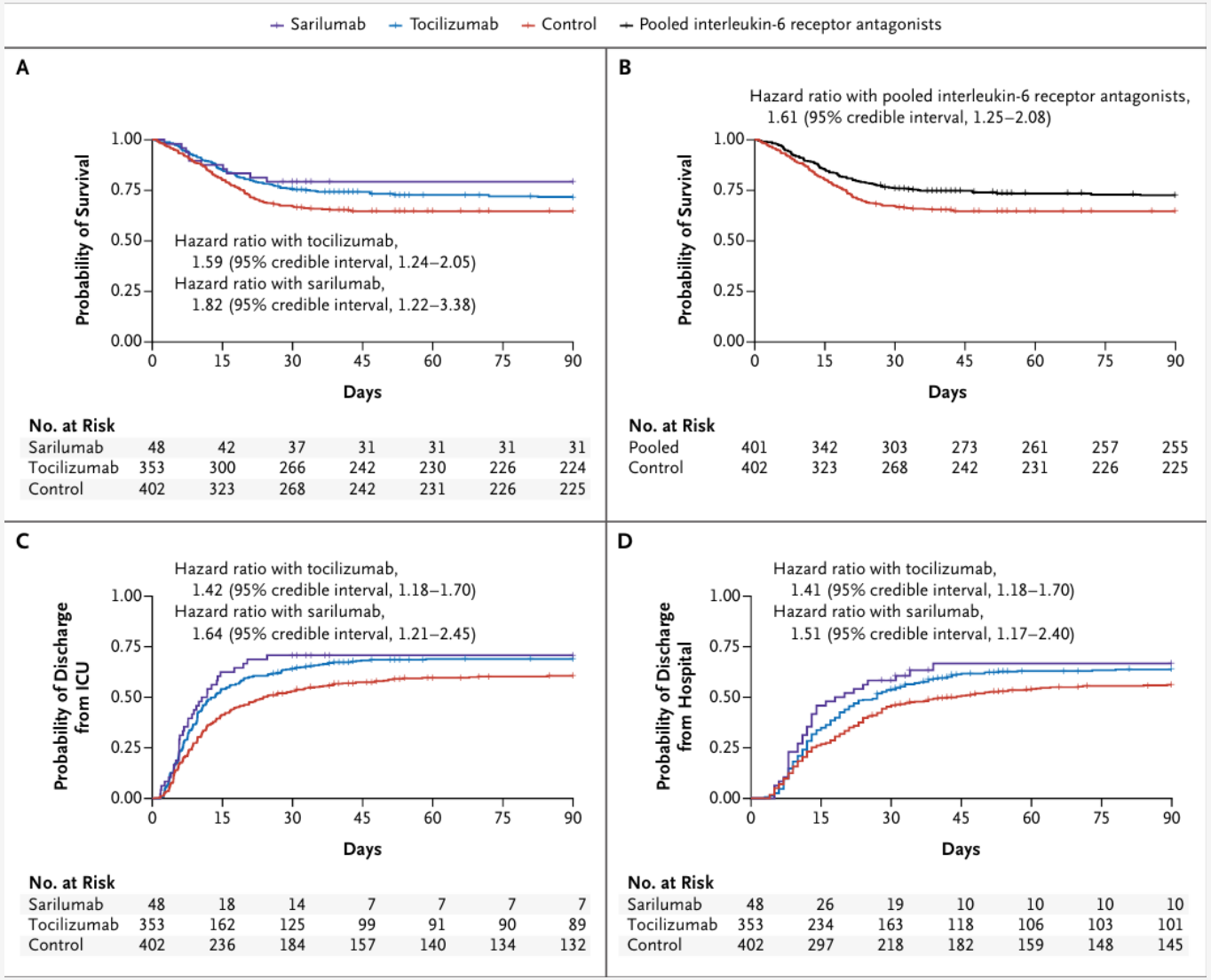
Table 2. Primary and Secondary Outcomes.*

Outcome or Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Primary outcome			
Organ support–free days			
Median (IQR)	10 (−1 to 16)	11 (0 to 16)	0 (−1 to 15)
Adjusted odds ratio			
Mean	1.65±0.23	1.83±0.44	1
Median (95% credible interval)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control — %	>99.9	99.5	—
Subcomponents of organ support–free days			
In-hospital death — no./total no. (%)	98/350 (28)	10/45 (22)	142/397 (36)
Concurrent with tocilizumab randomization	—	—	127/355 (36)†
Concurrent with sarilumab randomization	—	—	19/63 (30)†
Median no. of days free of organ support in survivors (IQR)	14 (7 to 17)	15 (6 to 17)	13 (4 to 17)
Primary in-hospital survival			
Adjusted odds ratio			
Mean	1.66±0.31	2.25±0.96	1
Median (95% credible interval)	1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)	1
Probability of superiority to control — %	99.6	99.5	—
Secondary analysis of primary outcome			
Adjusted odds ratio			
Mean	1.68±0.24	1.84±0.44	1
Median (95% credible interval)	1.66 (1.26 to 2.18)	1.77 (1.18 to 2.90)	1
Probability of superiority to control — %	>99.9	99.6	—
Secondary analysis of primary in-hospital survival			
Adjusted odds ratio			
Mean	1.67±0.31	2.24±0.94	1
Median (95% credible interval)	1.65 (1.15 to 2.34)	2.00 (1.17 to 4.69)	1
Probability of superiority to control — %	99.6	99.4	—



N Engl J Med 2021;384:1491-502.

Time to survival and ICU and hospital discharge



N Engl J Med 2021;384:1491-502.

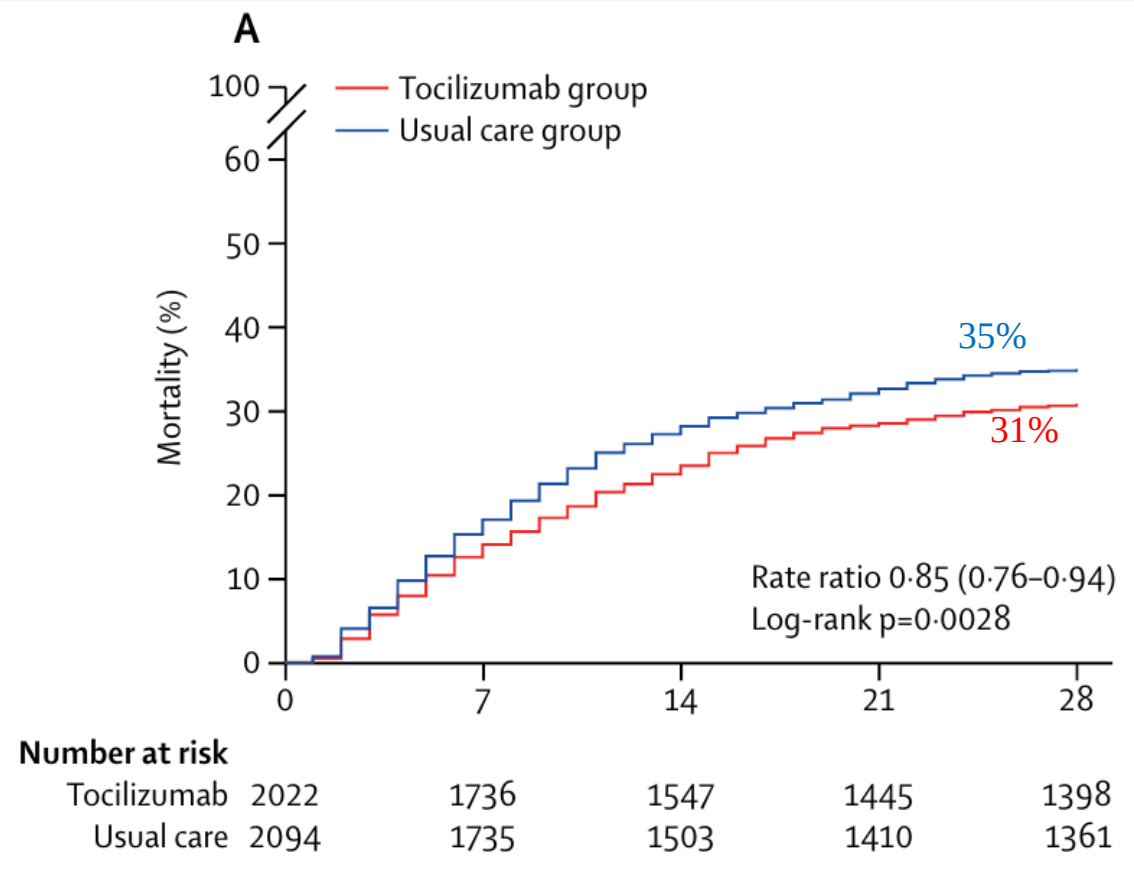
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

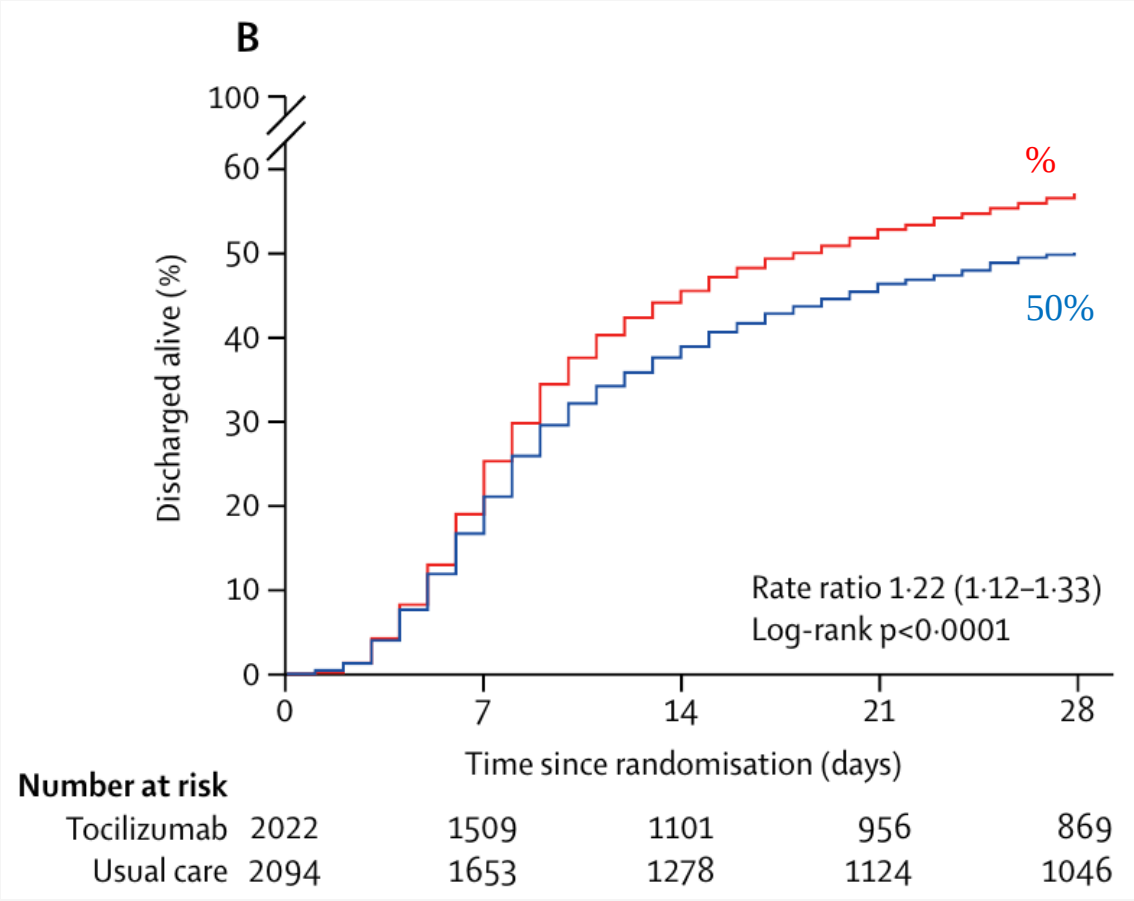
RECOVERY Collaborative Group*

- Randomized, controlled, open-label, platform trial, 4116 patients
- Hospitalized patients with progressive COVID-19 (SaO2 < 92% at RA, CRP ≥75 mg/L)
- IMV(14%), NIV(41%), O2 supply(45%)
- Corticosteroids (82%)
- IV tocilizumab (weight based) vs. Placebo
- Primary outcome
  - All cause mortality at 28 days

Lancet 2021; 397: 1637-45

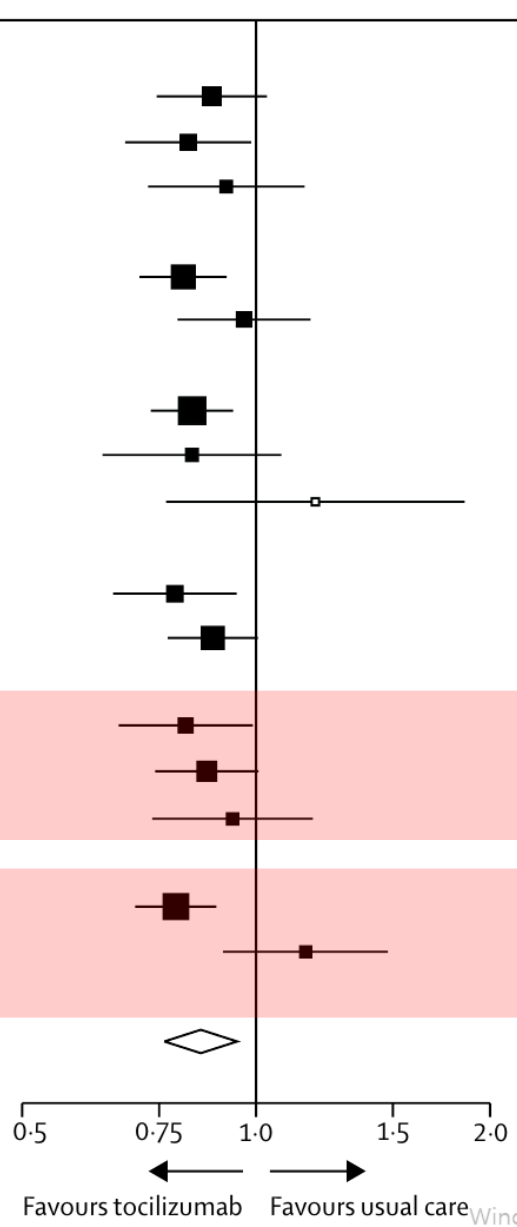
Effect of tocilizumab on 28-day mortality and hospital discharge





Lancet 2021; 397: 1637-45

	Tocilizumab group	Usual care group	Risk ratio (95% CI)
Age, years (χ^2_1=0·0; p=0·88)			
<70	273/1331 (21%)	309/1355 (23%)	0·88 (0·74–1·03)
70–79	212/478 (44%)	245/480 (51%)	0·82 (0·68–0·99)
≥80	136/213 (64%)	175/259 (68%)	0·92 (0·73–1·15)
Sex (χ^2_1=2·4; p=0·12)			
Men	417/1337 (31%)	529/1437 (37%)	0·80 (0·71–0·91)
Women	204/685 (30%)	200/657 (30%)	0·97 (0·80–1·18)
Ethnicity (χ^2_1=0·0; p=0·98)			
White	476/1530 (31%)	573/1597 (36%)	0·83 (0·73–0·94)
Black, Asian, or minority ethnic	99/354 (28%)	123/378 (33%)	0·83 (0·64–1·09)
Unknown	46/138 (33%)	33/119 (28%)	1·20 (0·77–1·88)
Days since symptom onset (χ^2_1=1·1; p=0·30)			
≤7	214/668 (32%)	256/660 (39%)	0·78 (0·65–0·94)
>7	407/1354 (30%)	473/1433 (33%)	0·88 (0·77–1·01)
Respiratory support at randomisation (χ^2_1=0·8; p=0·38)			
No ventilator support*	180/935 (19%)	214/933 (23%)	0·81 (0·67–0·99)
Non-invasive ventilation†	310/819 (38%)	366/867 (42%)	0·86 (0·74–1·00)
Invasive mechanical ventilation‡	131/268 (49%)	149/294 (51%)	0·93 (0·74–1·18)
Use of corticosteroids§ (χ^2_1=7·7; p=0·01)			
Yes	482/1664 (29%)	600/1721 (35%)	0·79 (0·70–0·89)
No	139/357 (39%)	127/367 (35%)	1·16 (0·91–1·48)
Unknown	0/1 (0%)	2/6 (33%)	..
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0·85 (0·76–0·94)**
			p=0·0028



Lancet 2021; 397: 1637-45

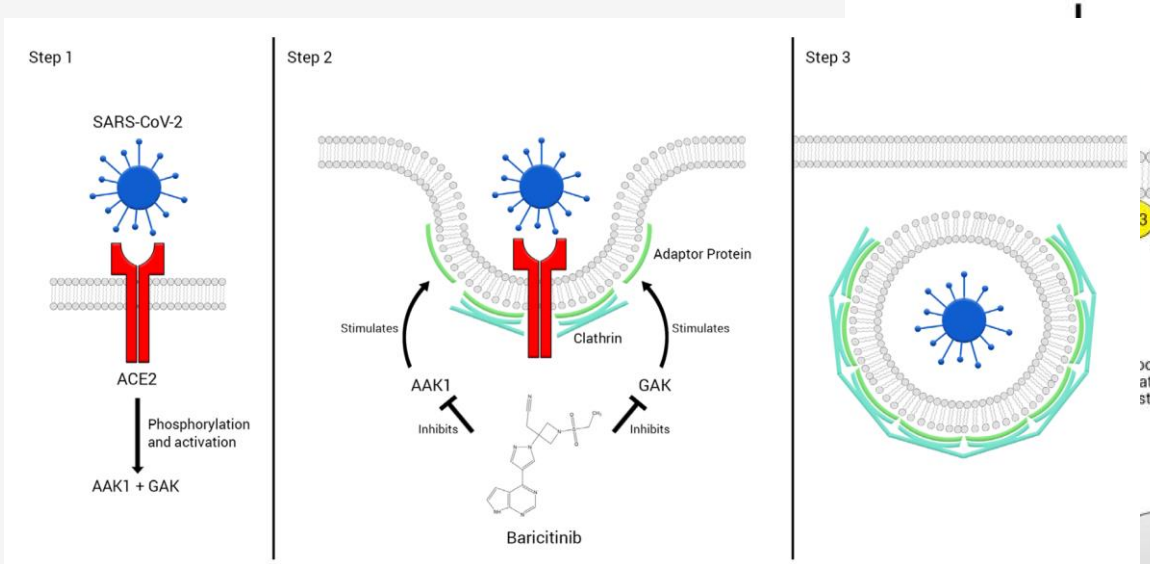
Comparison RCT of Tocilizumab

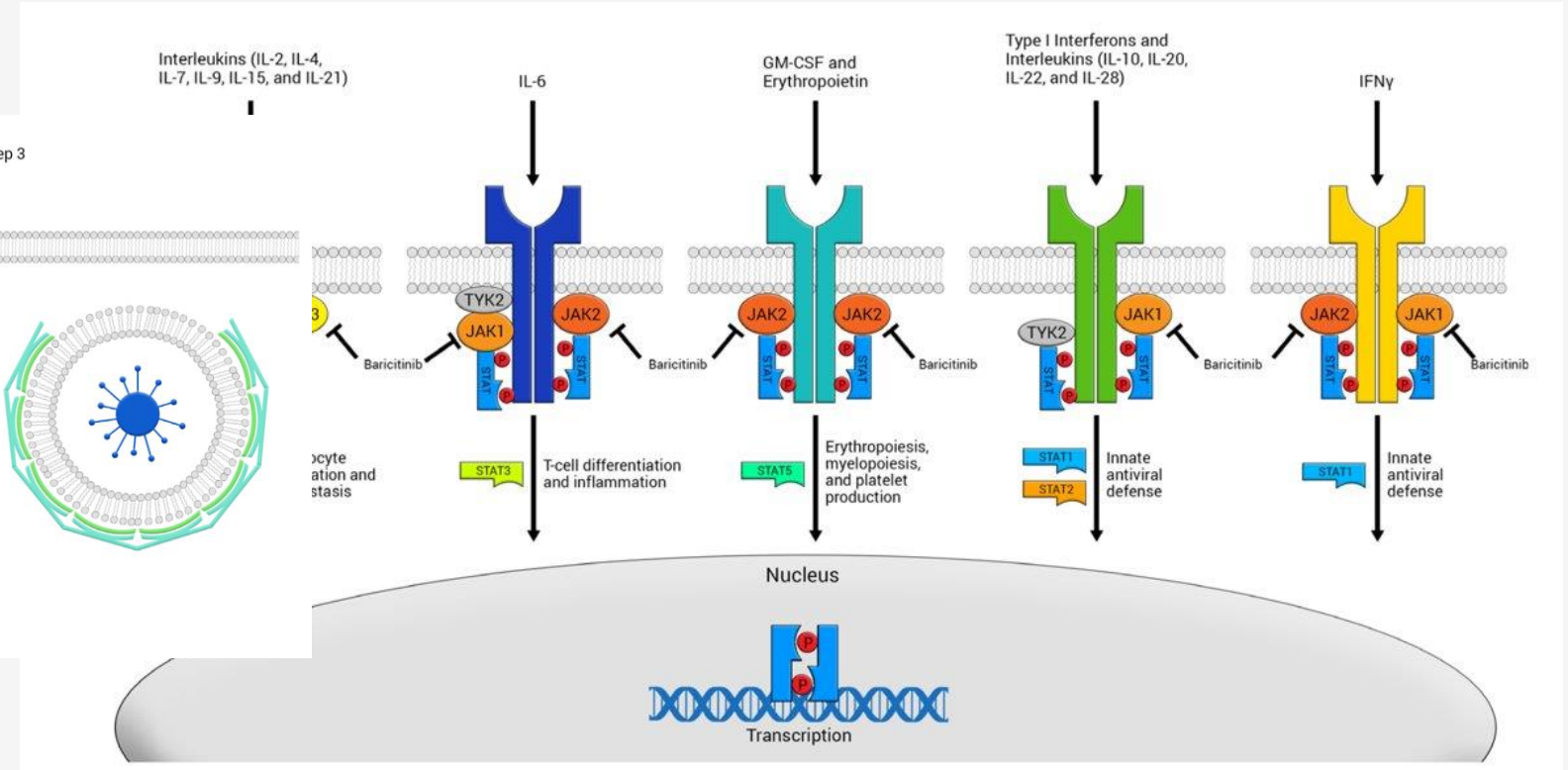
		BACC Bay	COVACTA	EMBACTA	REMAP-CAP	RECOVERY
Age		59.8	60.9	55	61.4	63
Respiratory support	No O2 supply	16%		9%		
	O2 only	80%	30%	64%	<1%	46%
	NIV	4%	30%	26%	61%	41%
	IMV		38%		29%	14%
Symptoms onset		9	12	8		9
Glucocorticoids		0%	25%	78%	93%	82%
C-reactive protein		110	170	136	136	143

- REMAP-CAP : within 24hr after ICU admission
- RECOVERY : progressive COVID-19

Baricitinib – Janus kinase inhibitor

- Janus kinase inhibitor – Jak1 & Jak 2
- Anti-cytokine properties and a potential anti-viral mechanism
- Used in auto-immune disease such as Rheumatoid arthritis



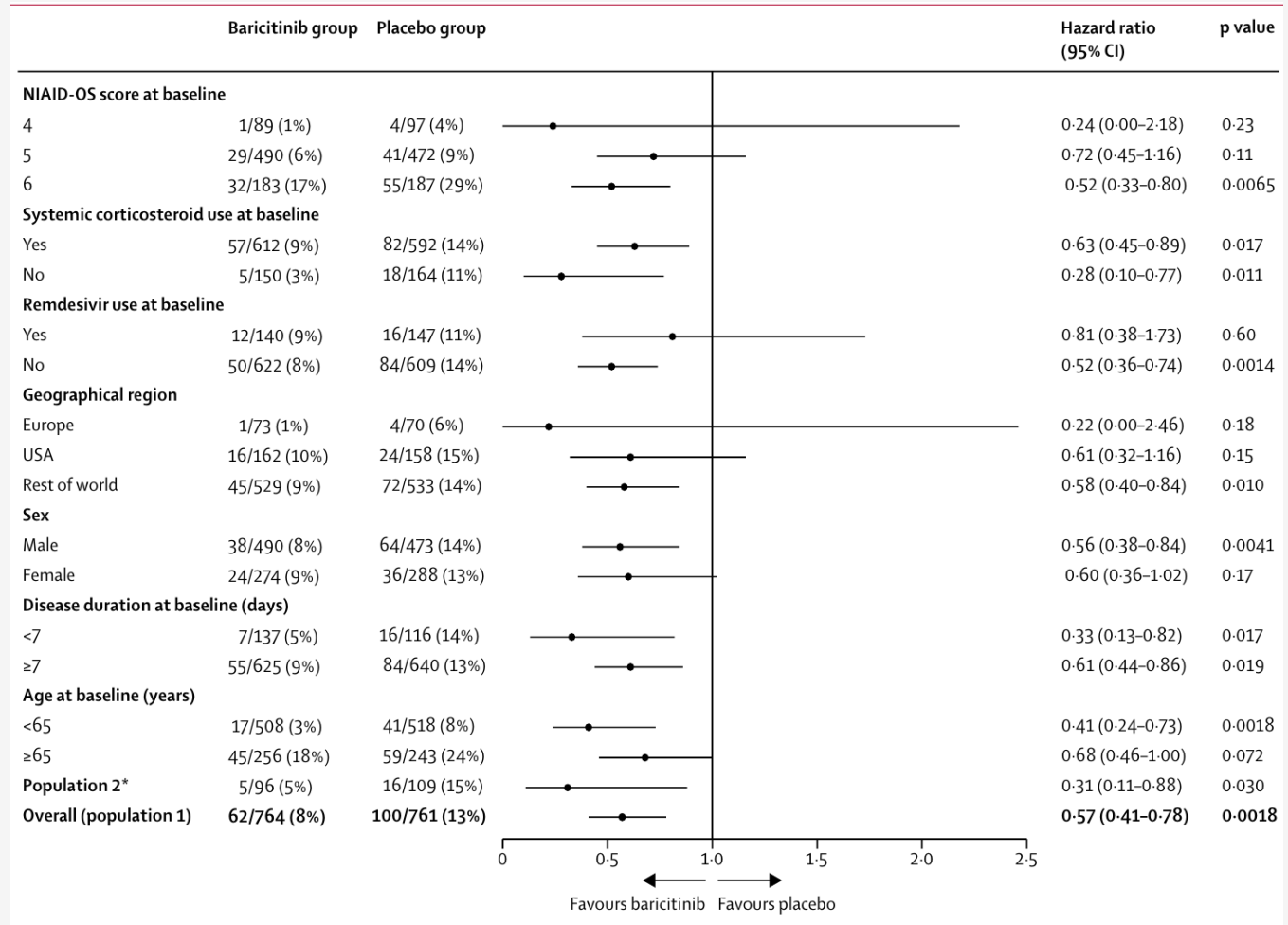


Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

- Phase 3, randomized, double-blind, placebo-controlled trial, from June 2020, to January 2021
- hospitalized with Covid-19 pneumonia & NIAID-OS 4-6
  - Bilateral pulmonary infiltrates
  - At least 1 elevated inflammatory marker (CRP, D-dimer, LDH or ferritin)
- SoC : antiviral treatment (18.9%), systemic glucocorticoids (79.3%)
- Baricitinib 4mg (n=764) + SoC vs. Placebo (n=761) + SoC up to 14 days
- Primary outcome
  - The proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28

Lancet Respir Med 2021; 9: 1407–18.

	Baricitinib group (n=764)	Placebo group (n=761)	Baricitinib vs placebo	
			Point estimate (95% CI)	p value*
Primary outcome				
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation (including ECMO), or death, by day 28†				
Population 1‡	27·8%	30·5%	OR 0·85 (0·67 to 1·08)	0·18
Population 2§	28·9%	27·1%	OR 1·12 (0·58 to 2·16)	0·73
Key secondary outcomes				
All-cause mortality	62/764 (8%)	100/761 (13%)	HR 0·57 (0·41 to 0·78)	0·0018
Likelihood of overall improvement on the NIAID-OS‡¶				
Day 4	..	..	OR 1·21 (1·00 to 1·47)	0·046
Day 7	..	..	OR 1·25 (1·04 to 1·49)	0·017
Day 10	..	..	OR 1·17 (0·97 to 1·41)	0·092
Day 14	..	..	OR 1·28 (1·05 to 1·56)	0·017
≥1-point improvement on NIAID-OS or live discharge from hospital†‡				
Day 4	25·2%	21·1%	OR 1·26 (0·98 to 1·61)	0·067
Day 7	49·8%	45·8%	OR 1·18 (0·95 to 1·46)	0·13
Day 10	65·0%	63·5%	OR 1·07 (0·86 to 1·34)	0·54
Day 14	75·6%	72·3%	OR 1·21 (0·95 to 1·55)	0·13
Median time to recovery (NIAID-OS), days	10·0 (9·0 to 11·0)	11·0 (10·0 to 12·0)	RR 1·11 (0·99 to 1·24)	0·15
Number of ventilator-free days‡	24·5 (0·39)	23·7 (0·39)	LSMD 0·75 (–0·0 to 1·5)	0·059
Duration of hospitalisation‡	12·9 (0·40)	13·7 (0·40)	LSMD –0·76 (–1·6 to 0·0)	0·063
Change from baseline in oxygen saturation from <94% to ≥94%				
Day 4	133/282 (47%)	119/282 (42%)	OR 1·20 (0·86 to 1·69)	0·29
Day 7	146/282 (52%)	146/282 (52%)	OR 0·97 (0·69 to 1·37)	0·88
Day 10	160/282 (57%)	148/282 (52%)	OR 1·15 (0·81 to 1·63)	0·43
Day 14	166/282 (59%)	166/282 (59%)	OR 0·95 (0·66 to 1·37)	0·79



Lancet Respir Med 2021; 9: 1407–18.

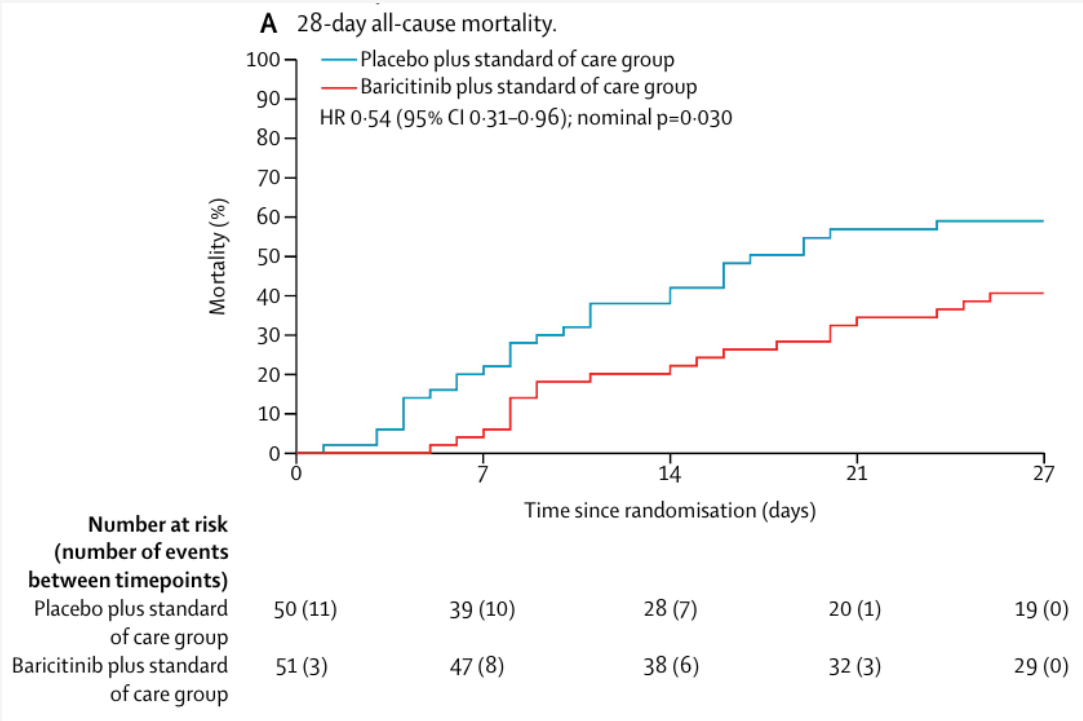
	Baricitinib group (n=750)	Placebo group (n=752)
Treatment-emergent adverse event	334 (45%)	334 (44%)
Mild	133 (18%)	115 (15%)
Moderate	90 (12%)	89 (12%)
Severe	111 (15%)	130 (17%)
Death due to adverse event*	12 (2%)	31 (4%)
Serious adverse event	110 (15%)	135 (18%)
Discontinuation from study treatment due to adverse event (including death)	56 (7%)	70 (9%)
Treatment-emergent infection	119 (16%)	123 (16%)
Serious infections	64 (9%)	74 (10%)
Venous thromboembolic event†	20 (3%)	19 (3%)
Deep vein thrombosis	4 (1%)	2 (<1%)
Pulmonary embolism	13 (2%)	9 (1%)
Other peripheral venous thrombosis	8 (1%)	10 (1%)
Major adverse cardiovascular event	8 (1%)	9 (1%)
Cardiovascular death	1 (<1%)	3 (<1%)
Myocardial infarction	4 (1%)	4 (1%)
Stroke	4 (1%)	4 (1%)
Gastrointestinal perforation	0	0

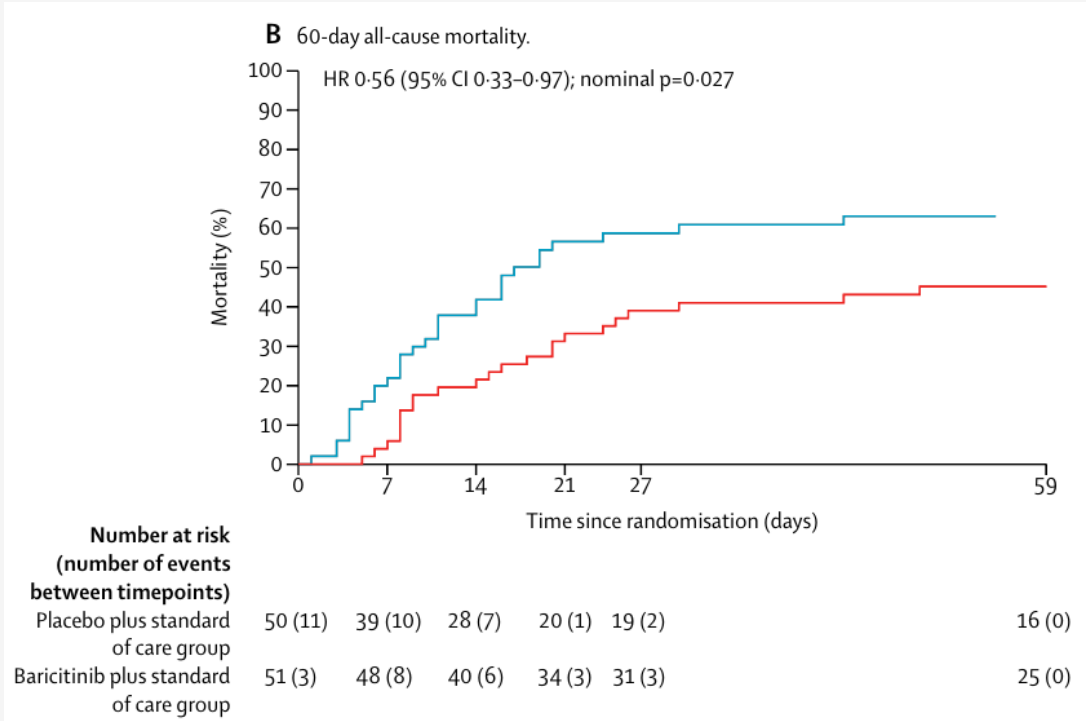
Lancet Respir Med 2021; 9: 1407–18.

Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial

- Expiratory, randomized, double-blind, placebo-controlled trial, from December 2020, to April 2021
- hospitalized with invasive MV or ECMO
- SoC : systemic glucocorticoids (86%)
- Baricitinib 4mg (n=51) + SoC vs. Placebo (n=50) + SoC up to 14 days
- Primary outcome
  - All cause mortality at day 28 and day 60

Lancet Respir Med 2022





HR 0.54 (95% CI 0.31-0.96); p=0.030

HR 0.56 (95% CI 0.33-0.97); p=0.027

Summary

- Natural history of COVID-19
  - Early – viral response
    - Antiviral agent, Convalescent plasma, Monoclonal antibody
    - As soon as possible – within 5-7 days after symptom and signs
  - Late – host immune response
    - Corticosteroids, Tocilizumab, Baricitinib


갸...감사합니다!
넙죽