COREB
mission nationale
Coordination Opérationnelle
Risque Epidémique et Biologique

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THERAPEUTIC

anRS
MALADIES INFECTIEUSES ÉMERGENTES

Scientific update on COVID-19

Updated on July 22nd 2021

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THERAPEUTIC

Questions:

- What drug showed clinical efficacy?
- What drugs did not show proven benefits?

COVID-19 Treatment

- **Dexamethasone** is the first drug to show life-saving efficacy in patients infected with COVID-19
- More data from clinical trials are needed

Classes of treatment

Anti viral effect

- (Hydroxy)chloroquine
- Ivermectin
- Lopinavir/ritonavir
- Remdesivir

Monoclonal antibody

- Anti-C5a IFX-1
- IL-1 R Antagonist
- IL-6 R Antagonist
- LY CoV 555/016
- REG CoV2

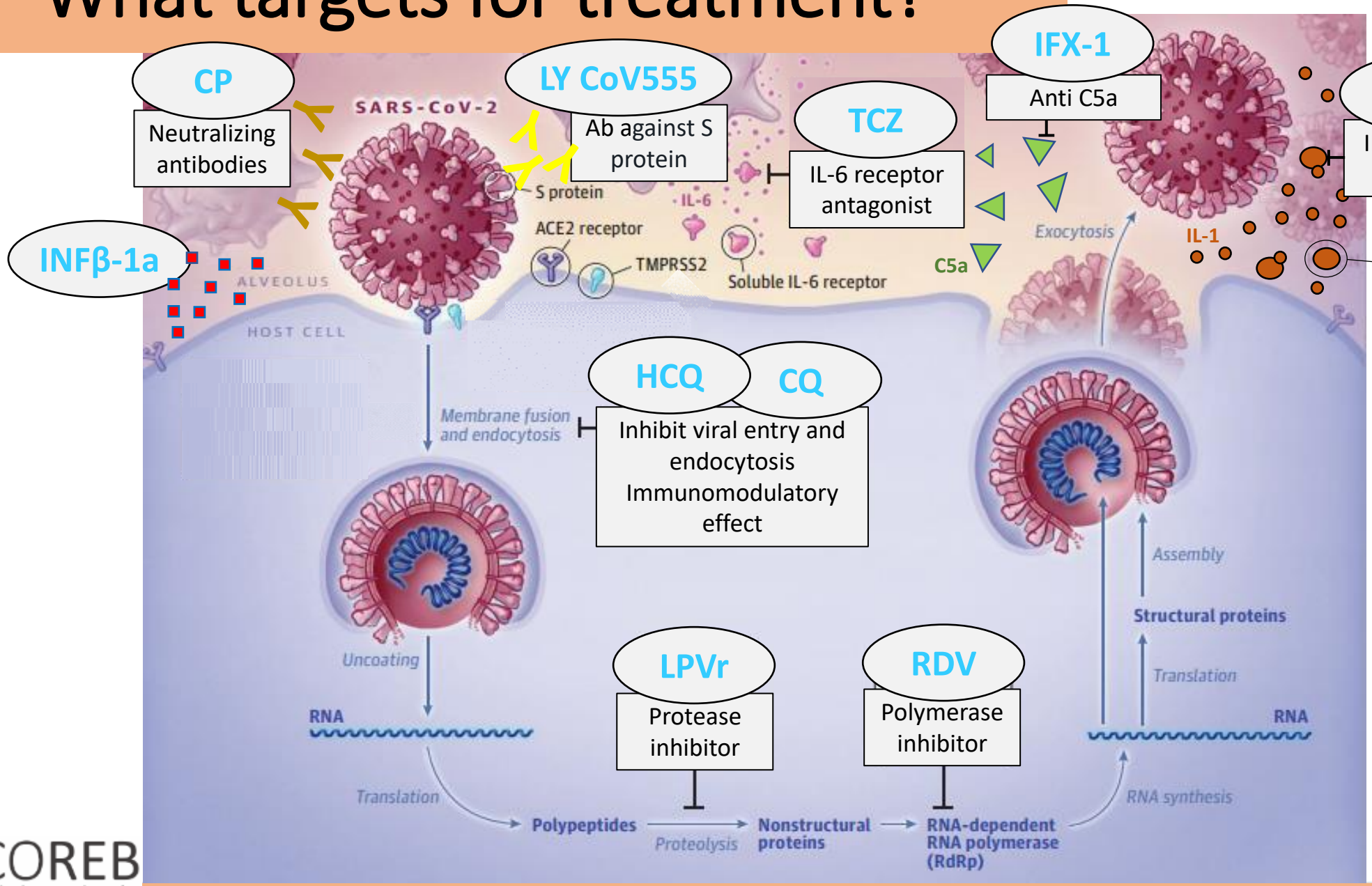
Immunomodulatory effect

- Corticosteroids
- INFβ-1a
- Janus Kinase (JAK) inhibitor

Passive immunity

- Convalescent plasma

What targets for treatment?



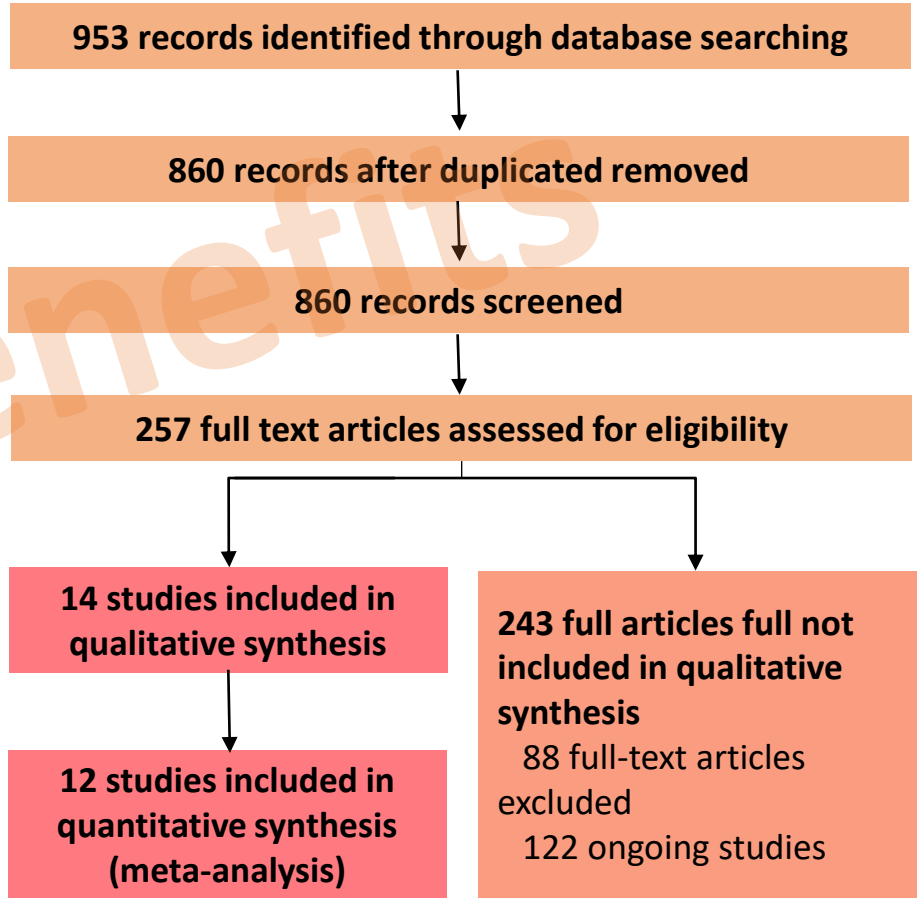
ANK: anakinra
CT: corticosteroids
CP: convalescent plasma
CQ: chloroquine
HCQ: hydroxychloroquine
IFX-1: vilobelimab
INFβ-1a: interferon beta
LPVr: lopinavir/ritonavir
RDV: remdesivir
TCZ: tocilizumab

Sanders JM *et al. JAMA* May 2020

Anti viral effect

Hydroxychloroquine (HCQ)

- Systematic review of randomized controlled trials (RCTs) , using standard Cochrane methods, academic study, UK
- **Inclusion criteria:** RCTs testing chloroquine or hydroxychloroquine in people with COVID-19, people at risk of COVID-19 exposure, and people exposed to COVID-19
- **Data collection:** Two review authors independently assessed eligibility of search results, extracted data from the included studies, and assessed risk of bias using the Cochrane "Risk of bias" tool
- **Outcomes**: Death due to any cause, negative PCR for SARS-CoV-2 on respiratory samples at D14 from enrolment, proportion admitted to hospital, progression to mechanical ventilation, length of hospital admission, time to clinical improvement, time to negative PCR for SARS-CoV-2 on respiratory samples, any adverse events…



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Singh B *et al*. *Cochrane Datatbase syst Rev Feb* 2021

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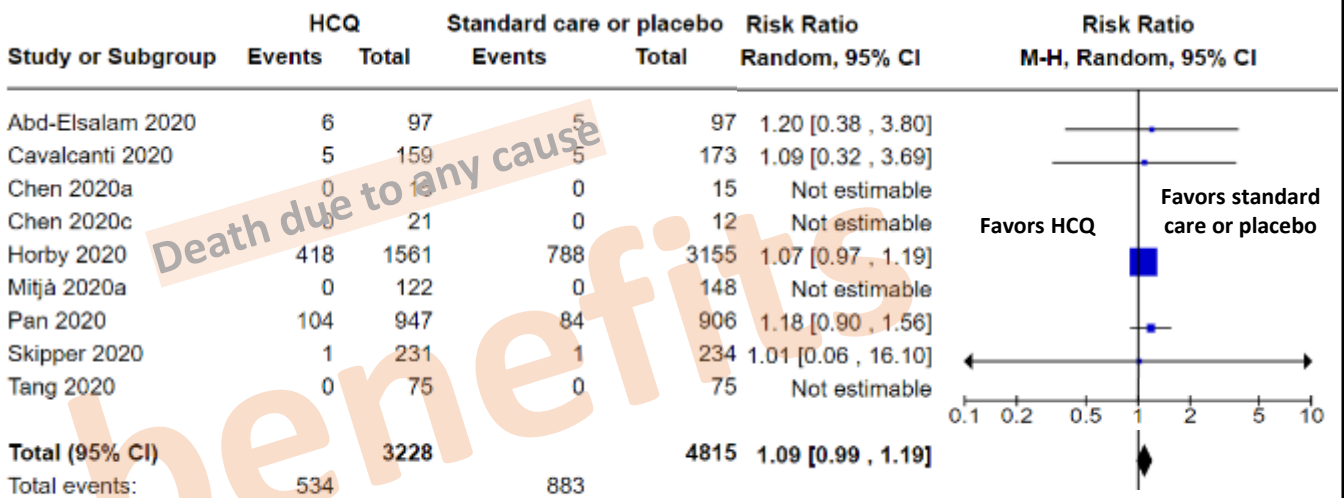
Anti viral effect

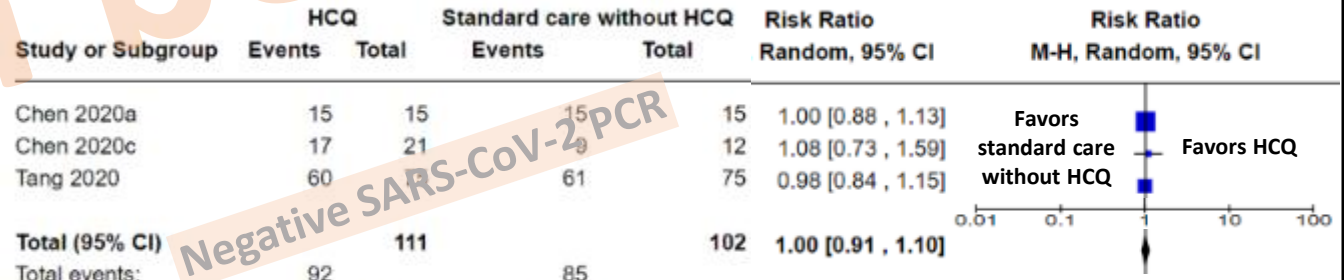
Hydroxychloroquine (HCQ)

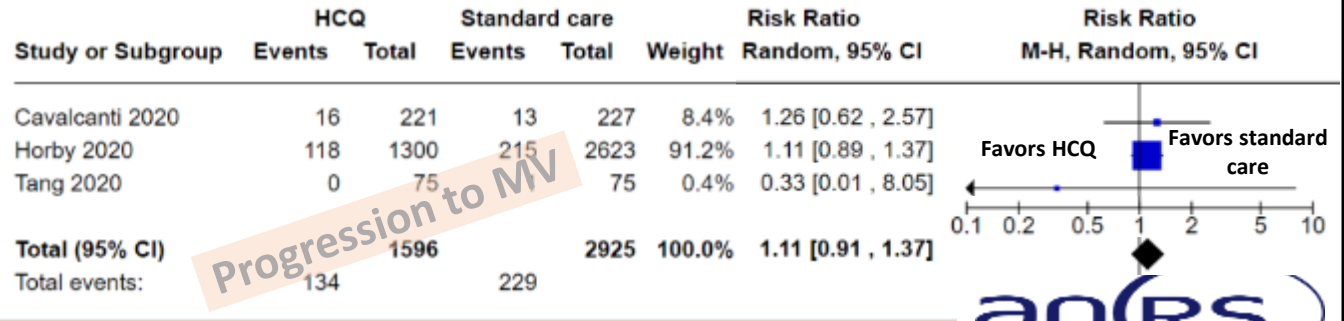
- HCQ makes little or no difference to **death due to any cause**, compared with no HCQ; RR: 1,09, $_{95\%}$CI [0,99:1,19]; 8040 participants; 9 trials

- HCQ may make little or no difference to the **likelihood of a negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment**; RR: 1, $_{95\%}$CI [0,91:1,10]; 213 participants; 3 trials

- HCQ probably results in little to no difference in **progression to mechanical ventilation**; RR: 1,11 $_{95\%}$CI [0,91:1,37]; 4521 participants; 3 trials







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MV: mechanical ventilation

Singh B *et al*. *Cochrane Datatbase syst Rev Feb* 2021

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Anti viral effect

Lopinavir/ritonavir (LPVr)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Cao	Randomized, controlled, open-label	LPVr *vs.* SoC (**Hospitalized**)	**N= 199** $SaO_2 \leq 94\%$ or $PaO_2/FiO_2 < 300$ mm Hg	Time to clinical improvement	LPVr group **not associated** with a difference in time to clinical improvement HR: 1,31 $_{95\%}$CI[0,95-1,80]
RECOVERY	Randomized, controlled, open-label	LPVr + SoC *vs.* SoC (**Hospitalized**)	**N= 5 040** Not specified	28-day all-cause mortality	LPVr + SoC group: 364/1616 (23%) *vs.* SoC group 767/3424 (22%); RR: 1,03 $_{95\%}$CI[0,91-1,17], p=0,60
Schoergenhofer	Experimental	One group (**Hospitalized**)	**N= 8** Non ICU patients	LPVr plasma concentration	Approximately 2-fold higher than HIV patients receiving the same dose (7.1 µg/mL) 60 to 120-fold higher concentrations are required to reach the assumed LPV EC_{50}

No virological data on some studies

LPVr : Lopinavir/ritonavir
SoC: Standard of Care

RECOVERY *Lancet* Oct 2020

Cao B *et al. NEJM* May 2020
Schoergenhofer *et al. Ann Int Med* May 2020

Anti viral effect

Lopinavir/ritonavir (LPVr)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
SOLIDARITY (WHO)	Multicenter, randomized, open-label, non-placebo-controlled	LPVr *vs.* control (**Hospitalized**)	**N= 2 791** Study stopped for Futility	All-cause mortality	LPVr group : 148/1399 (9,7%) *vs.* placebo group: 146/1372 (10,3%); rate ratio: 1,00; $_{95\%}$CI[0,79-1,25]; p= 0,97
Zhang	Systematic review and meta-analysis	LPVr *vs.* control specified (**Hospitalized**)	**N= 4 023** Not specified	ARDS and Mortality rate	ARDS rate: LPVr group 15,6% *vs.* control group 24,2%; p= 0,49 Mortality rate: LPVr group 6,2% *vs.* control group 5,5%; p= 0,93
DISCOVERY*	Multicenter, randomized, open-label, superiority-controlled	LPVr + SoC *vs.* SoC (**Hospitalized**)	**N= 150** $SaO_2 \leq 94\%$ or requiring supplemental O_2	D15 clinical status	LPVr *vs.* control; adjusted odds ratio: 0,83; $_{95\%}$CI[0,55-1,26]; p= 0,39

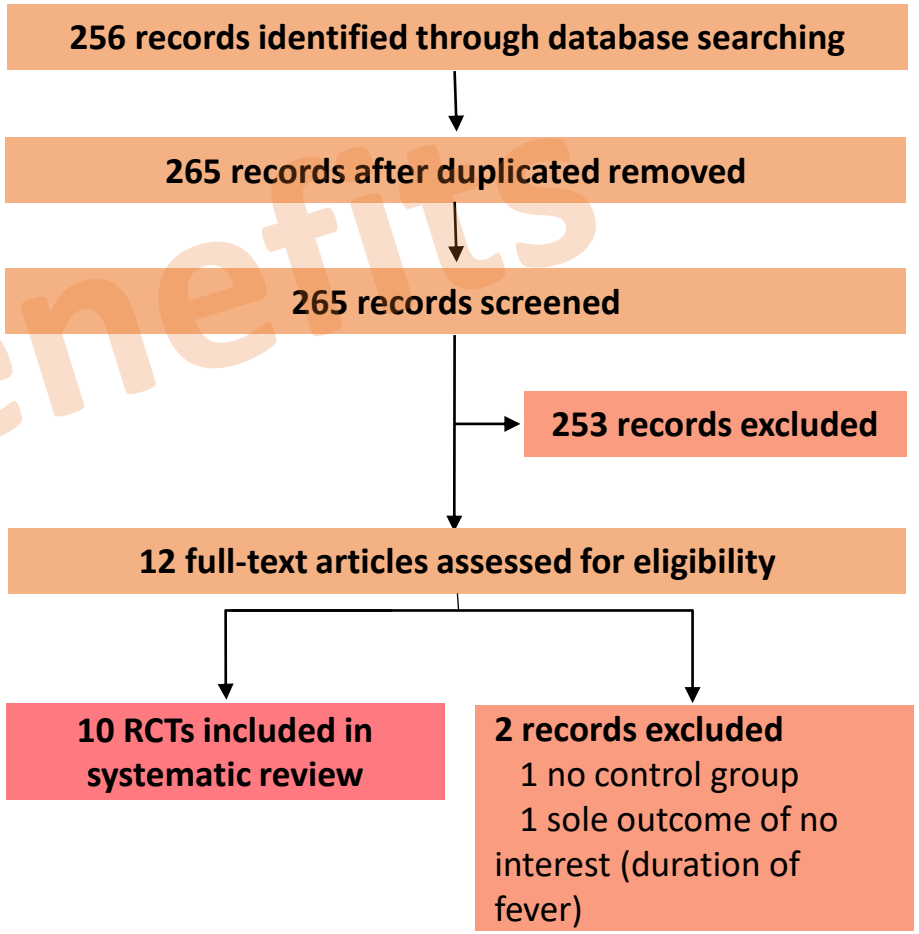
* Discovery study is included in Solidarity study

No virological data on some studies

Anti viral effect

Ivermectin (IVM)

- Systematic review of randomized controlled trials (RCTs) , academic study, USA/Peru/Brazil
- **Inclusion criteria:** RCTs assessing ivermectin effects on COVID-19 adult patients, hospitalized and non-hospitalized, irrespective of severity
- **Data collection:** Two investigators independently screened titles and abstracts, data extracted from five databases and preprints, and assessed risk of bias using the Cochrane "Risk of bias" 2.0 tool
- **Outcomes**: all-cause mortality, length of hospital stay, and adverse events (AE), SARS-CoV-2 clearance on respiratory samples, clinical improvement, need for mechanical ventilation, and severe adverse events (SAE)



Anti viral effect

Ivermectin (IVM)

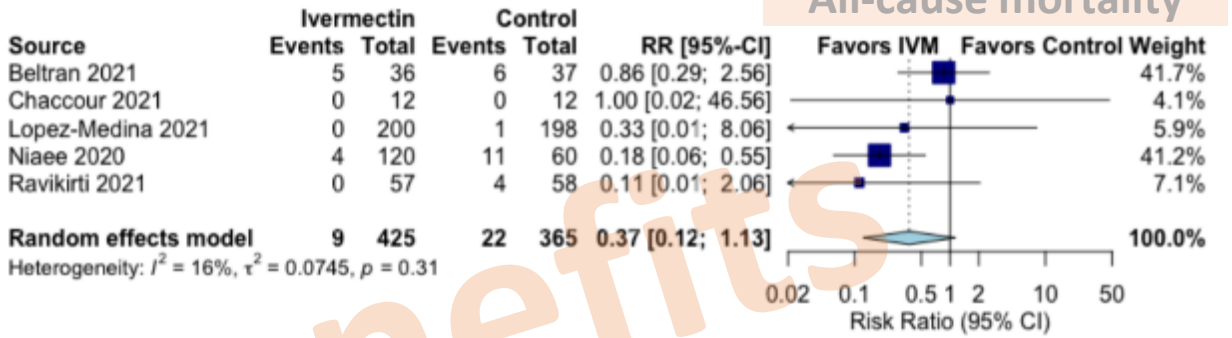
- IVM did not have effect on **all-cause mortality** compared with controls; RR: 0,37, $_{95\%}$CI [0,12:1,13]; 425 participants; 5 trials

- IVM did not have effect on **length of stay** compared with controls; Mean difference: 0,72, $_{95\%}$CI [-0,862:2,29]; 176 participants; 3 trials

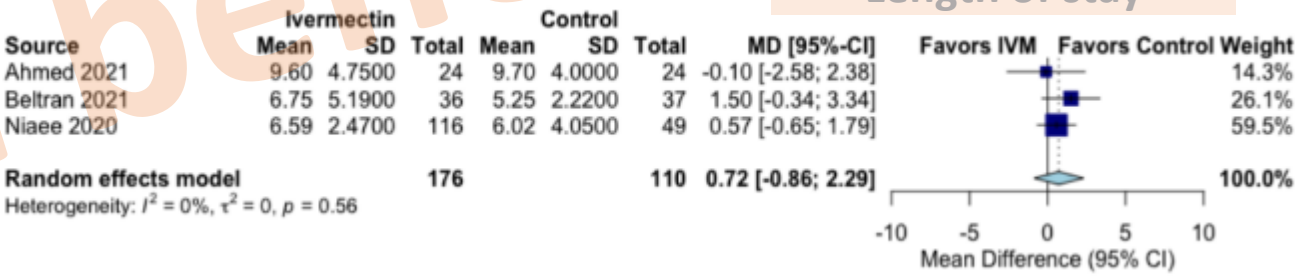
- IVM did not have effect on **adverse events** compared with controls; RR: 0,95, $_{95\%}$CI [0,79:1,07]; 425 participants; 5 trials

- No effect of IVM on **severe adverse events** in comparison to the controls; RR: 1,39, $_{95\%}$CI [0,36:5,30]; 425 participants; 5 trials

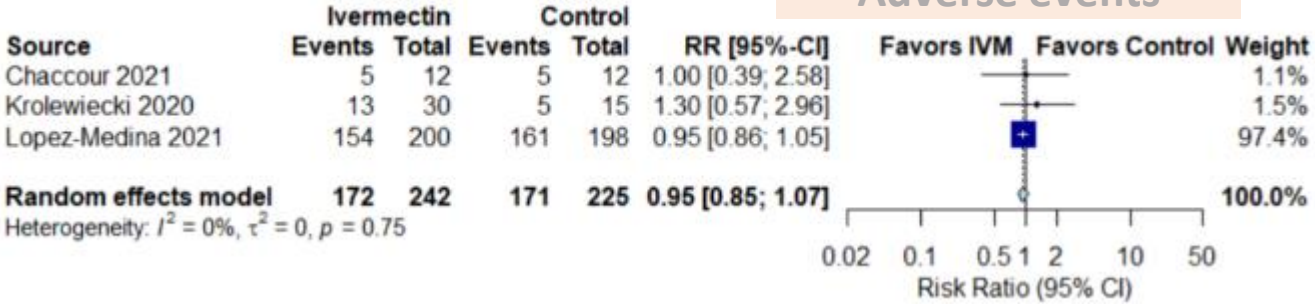
All-cause mortality



Length of stay



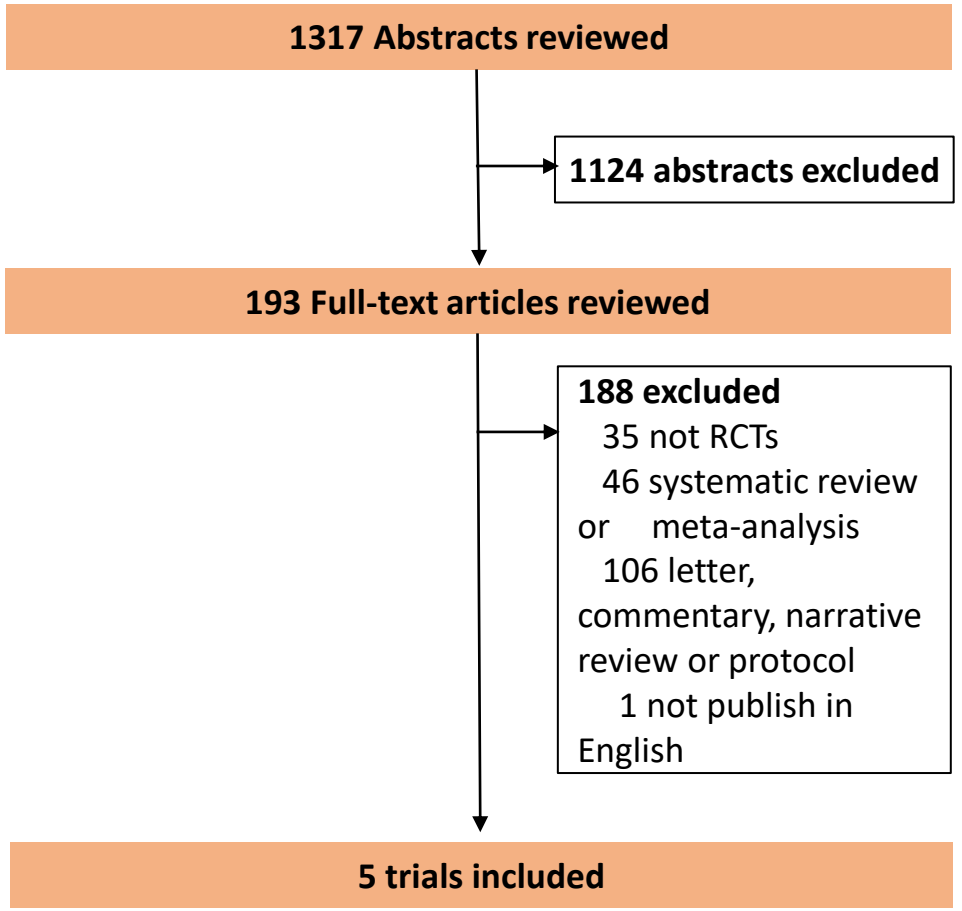
Adverse events



Anti viral effect

Remdesivir (RDV)

- Systematic review and meta-analysis of randomized controlled trials (RCTs), academic study, USA
- **Inclusion criteria:** English-language, RCTs reporting on remdesivir for treatment of adults with confirmed or suspected COVID-19. Studies were eligible if they compared remdesivir *versus* placebo, standard care, or another agent
- **Data collection:** Two investigators; one abstracted data (study information, population, disease severity, intervention…), a second reviewer verified data. The Cochrane Risk of Bias Tool and Grading of Recommendations Assessment, Development and Evaluation (GRADE) method were used
- **Outcomes**: all-cause mortality, percentage of patients who recovered, and serious adverse events (SAE)



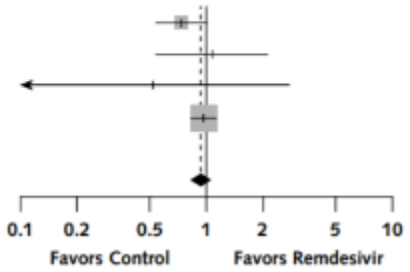
Anti viral effect

Remdesivir (RDV)

- Ten-day course of remdesivir probably results in little to no reduction in **mortality** compared with controls; RR: 0,93, $_{95\%}$CI [0,82:1,06]; 3635 participants; 4 trials
- Ten-day course of remdesivir may result in a small reduction in the **proportion of patients receiving mechanical ventilation (MV)** compared with controls; RR: 0,71, $_{95\%}$CI [0,56:0,90]; 887 participants; 3 trials
- Ten-day course of remdesivir probably reduces **serious adverse events (SAE)** by a moderate amount compared with controls; RR: 0,75, $_{95\%}$CI [0,63:0,90]; 880 participants; 3 trials

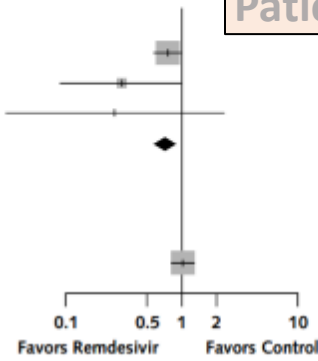
Mortality

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR (95% CI)
Beigel et al [ACTT-1], 2020 (5)	Placebo	59	541	77	521	0.74 (0.54–1.01)
Wang et al, 2020 (13)	Placebo	22	158	10	78	1.09 (0.54–2.18)
Spinner et al [SIMPLE-2], 2020 (12)	Usual care	2	193	4	200	0.52 (0.10–2.80)
Pan et al [Solidarity], 2020 (4)	Usual care	301	2743	303	2708	0.98 (0.84–1.14)
Fixed-effects model		384	3635	394	3507	0.93 (0.82–1.06)
Heterogeneity: $I^2 = 6\%$						



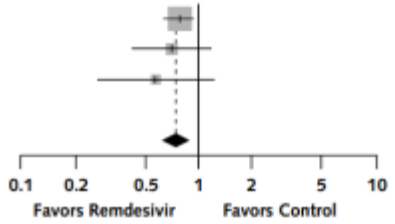
Patients with MV

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR
Proportion receiving ventilation/ECMO at follow-up*						
Beigel et al [ACTT-1], 2020 (5)	Placebo	95	541	121	521	0.76 (0.59–0.96)
Wang et al, 2020 (13)	Placebo	4	153	7	78	0.29 (0.09–0.97)
Spinner et al [SIMPLE-2], 2020 (12)	Usual care	1	193	4	200	0.26 (0.03–2.30)
Fixed-effects model		100	887	132	799	0.71 (0.56–0.90)
Heterogeneity: $I^2 = 38\%$						
Subsequent need for ventilation†						
Pan et al [Solidarity], 2020 (4)	Usual care	295	2489	284	2475	1.03 (0.89–1.20)



SAE

Study, Year (Reference)	Control	Remdesivir Events, *n*	Remdesivir Total, *n*	Control Events, *n*	Control Total, *n*	RR
Beigel et al [ACTT-1], 2020 (5)	Placebo	131	532	163	516	0.78 (0.64–0.95)
Wang et al, 2020 (13)	Placebo	28	155	20	78	0.70 (0.43–1.17)
Spinner et al [SIMPLE-2], 2020 (12)	Usual care	10	193	18	200	0.58 (0.27–1.22)
Fixed-effects model		169	880	201	794	0.75 (0.63–0.90)
Heterogeneity: $I^2 = 0\%$						

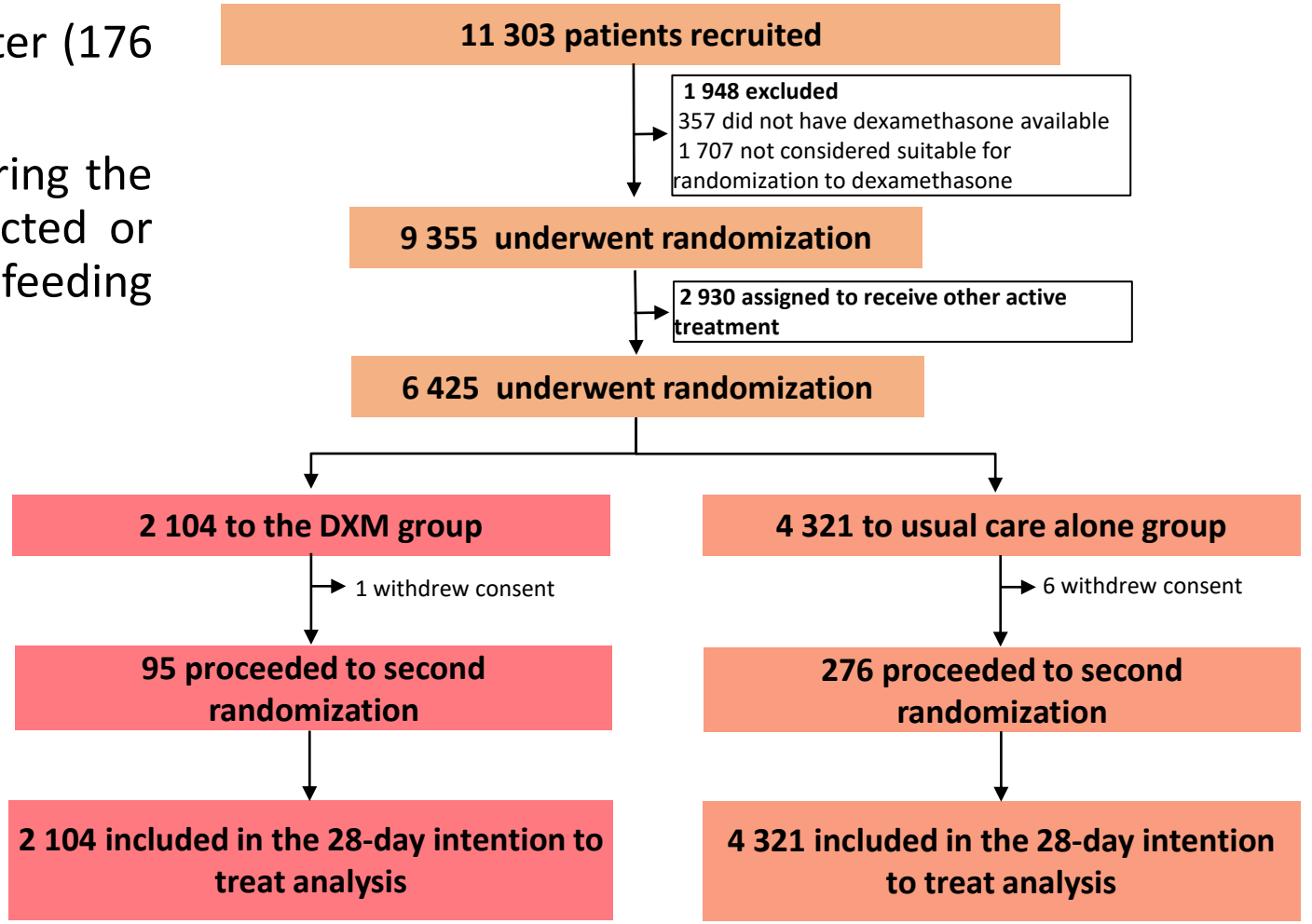


Kaka SA *et al*. Ann Intern Med *May* 2021

Immunomodulatory effect

Corticosteroids (CT) - 1

- Randomized, controlled, open-label, multi center (176 hospitals), academic study, UK (RECOVERY)
- **Inclusion criteria** : age ≥ 9yo (age changed during the study)), SARS-CoV-2 infection (clinically suspected or laboratory confirmed), pregnant or breast-feeding women were eligible
- **Primary outcome**: all-cause mortality within 28 days after randomization
- **Secondary outcome**: time until discharge from hospital, invasive mechanical ventilation (including ECMO) or death (among patients not receiving invasive mechanical ventilation at randomization)
- **6 425** participants; **4 321 usual care alone** group**, 2 104 DXM** group (2:1)



DXM: dexamethasone

RECOVERY *collaborative group NEJM* Jul 2020

Immunomodulatory effect

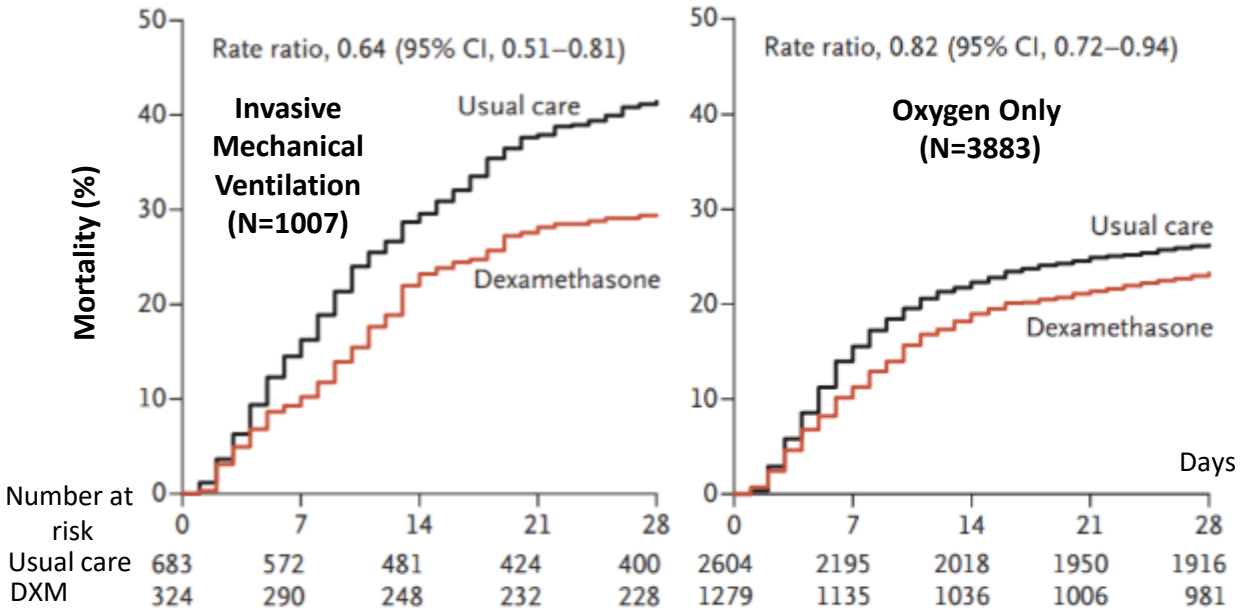
Corticosteroids (CT) - 1

	Treatment assignment	
Characteristics	**DXM (N=2 104)**	**Usual care (N=4 321)**
Age ≥ 70 yr – no (%)	963 (45)	1817 (42)
Female sex – no (%)	766 (36)	1572 (36)
Coexisting conditions		
Diabetes – no (%)	521 (25)	1025 (24)
Heart disease – no (%)	586 (49,1)	1171 (27)
Chronic lung disease – no (%)	415 (20)	931 (22)
SARS-CoV-2 test result		
Positive – no (%)	20 (18-22)	18 (18-20)
Respiratory support received		
No oxygen – no (%)	501 (24)	1034 (24)
Oxygen only – no (%)	1279 (61)	2604 (60)
Invasive mechanical ventilation – no (%)	324 (15)	683 (16)

Immunomodulatory effect

Corticosteroids (CT) - 1

- **Day 28 mortality**: 482/2104 (22,9%) DXM group *vs.* 1110/4321 (25,7%) usual care group, risk ratio 0,83 $CI_{95\%}$[0,75-0,93]
- **Discharged from hospital within 28 days**: 1413/2104 (67,2%) DXM group *vs.* 2745/4321 (63,5%) usual care group, risk ratio 1,10 $CI_{95\%}$[1,03-1,17]
- **Invasive mechanical ventilation or death**: 456/1780 (25,6%) DXM group *vs.* 994/3638 (27,3%) usual care group, risk ratio 0,92 $CI_{95\%}$[0,84-1,01]
- **<u>Limits</u>:** Preliminary report, patients without confirmed SARS-CoV-2 positive PCR included, age of inclusion changed during the study, absence of viral load follow-up



Respiratory support and randomization	DXM	Usual care	Rate ratio $CI_{95\%}$
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	1–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	2–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**5–0.93)**
			<0.001

categories: 11.5

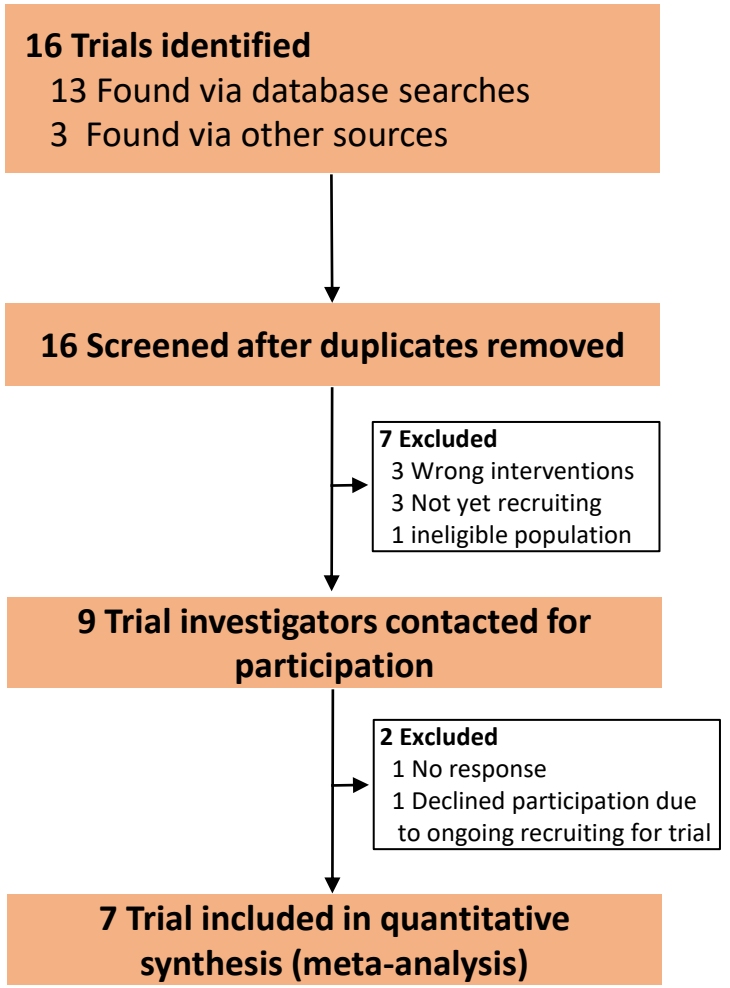
0.50 0.75 1.00 1.50 2.00

RECOVERY *collaborative group NEJM* Jul 2020

Immunomodulatory effect

Corticosteroids (CT) - 2

- Prospective Meta-analysis, academic study, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
- **Objective:** estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality
- **Primary outcome**: all-cause mortality at 28 days after randomization
- **Secondary outcome**: investigator-defined serious adverse events
- 1703 included participants; **678** (40%) **corticosteroid group** (systemic dexamethasone, hydrocortisone, or methylprednisolone); **1025** (60%) **usual care or placebo group**

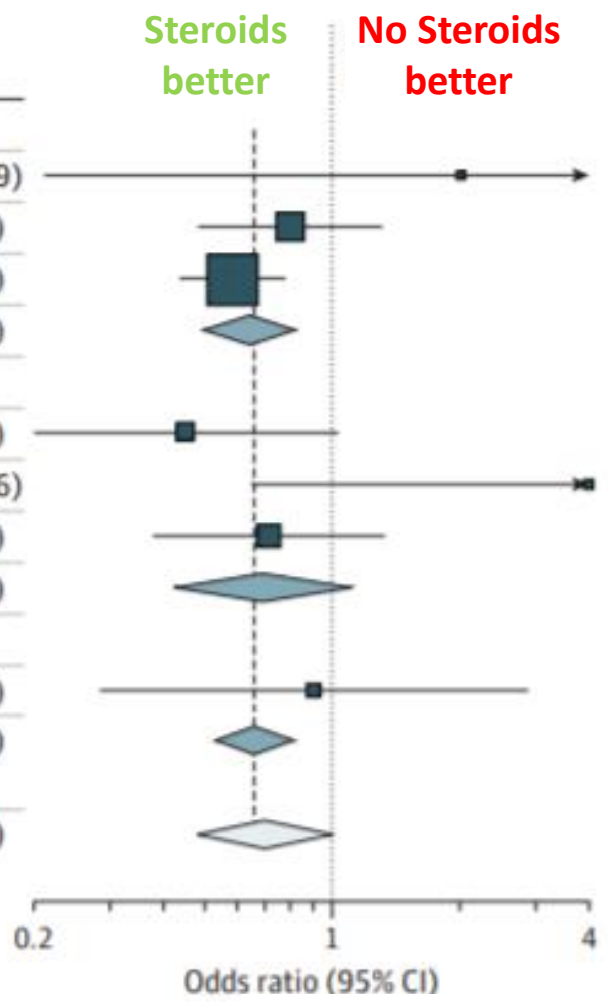


Immunomodulatory effect

Corticosteroids (CT) - 2

- 222/678 deaths among patients randomized to corticosteroids group *vs.* 425/1025 deaths among patients randomized to usual care or placebo; OR: 0,66 $IC_{95\%}$ [0,53-0,82]; p < 0,001 fixed-effect meta-analysis)
- **Association with mortality**: **DXM**: 0,64 $IC_{95\%}$ [0,5-0,82]; p<0,001 (3 trials), **HC**: 0,69 $IC_{95\%}$ [0,43-1,12]; p=0,13 (3 trials), **mPred**: 0,91 $IC_{95\%}$ [0,29-2,87]; p=0,87 (1 trial)
- **Limits**: risk of selective reporting or of publication bias, missing outcome data, trials only recruited adults, effect of corticosteroids on children remains unclear

Drug and trial	No. of deaths/total No. of patients: Steroids	No steroids	Odds ratio (95% CI)
Dexamethasone			
DEXA-COVID 19	2/7	2/12	2.00 (0.21-18.69)
CoDEX	69/128	76/128	0.80 (0.49-1.31)
RECOVERY	95/324	283/683	0.59 (0.44-0.78)
Subgroup fixed effect	166/459	361/823	0.64 (0.50-0.82)
Hydrocortisone			
CAPE COVID	1/75	20/73	0.46 (0.20-1.04)
COVID STEROID	6/15	2/14	4.00 (0.65-24.66)
REMAP-CAP	26/105	29/92	0.71 (0.38-1.33)
Subgroup fixed effect	43/195	51/179	0.69 (0.43-1.12)
Methylprednisolone			
Steroids-SARI	13/24	13/23	0.91 (0.29-2.87)
Overall (fixed effect)	222/678	425/1025	0.66 (0.53-0.82)
P = .31 for heterogeneity			
Overall (random effects[a]	222/678	425/1025	0.70 (0.48-1.01)



DXM: dexamethasone
HC: hydrocortisone - mPred: methylprednisolone

Sterne *et al. JAMA* Sep 2020

Immunomodulatory effect

Corticosteroids (CT) - 3

Author	CT	Design	Groups	Participants	Primary outcome	Main results (primary outcome)
Fadel R	**mPred**	Multi-center, quasi-experimental	mPred *vs.* no mPred	**N=213** Moderate to severe COVID-19, Median time to CT initiation from admission: 2 days (1-4)	Escalation of care from ward to ICU	SoC group 31 (44,3%) *vs.* mPred group 32 (27,3%) OR: 0,47 $_{95\%}$CI[0,25-0,88], p= 0,017
					New requirement for MV	SoC group 26 (36,6%) *vs.* CT group 26 (21,7%) OR: 0,47 $_{95\%}$CI[0,25-0,92], p= 0,025
					Death	SoC group 21 (26,3%) *vs.* CT group 18 (13,6%) OR: 0,45 $_{95\%}$CI[0,22-0,91], p= 0,024
Nelson B	**mPred**	Case-control study	mPred *vs.* control	**N=117** Requiring MV Median time from symptom onset to admission: 7 days (3–8)	D28 ventilator-free after admission	mPred group 6,2 *vs.* control group 3,14, p=0,044

Immunomodulatory effect

Corticosteroids (CT) - 4

Author	CT	Design	Groups	Participants	Primary outcome	Main results (primary outcome)
Prado Jeronimo	**mPred**	Parallel, double-blind, placebo-controlled, randomized	mPred *vs.* placebo	**N=416** Suspected COVID-19 hospitalized patients Median time from illness onset to randomization: 13 days (9–16)	D28 mortality	mPred group 72/194 (37,1%) *vs.* placebo group 76/199 (38,2%) HR: 0,924 $_{95\%}$CI[0,669-1,275]; p= 0,629
Tomazini	**DXM**	Multicenter, randomized, open-label	DXM + SoC *vs.* SoC	**N= 299** Receiving MV, Median time since symptom onset: DXM group: 9 days (7-11) vs. SoC group 10 days (6-12)	Ventilator-free days during the first 28 days	**Study interrupted** DXM + SoC group 6,6 $IC_{95\%}$ [5-8,2] *vs.* SoC group 4,0 $_{95\%}$CI[2,9-5,4]; p= 0,04

mPred: methylprednisolone - DXM: dexamethasone
MV: mechanical ventilation

Prado Jeronimo *et al. CID* Aug 2020
Tomazini BM *et al. JAMA* Sep 2020

Immunomodulatory effect

Corticosteroids (CT) - 5

Author	CT	Design	Groups	Participants	Primary outcome	Main results (primary outcome)
Dequin	**HC**	Multicenter randomized double-blind	HC *vs.* placebo	**N=149** Critically ill, acute respiratory failure Median durations of symptoms prior to randomization: HC group 9 days (7-11,5) vs. placebo group 10 days (8-12)	D21 treatment failure	**Study stopped early** HC group 32/76 (42,1%) *vs.* placebo group 37/76 (50,7%) p= 0,29
Angus	**HC**	Multicenter, open label trial	HC *vs.* placebo	**N=384** Admitted in ICU for respiratory or cardiovascular organ support	D21 respiratory and cardiovascular organ support–free	**Study stopped early** No treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions

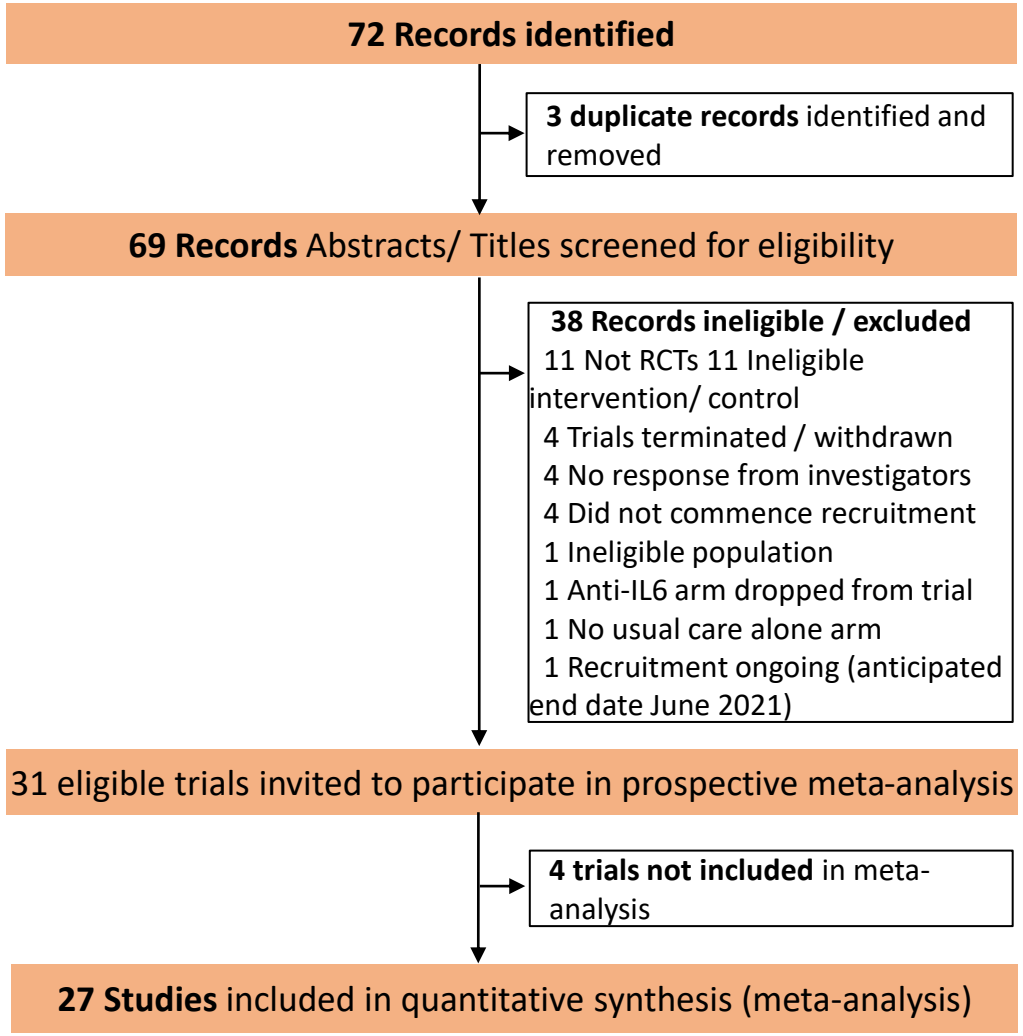
HC: hydrocortisone

Dequin PF *et al. JAMA* Sep 2020
Angus DC *et al. JAMA* Sep 2020

Immunomodulatory effect

IL-6 Receptor Antagonist

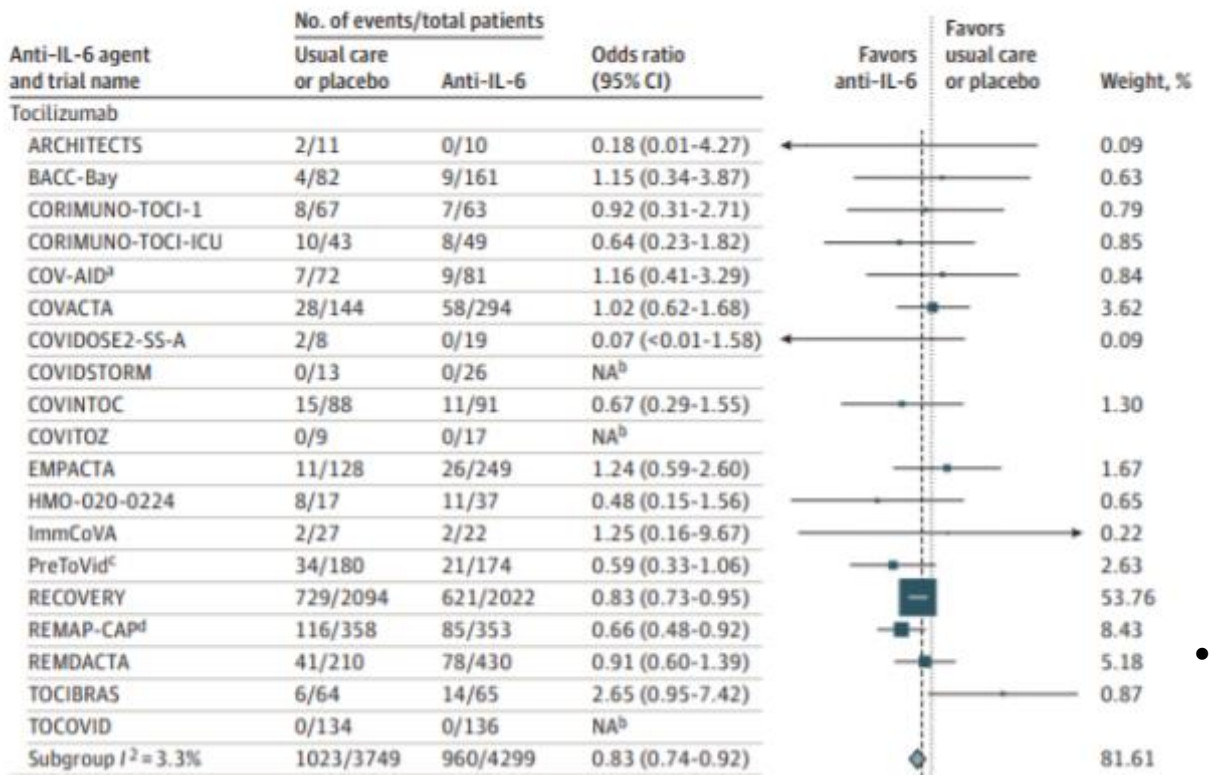
- Prospective meta-analysis, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
- **Inclusion criteria:** clinical trials, hospitalized COVID-19 patients, administration of IL-6 antagonists compared with usual care or placebo
- **Data collection:** systematic searches of ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform. Search terms employed included IL-6, IL-6 antagonist, tocilizumab, sarilumab, COVID-19, SARS-CoV-2. Bias assessed using version 2 of the "Cochrane Risk of Bias". GRADE approach used to assess certainty of the evidence
- **Outcomes**: all-cause mortality at 28 days after randomization



Immunomodulatory effect

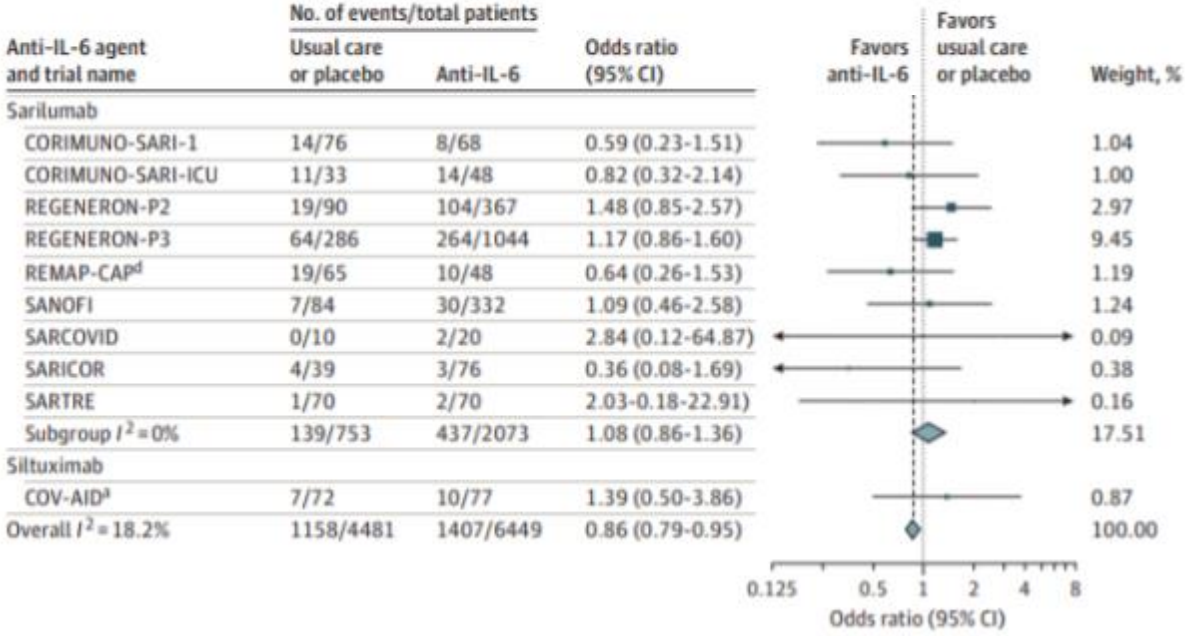
IL-6 Receptor Antagonist

- **D28 all-cause mortality tocilizumab:** 960/4299 (22%) tocilizumab group *vs.* 1023/3749 (25%) usual care or placebo group; OR: 0,83, $_{95\%}$CI [0,74:0,92]; p<0,001, 8048 participants; 19 trials.
- **D28 all-cause mortality sarilumab:** 473/2073 (26%) sarilumab group vs. 139/753 (25%) usual care or placebo group; OR: 1,08, $_{95\%}$CI [0,86:1,36]; p=0,52, 2826 participants; 9 trials



Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	2/11	0/10	0.18 (0.01-4.27)	0.09
BACC-Bay	4/82	9/161	1.15 (0.34-3.87)	0.63
CORIMUNO-TOCI-1	8/67	7/63	0.92 (0.31-2.71)	0.79
CORIMUNO-TOCI-ICU	10/43	8/49	0.64 (0.23-1.82)	0.85
COV-AID[a]	7/72	9/81	1.16 (0.41-3.29)	0.84
COVACTA	28/144	58/294	1.02 (0.62-1.68)	3.62
COVIDOSE2-SS-A	2/8	0/19	0.07 (<0.01-1.58)	0.09
COVIDSTORM	0/13	0/26	NA[b]	
COVINTOC	15/88	11/91	0.67 (0.29-1.55)	1.30
COVITOZ	0/9	0/17	NA[b]	
EMPACTA	11/128	26/249	1.24 (0.59-2.60)	1.67
HMO-020-0224	8/17	11/37	0.48 (0.15-1.56)	0.65
ImmCoVA	2/27	2/22	1.25 (0.16-9.67)	0.22
PreToVid[c]	34/180	21/174	0.59 (0.33-1.06)	2.63
RECOVERY	729/2094	621/2022	0.83 (0.73-0.95)	53.76
REMAP-CAP[d]	116/358	85/353	0.66 (0.48-0.92)	8.43
REMDACTA	41/210	78/430	0.91 (0.60-1.39)	5.18
TOCIBRAS	6/64	14/65	2.65 (0.95-7.42)	0.87
TOCOVID	0/134	0/136	NA[b]	
Subgroup I^2 = 3.3%	1023/3749	960/4299	0.83 (0.74-0.92)	81.61

Favors anti-IL-6 | Favors usual care or placebo



Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Sarilumab				
CORIMUNO-SARI-1	14/76	8/68	0.59 (0.23-1.51)	1.04
CORIMUNO-SARI-ICU	11/33	14/48	0.82 (0.32-2.14)	1.00
REGENERON-P2	19/90	104/367	1.48 (0.85-2.57)	2.97
REGENERON-P3	64/286	264/1044	1.17 (0.86-1.60)	9.45
REMAP-CAP[d]	19/65	10/48	0.64 (0.26-1.53)	1.19
SANOFI	7/84	30/332	1.09 (0.46-2.58)	1.24
SARCOVID	0/10	2/20	2.84 (0.12-64.87)	0.09
SARICOR	4/39	3/76	0.36 (0.08-1.69)	0.38
SARTRE	1/70	2/70	2.03-0.18-22.91)	0.16
Subgroup I^2 = 0%	139/753	437/2073	1.08 (0.86-1.36)	17.51
Siltuximab				
COV-AID[a]	7/72	10/77	1.39 (0.50-3.86)	0.87
Overall I^2 = 18.2%	1158/4481	1407/6449	0.86 (0.79-0.95)	100.00

Favors anti-IL-6 | Favors usual care or placebo

0.125 | 0.5 | 1 | 2 | 4 | 8

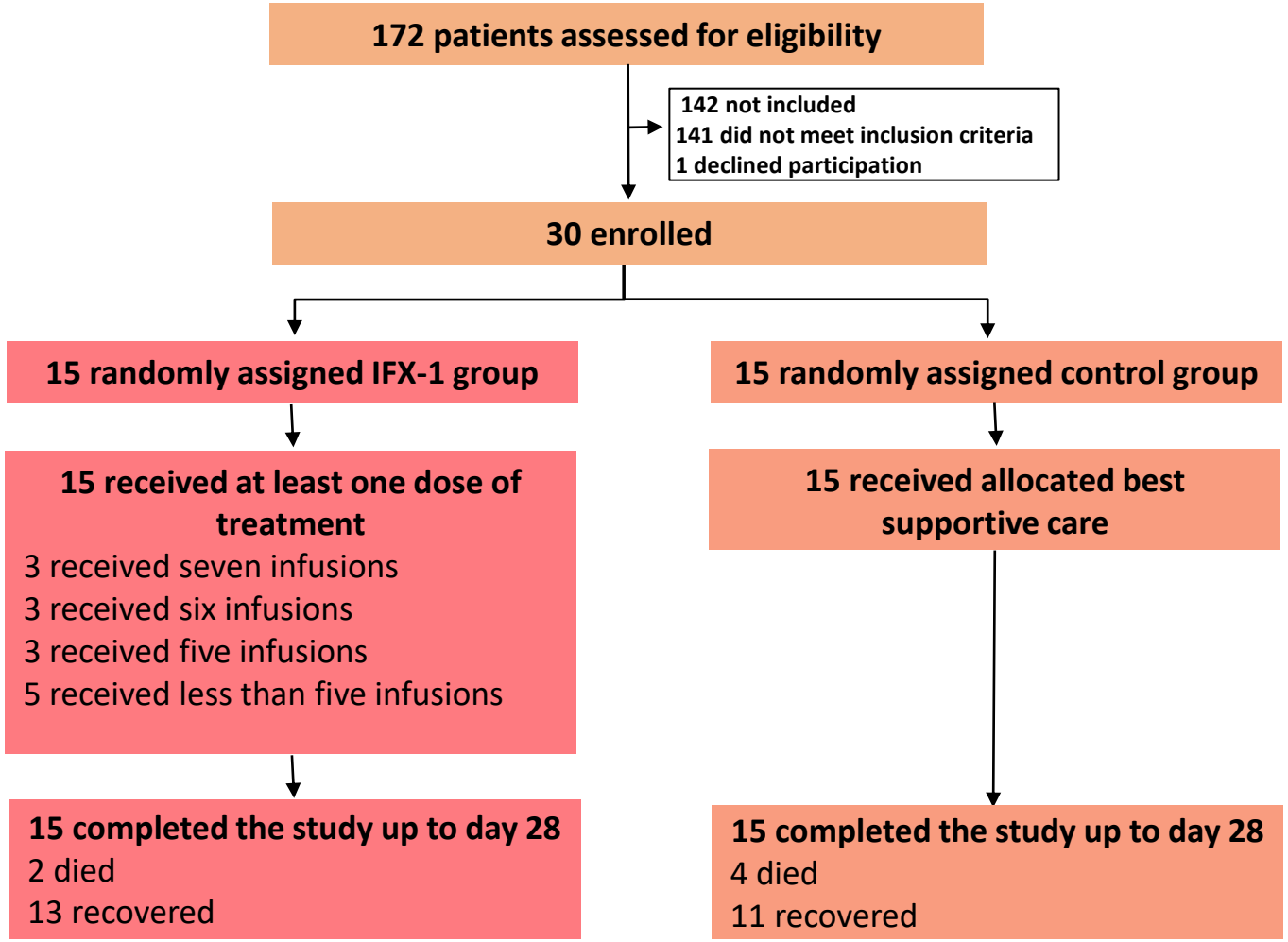
Odds ratio (95% CI)

- **D28 all-cause mortality overall IL-6 Receptor antagonist:** 1407/6449 (22%) IL6 group vs. 1158/4481 (25%) usual care or placebo group; OR: 0,86, $_{95\%}$CI [0,79:0,95]; p=0,003

Monoclonal antibody

Vilobelimab (IFX-1)

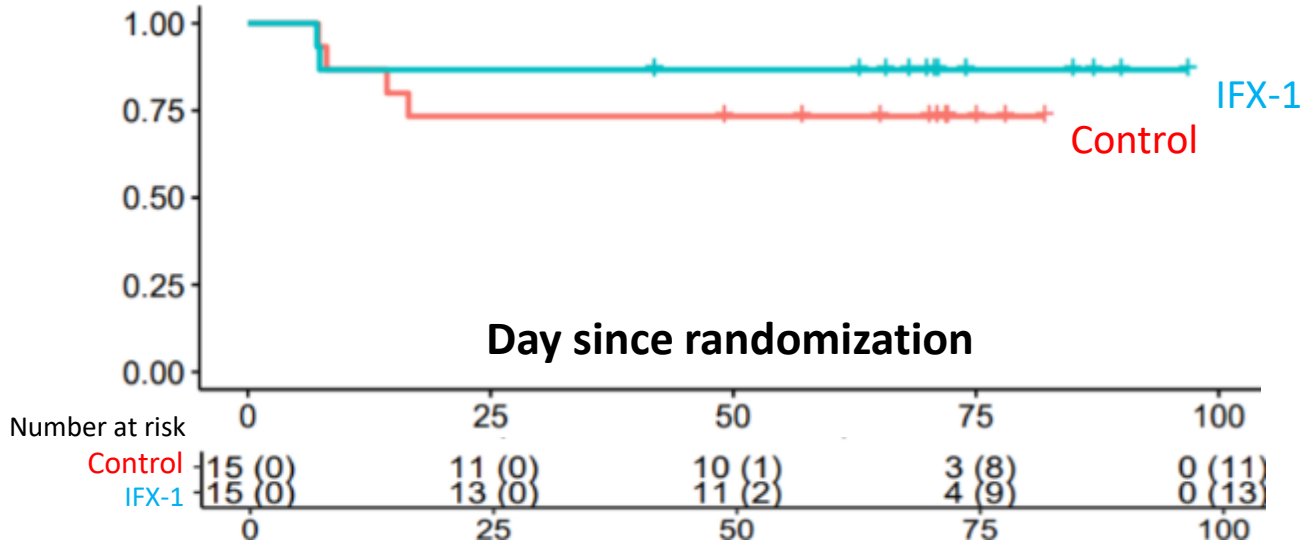
- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria** : age ≥ 18yo, severe pneumonia (PaO_2/FiO_2 between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive ventilation
- **Primary outcome**: Day 5 PaO_2/FiO_2 percentage change from the baseline
- **Secondary outcome**: Day 28 mortality
- **30** participants; **15 control** group**, 15 IFX-1 treated** group (1:1)



Monoclonal antibody

Vilobelimab (IFX-1)

- **Day 5 PaO_2/FiO_2 percentage change**: no differences; IFX-1 group (17%) *vs*. control group (41%); difference –24% $_{95\%}$CI[–58-9], p=0,15
- **D28 mortality**: IFX-1 group 13%; $_{95\%}$CI[0-31] *vs*. control group 27 %; $_{95\%}$CI[7-49]; HR=0,65 $_{95\%}$CI[0,1-4,14]



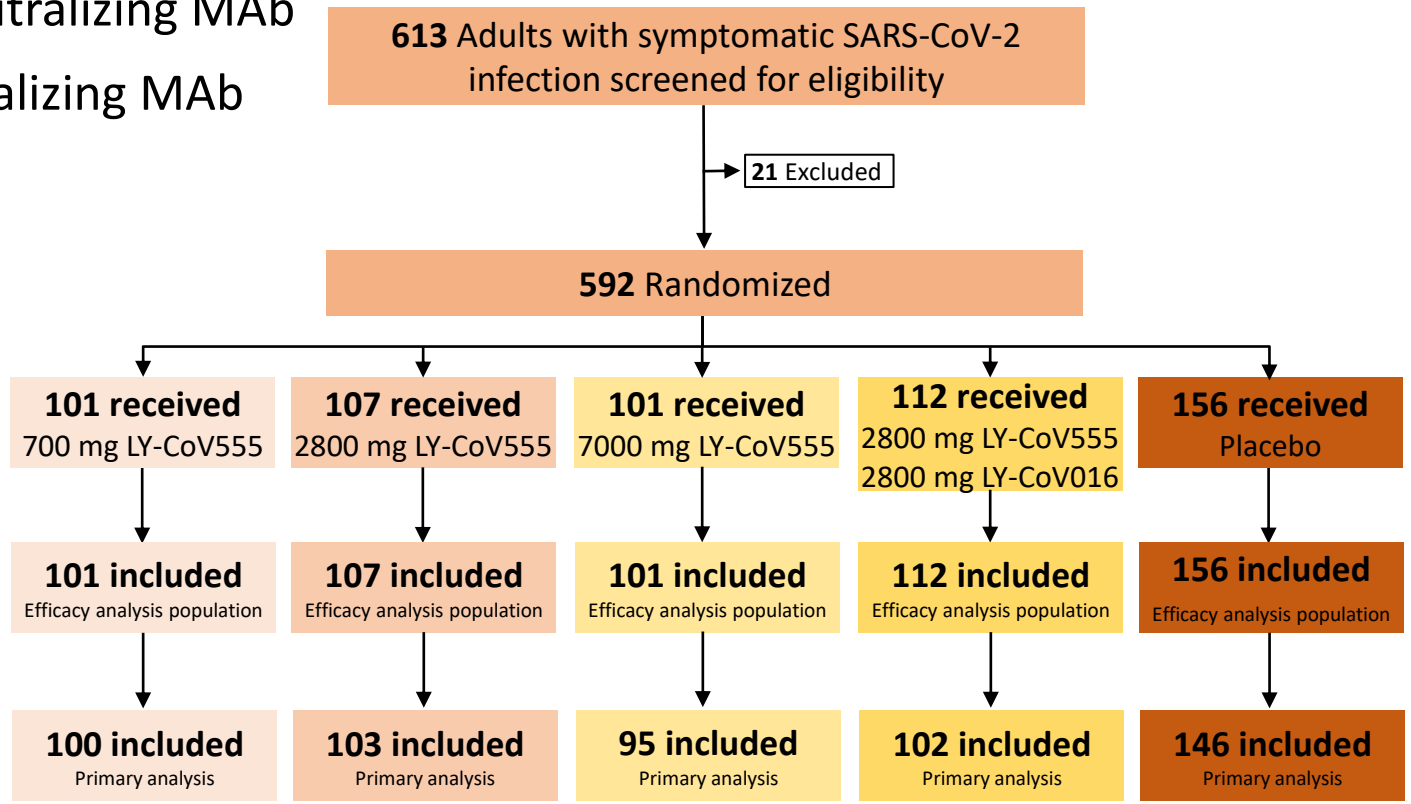
- **Limits**: patient heterogeneity, open label study, very low number of participants (15 in each group)

Characteristics	IFX-1 (N=15)	Control (N=15)
Age, mean (SD) - yr	58 (9)	63 (8)
Male sex – no (%)	11 (73)	11 (73)
Coexisting conditions		
Hypertension – no (%)	6 (40)	3 (20)
Diabetes – no (%)	4 (27)	4 (27)
Obesity – no (%)	2 (13)	4 (27)
Respiratory support		
Intubated at randomization – no (%)	8 (53)	10 (67)
Oxygen mask – no (%)	6 (40)	2 (13)
Nasal cannula – no (%)	1(7)	3 (20)

Monoclonal antibody

LY-CoV555 and LY-CoV016 - 1

- **LY-CoV555** (bamlanivimab): potent antispike neutralizing MAb
- **LY-CoV016** (etesevimab): potent antispike neutralizing MAb
- Randomized, double-blind, placebo-controlled, multicenter, USA (BLAZE-1)
- **Inclusion criteria** : age ≥ 18yo, not hospitalized, ≥ 1 mild or moderate COVID-19 symptoms, first positive SARS-CoV-2 viral infection ≤3 days prior to start of the infusion
- **Primary outcome**: effect of LY-CoV555 monotherapy and combination therapy with LY-CoV555 and LY-CoV016 compared with placebo on SARSCoV-2 log viral load from baseline to day 11 (±4 days)



- **577** participants; **101 LY-CoV555 700 mg** group, **107 LY-CoV555 2800 mg** group, **101 LY-CoV555 7000 mg** group, **112 LY-CoV555 2800 mg + LY-CoV016 2800 mg** group, **156 placebo** group

Monoclonal antibody

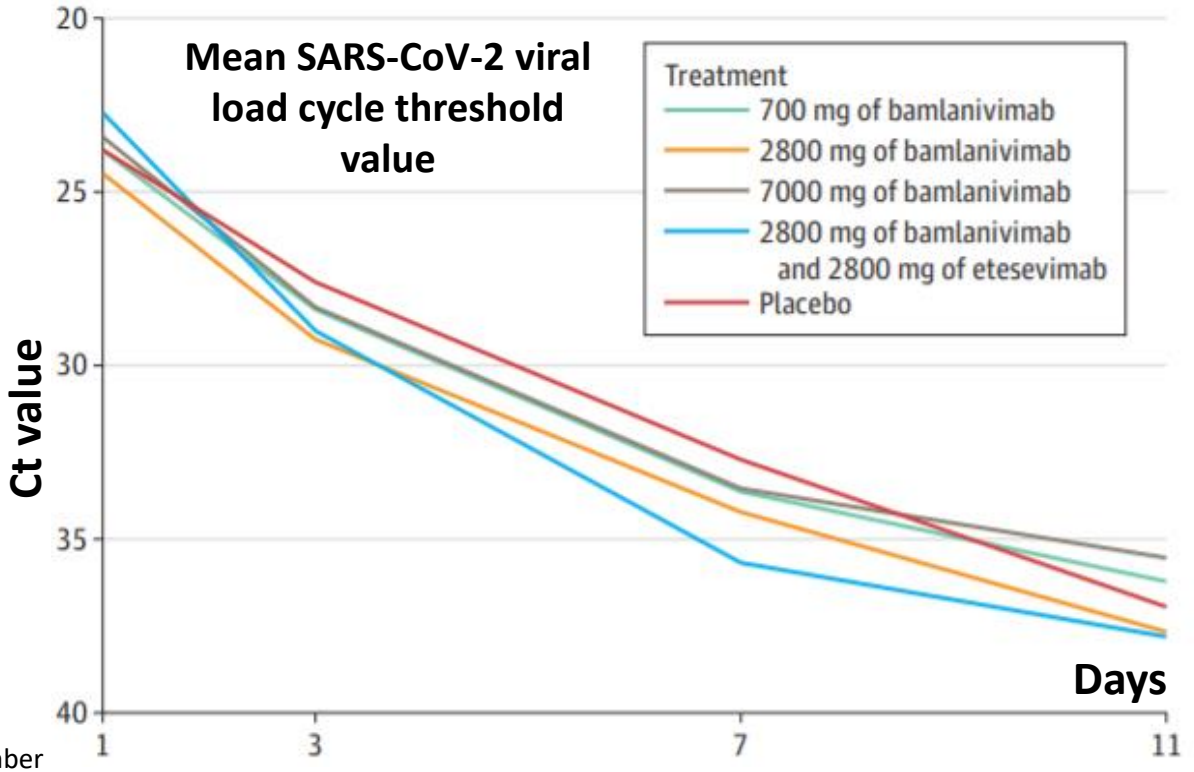
LY-CoV555 and LY-CoV016 - 1

Characteristics	LY-CoV555			LY-CoV555 + LY-CoV016	Placebo
	700 mg N=101	2800 mg N=107	7000 mg N=101	2800 mg + 2800 mg N= 112	N= 156
Age (y) – median (IQR)	39 (31-58)	45 (31-56)	46 (34-55)	44 (30-60)	46 (35-57)
Female sex – no (%)	63 (62.4)	51 (47.7)	58 (57.4)	58 (51.8)	85 (54.5)
BMI (kg/m²) – median (IQR)	28,8 (25,1-35,4)	30,4 (25,6-34,0)	27,8 (24,7-32,3)	27,2 (22,9-33,0)	29,2 (25,9-34,2)
Duration of symptoms (days) , median (IQR)	5 (3-6)	4 (3-6)	4 (2-7)	4 (3-5)	4 (3-6)
SARS-CoV-2 Ct – mean (SD)	23,8 (6,5)	24,5 (7,6)	23,4 (6,8)	22,7 (8,0)	23,8 (7,8)
COVID-19 severity					
Mild – no (%)	83 (82,2)	79 (73,8)	70 (69,3)	92 (82,1)	125 (80,1)
Moderate – no (%)	18 (17,8)	28 (26,2)	31 (30,7)	20 (17,9)	31 (19,9)

Monoclonal antibody

LY-CoV555 and LY-CoV016 - 1

- **D11 change from baseline SARS-CoV-2 viral load**: -3,72 700 mg group *vs.* - 4,08 2800 mg group *vs.* -3,49 7000 mg group, -4,37 combination treat group, -3,80 placebo group
- **Compared with placebo, differences in the change in log viral load at D11**: 700 mg group 0,09; $_{95\%}$ CI[–0,35 - 0,52], p=0,69, *vs.* 2800 mg group -0.27; $_{95\%}$ CI[-0,71 - 0,16], p=0,21, *vs.* 7000 mg group 0.31; $_{95\%}$ CI[-0,13 - 0,76], p=0,16 *vs.* combination treatment –0,57 $_{95\%}$ CI, [–1,00 - –0,14], p = 0,01
- **Limits:** small patient population, trial originally designed as a safety and biomarker study
- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**



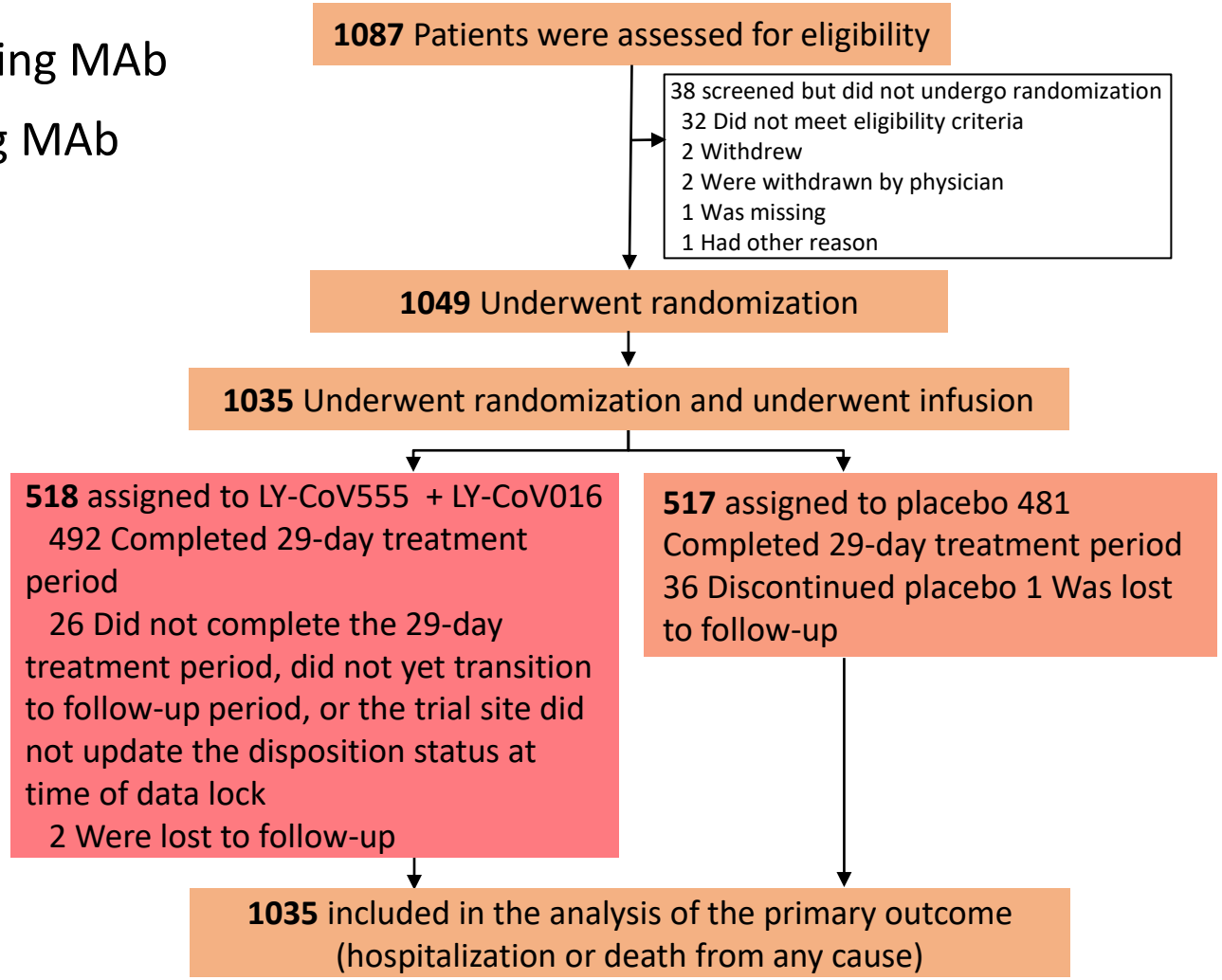
Treatment, Number	1	3	7	11
700 mg LY-CoV555	101	96	98	100
2800 mg LY-CoV555	107	98	101	103
7000 mg LY-CoV555	101	93	95	95
2800 mg LY-CoV555 and 2800 mg LY-CoV016	109	96	95	102
Placebo	152	141	142	146

Gottlieb RL *et al. JAMA* Jan 2021

Monoclonal antibody

LY-CoV555 and LY-CoV016 - 2

- **LY-CoV555** (bamlanivimab): potent antispike neutralizing MAb
- **LY-CoV016** (etesevimab): potent antispike neutralizing MAb
- Randomized, double-blind, placebo-controlled, multicenter, USA (BLAZE-1)
- **Inclusion criteria** : age ≥ 12yo, not hospitalized, ≥ 1 mild or moderate COVID-19 symptoms, first positive SARS-CoV-2 viral infection ≤3 days prior to start of the infusion
- **Primary outcome**: Day-29 Covid-19–related hospitalization (acute care for ≥24 hours) or death from any cause
- **1035** participants; **518 LY-CoV555 + LY-CoV016** group**, 517 placebo** group (1:1)



Monoclonal antibody

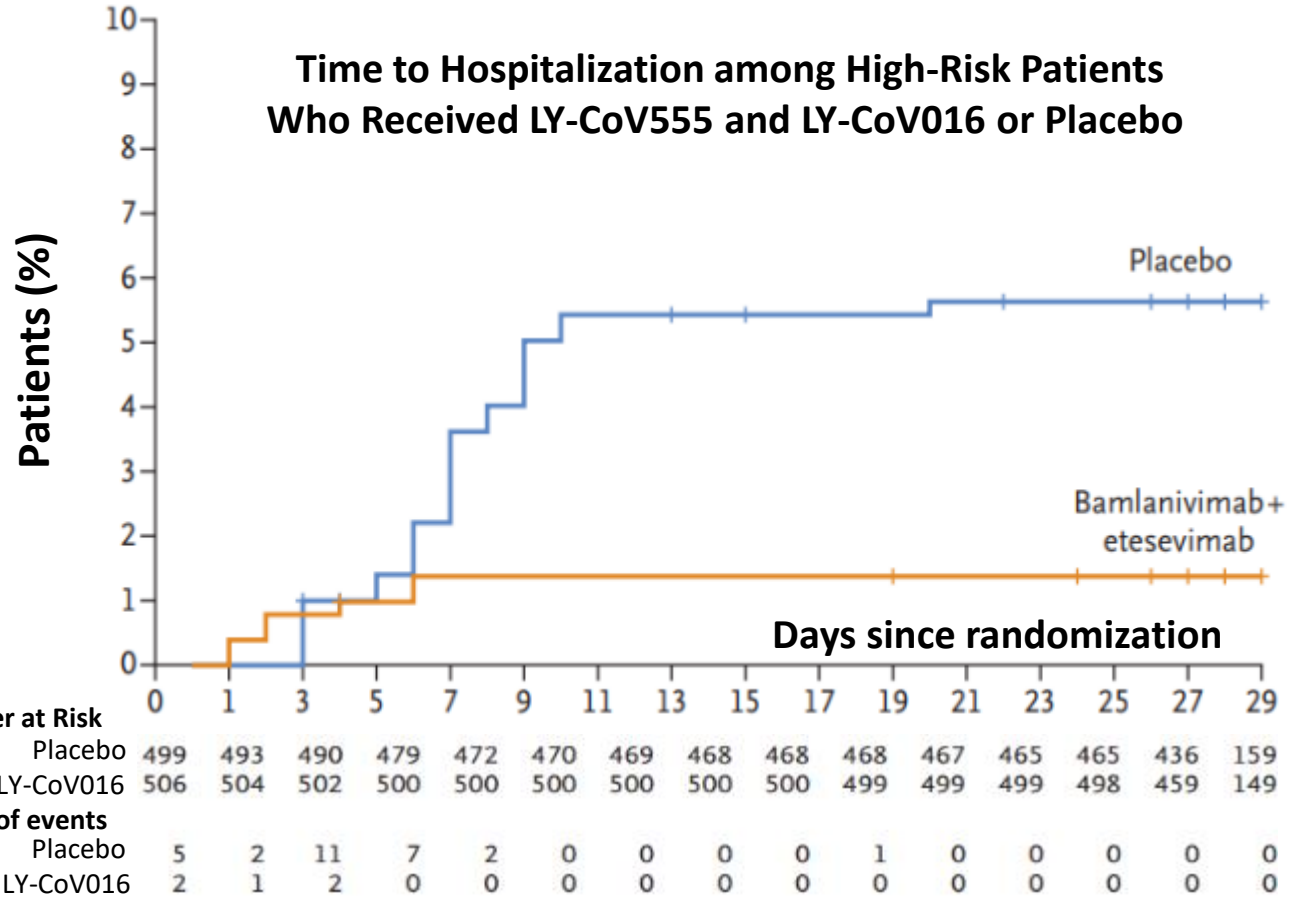
LY-CoV555 and LY-CoV016 - 2

Characteristics	LY-CoV555 + LY-CoV016	Placebo
	N= 518	N= 517
Age (y) – mean (SD)	54,3 (17,1)	53,3 (16,4)
BMI (kg/m²) – median (IQR)	34,14	33,90
Median days from symptom onset to randomization — no (range)	4 (0–29)	4 (0–13)
SARS-CoV-2 viral load (Ct) – mean	23,98	23,97
Risk of severe Covid-19		
High – no/total no (%)	493/518 (95,2)	490/517 (94,8)
Low – no/total no (%)	25/518 (4,8)	27/517 (5,2)
COVID-19 severity		
Mild – no (%)	397 (76,6)	403 (77,9)
Moderate – no (%)	121 (23,4)	114 (22,1)

Monoclonal antibody

LY-CoV555 and LY-CoV016 - 2

- **Day-29 Covid-19–related hospitalization or death from any cause** : 11/518 (2,1%) LY-CoV555 and LY-CoV016 group *vs.* 36/517 (7%) placebo group. Absolute risk difference: -4,8%; $_{95\%}$ CI[-7,4 -2,3], relative risk difference: 70%, p<0,001
- **Death** : 0/518 LY-CoV555 and LY-CoV016 group *vs.* 10/517 (2%) placebo group. Of these 10 deaths, 9 were deemed to be Covid-19–related by trial staff who were unaware of the trial-group assignments
- **Limits:** low number of participant receiving immunosuppressive agents, study limited to the United States
- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**

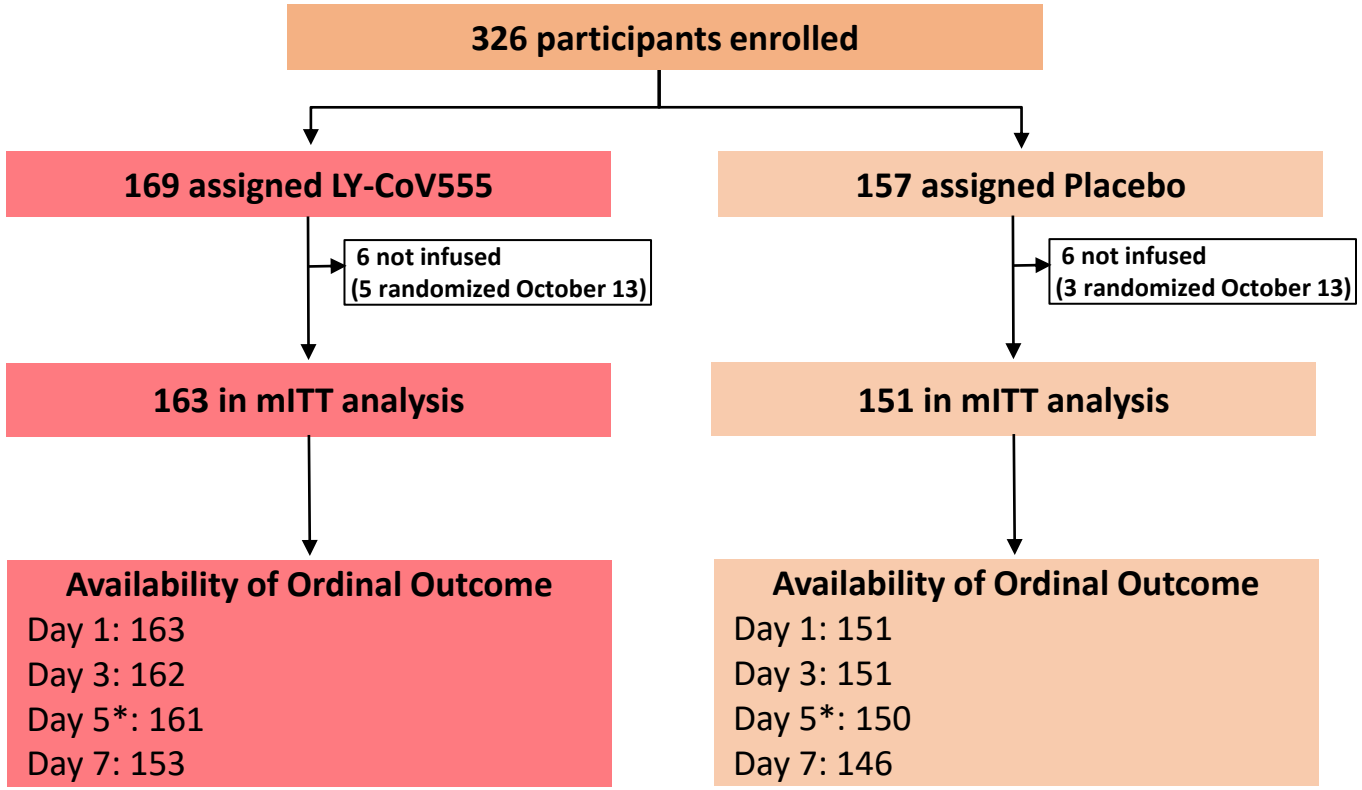


Dougan M *et al. NEJM* Jul 2021

Monoclonal antibody

LY-CoV555

- **LY-CoV555 = LY3819253 = bamlanivimab;** potent antispike neutralizing MAb
- ACTIV-3/TICO (Therapeutics for Inpatients with COVID-19) platform, therapeutic agents platform trial
- **Inclusion criteria** : hospitalized patients, documented SARS-CoV-2 infection, duration of Covid-19 symptoms < 12 days
- **Primary outcome**: time to sustained recovery, time to hospital discharge
- **Secondary out come**: death from any cause, safety
- **314** participants; **163 LY-CoV555** group**, 151 placebo** group (1:1)



* Primary measure of efficacy in stage 1

Monoclonal antibody

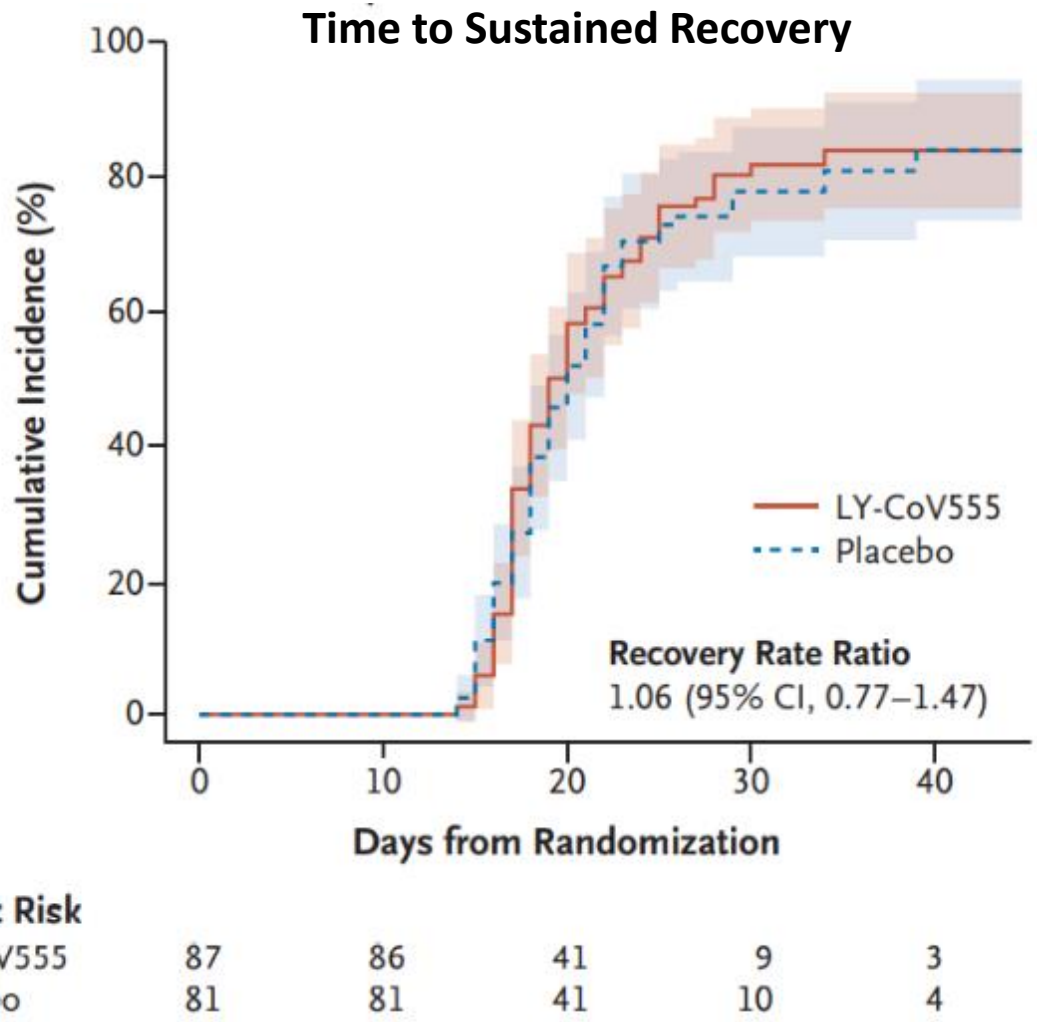
LY-CoV555

Characteristics	LY-CoV555 (N=163)	Placebo (N=151)
Age (y) – median (IQR)	63 (50-72)	59 (48-71)
Female sex – no (%)	66 (40)	71 (47)
BMI ≥ 30 kg/m² – no (%)	81 (50)	83 (55)
Duration of symptoms (days) , median (IQR)	7 (5-9)	8 (5-9)
Coexisting conditions		
Hypertension requiring medication – no (%)	82 (50)	72 (48)
Diabetes requiring medication – no (%)	54 (33)	36 (24)
Renal impairment – no (%)	24 (15)	9 (6)
Noninvasive ventilation or high-flow device – no (%)	30 (18)	18 (12)
Invasive ventilation or ECMO	0	0
Associated medication		
Remdesivir – no (%)	60 (37)	66 (44)
Glucocorticoid – no (%)	80 (49)	74 (49)

Monoclonal antibody

LY-CoV555

- **Time to sustained recovery**: 71/87 (82%) Ly-CoV555 group *vs.* 64/81 (79%) placebo group, rate ratio 1,06 $CI_{95\%}$[0,77-1,47]
- **Time to hospital discharge**: 143/163 (88%) Ly-CoV555 group *vs.* 136/151 (79%) placebo group, rate ratio 0,97 $CI_{95\%}$[0,78-1,20]
- **Death**: 9/163 (6%) Ly-CoV555 group *vs.* 5/151 (3%) placebo group, hazard ratio 2,00 $CI_{95\%}$[0,67-5,99]; p=0,22
- **Safety** (composite outcome): 49/163 (30%) Ly-CoV555 group *vs.* 37/151 (25%) placebo group, hazard ratio 1,25 $CI_{95\%}$[0,81-1,93]; p=0,31
- **Limitation**: inability to make definitive statements about the safety (small sample size, short follow-up duration)



Monoclonal antibody

LY-CoV555 and REGN-COV2

- **LY-CoV555 = bamlanivimab;**
- **REGN-COV2 = casirivimab and imdevimab**
- **Inclusion criteria** : adults (>18 years), mild- to moderate COVID-19 infection, no supplemental O_2, received NmAb infusion (LY-CoV555 or REGN-COV2), not hospitalized, first onset symptoms ≤ 10 days
- **Primary outcome**: hospitalization with a COVID-19 diagnosis between one and 30 days after the index date
- **Secondary outcome**: length of inpatient stay for hospitalized patients, post-index ER/clinic visits, and post-index death
- **707** received NmAb (**533** LY-CoV555, **154 REGN-COV2**), **1709 control** group

Characteristics	NmAb (N=707)	Control (N=1709)
Age (y) – mean (SD)	59,8 (15,9)	58,1 (15,2)
BMI ≥ 35 kg/m² – no (%)	232 (32,8)	306 (17.9)
Duration of symptoms before infusion (days) – mean (SD)	6,15 (2,76)	-
Coexisting conditions		
Chronic pulmonary disease – no (%)	96 (13,6)	240 (14,0)
Diabetes without complications – no (%)	132 (18,7)	278 (16,3)
Diabetes with complications – no (%)	27 (3,8)	115 (6,7)
Renal disease – no (%)	40 (5,7)	129 (7,5)
Congestive heart failure– no (%)	22 (3,1)	95 (5,6)

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

ER: emergency room
NmAb: Neutralizing monoclonal antibody

Verderese JP *et al. CID* Jun 2021

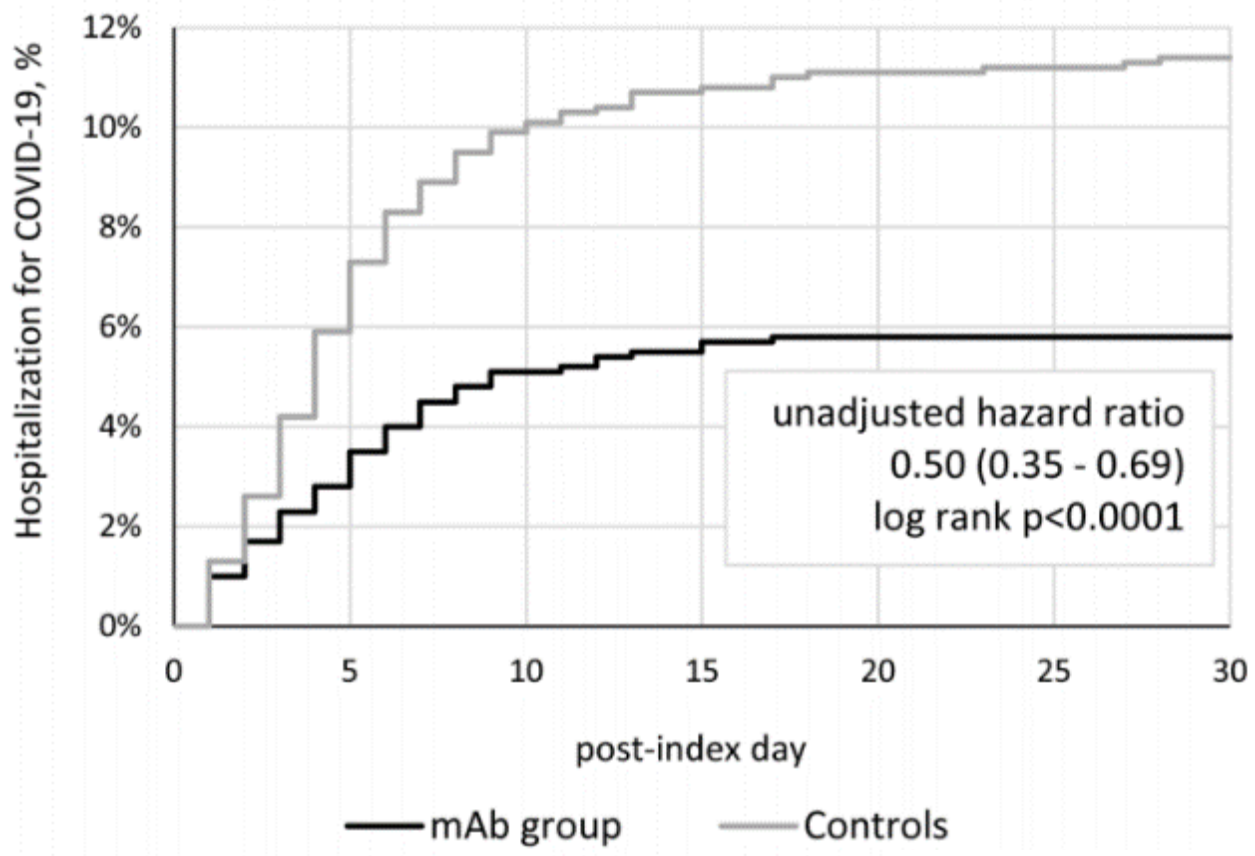
anrs MALADIES INFECTIEUSES ÉMERGENTES

Monoclonal antibody

LY-CoV555 and REGN-COV2

- **Hospitalization rate:** 41/707 (5,8%) NmAb group *vs.* 195/1709 (11,4%) control group; p<0,0001
- **Length of inpatient stay (days):** 5,2 ± 4,6 NmAb group *vs.* placebo group 7,4 ± 8,1; p=0,02
- **ER visits within 30 days post-index:** 57/707 (8,1%) NmAb group *vs.* 210/1709 (12,3%) placebo group; p=0,003
- **Hospitalisation-free survival**: longer NmAb group vs. control group; unadjusted HR: 0,5 $CI_{95\%}$[0,35-0,69]; p<0,0001
- **Limitations**: retrospective study using electronics medical record (EMR)
- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**

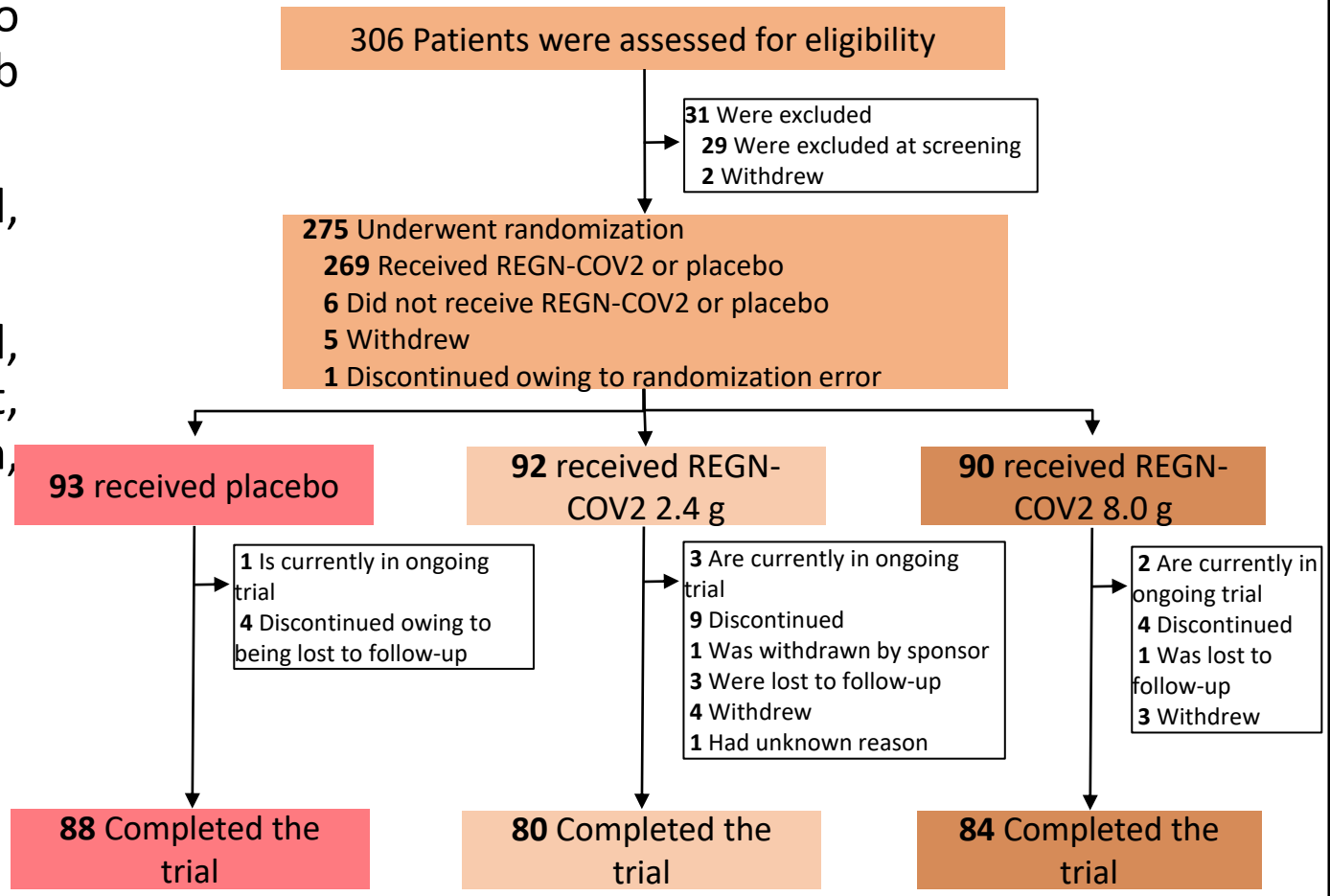
Hospitalizations for COVID-19 in patients who received a NmAb infusion and controls (censored at 30 days)



Monoclonal antibody

REGN-COV2

- **REGN-COV2**: antibody cocktail containing two SARS-CoV-2 neutralizing antibodies (casirivimab and imdevimab)
- Randomized, double-blind, placebo-controlled, multicenter, phase 1–3 study
- **Inclusion criteria** : age ≥ 18yo, not hospitalized, positive SARS-CoV-2 antigen or molecular test, symptom onset ≤ 7 days before randomization, O_2 saturation ≥93% (room air)
- **Primary outcome**: D7 viral load (VL) average change
- **Secondary outcome**: safety
- **275** participants; **90 REGN-COV2 high dose** group, **92 REGN-COV2 low dose** group, **93 placebo** group (1:1:1)



Weinreich DM *et al. NEJM* Dec 2020

Monoclonal antibody

REGN-COV2

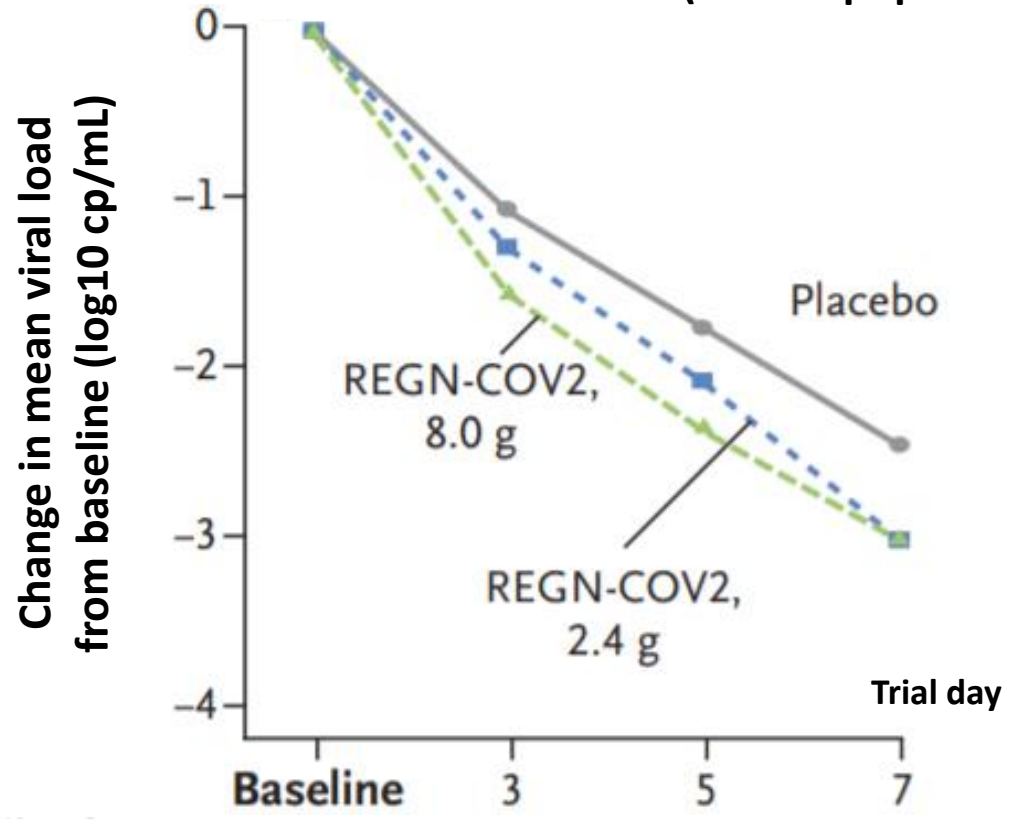
Characteristics	REGN-COV2 (N=182)	Placebo (N=93)
Age (y) - median (IQR)	43,0 (35,0–52,0)	45,0 (34,0–54,0)
Female sex - no (%)	98 (54)	43 (46)
BMI (kg/m²) - mean (SD)	30,51 (6,87)	29,73 (7,15)
Days from symptom onset to randomization - median (range)	3,0 (0–8)	3,0 (0–8)
Positive baseline qualitative RT-PCR - no (%)	147 (81)	81 (87)
Viral load (log_{10} copies/mL) - mean (SD)	5,02 (2,50)	4,67 (2,37)
Baseline serum C-reactive protein (mg/L) - Mean (SD)	11,7 (24,4)	21,5 (43,5)
At least one risk factor for hospitalization - no (%) Age > 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromise	118 (65)	58 (62)

Monoclonal antibody

REGN-COV2

- **Time-weighted average change in viral load from day 1 through day 7**: −1,74 $_{95\%}$CI[−1,95 - −1,53] REGN-COV2 group *vs.* −1,34 $\log_{10}$ cp/mL $_{95\%}$CI[−1,60 - −1,08] placebo group
- **Viral load difference *vs.* placebo at day 7**: −0,41 $\log_{10}$ cp/mL $_{95\%}$CI[−0,71 - −0,10]
- **Safety:** Grade 3 or 4 event: 1/176 (0,56%) REGN-COV2 group *vs.* 1/93 (1,07%) placebo group, Event that led to infusion interruption 1/176 (0,56%) REGN-COV2 group *vs.* 1/93 (1,07%) placebo group, none led to death
- **Limits:** interim analysis
- **Importance to check the impact of variants on the neutralizing capacity of said antibodies**

Viral load over time (overall population)



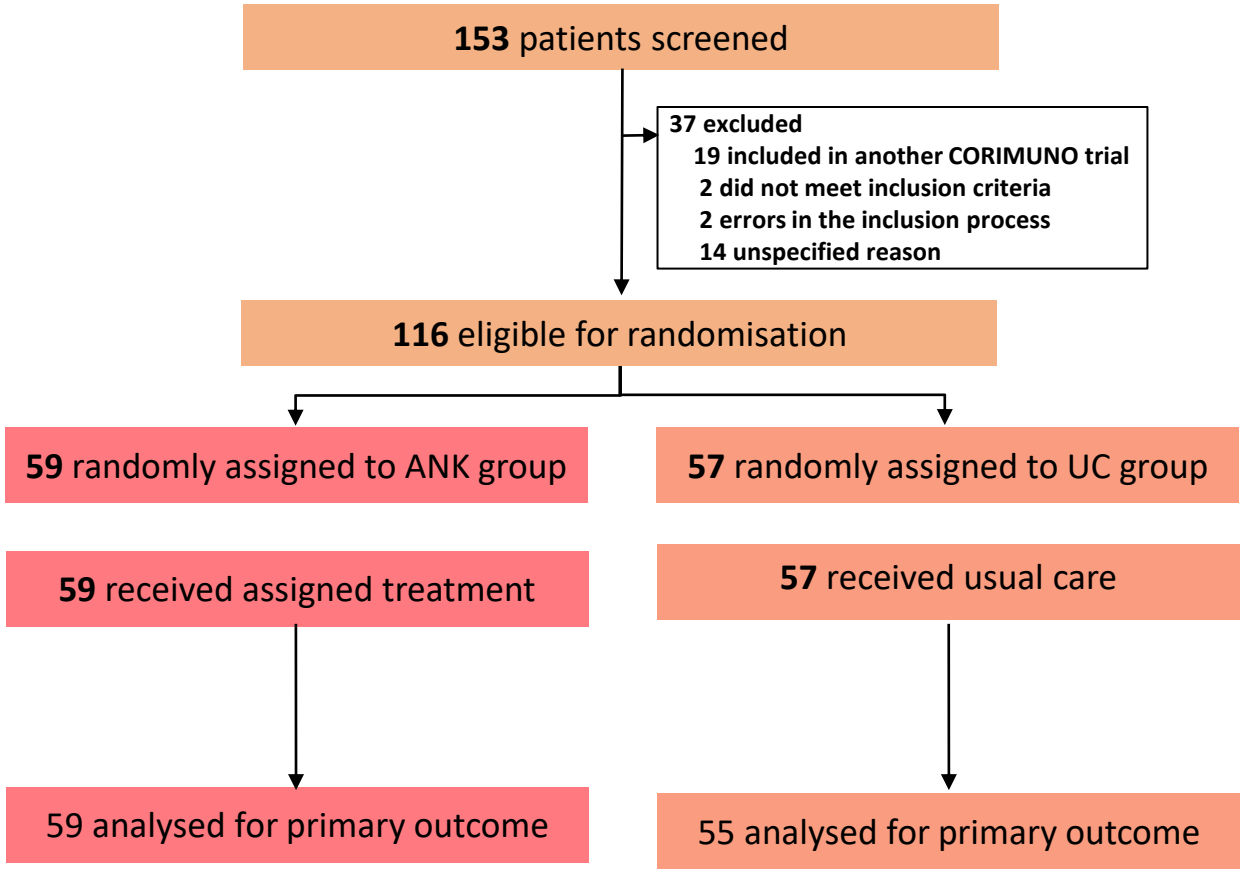
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

Weinreich DM *et al. NEJM* Dec 2020

Monoclonal antibody

Anakinra (ANK)

- **Anakinra**: recombinant human IL-1 receptor antagonist
- Multicenter, open-label, Bayesian randomized clinical trial, France (CORIMUNO-ANA-1)
- **Inclusion criteria** : positive SARS-CoV-2 RT-PCR or chest CT scan typical of COVID-19 pneumonia, mild-to-moderate, severe, or critical pneumonia (O_2 flow of >3 L/min *via* mask or nasal cannula and WHO-CPS score ≥5 points)
- **Coprimary outcome**: proportion of patients who had died or needed NIV or MV (WHO-CPS score of >5 points) at D4, survival with no need for MV or NIV at D14
- **116** participants; **59 ANK** group, **57 usual care** group (1:1)



MV: mechanical ventilation UC: usual care
NIV: non-invasive ventilation

The CORIMUNO-19 Collaborative group. *Lancet Resp Med* Jan 2021

Monoclonal antibody

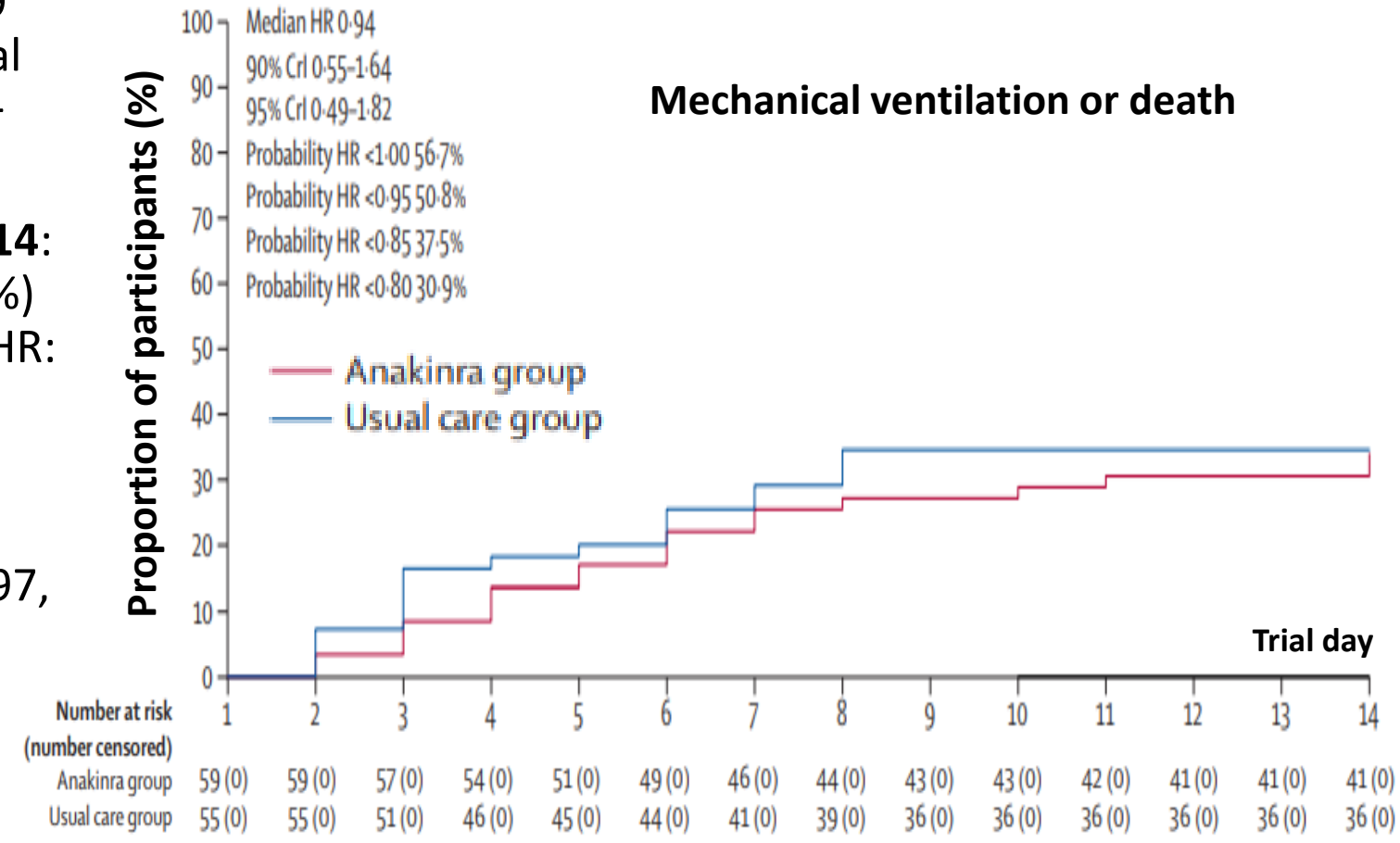
Anakinra (ANK)

Characteristics	Anakinra (N=59)	Usual care (N=55)
Age (y) - median (IQR)	67,0 (55,5–74,3)	64,9 (59,5–78,3)
Female sex - no (%)	16 (27)	18 (33)
BMI (kg/m²) - median (IQR)	27,4 (24,9-32,0)	26,8 (24,7-31,5)
Coexisting conditions		
Chronic cardiac disease - no (%)	22 (37%)	14 (25%)
Diabetes - no (%)	19 (32%)	15 (27%)
Chronic kidney disease (stage 1 to 3) or dialysis - no (%)	5 (8%)	3 (5%)
Others		
O_2 flow (L/min) - median (IQR)	5,0 (4,0–7,0)	6,0 (4,0–9,0)
Respiratory rate (breaths/min) - median (IQR)	28,0 (24,0–32,0)	28,0 (23,0–36,0)
C-reactive protein (mg/L) - median (IQR)	121,0 (77,0–198,0)	120,0 (87,0–191,5)
Time from symptoms onset to randomization (days) - median (IQR)	10,0 (8,0–13,0)	10,0 (7,0–13,0)

Monoclonal antibody

Anakinra (ANK)

- **WHO-CPS score of >5 points) at D4**: 21/59 (36%) anakinra group *vs.* 21/55 (38%) usual treatment group, median posterior ARD: –2,5%, $_{90\%}$CI[−17,1 - 12,0]
- **Survival with no need for MV or NIV at D14**: 28/59 (47%) anakinra group *vs.* 28/55 (51%) usual treatment group, median posterior HR: 0,97, $_{90\%}$CI[0,62 - 1,52]
- **Overall mortality at D90**: 16/59 (27%) anakinra group *vs.* 15/55 (27%) usual treatment group, median posterior HR: 0,97, $_{95\%}$CI[0,46 - 2,04]
- **Limits**: not blinded trial, usual care may differed among centers, small sample size
- **<u>Study stopped early for futility</u>**

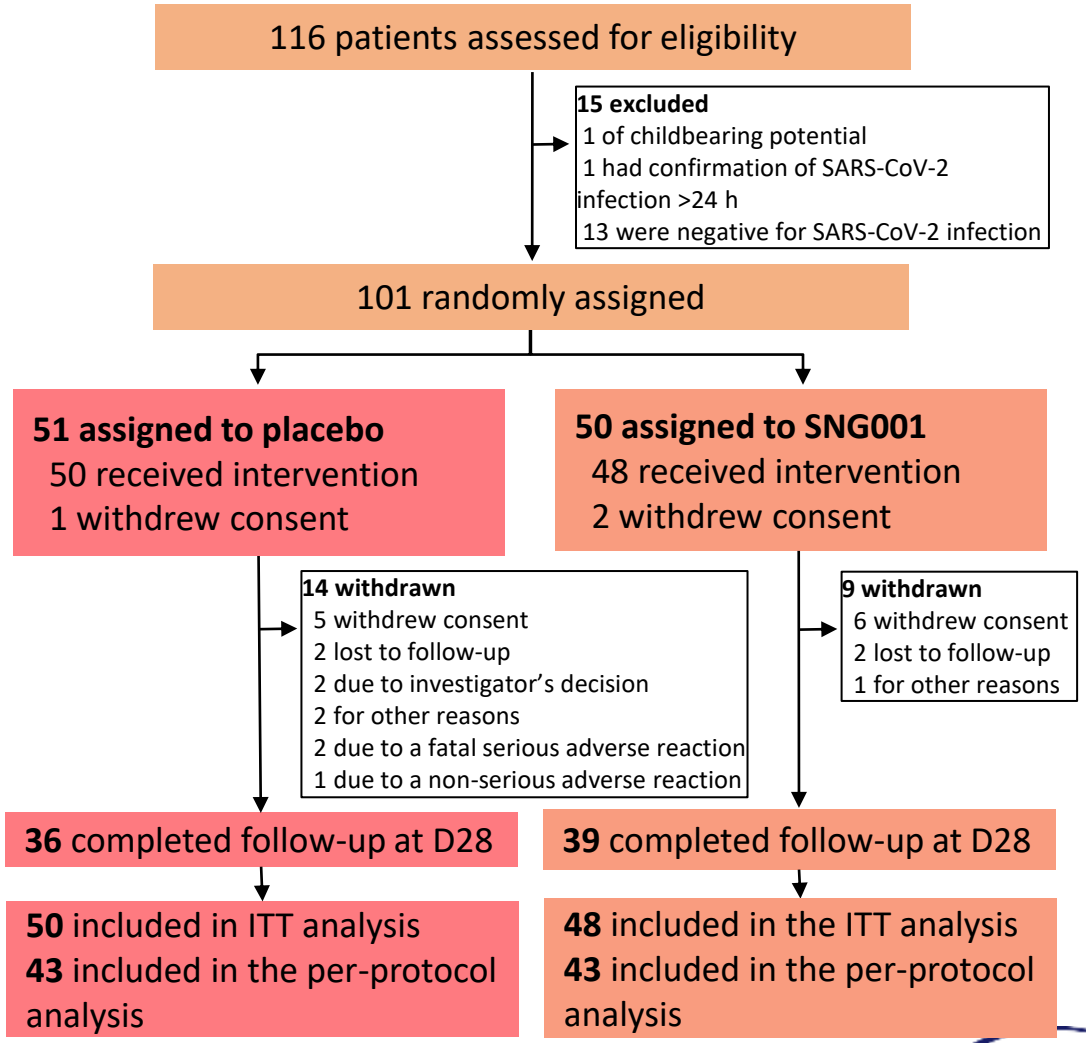


The CORIMUNO-19 Collaborative group. *Lancet Resp Med* Jan 2021

Immunomodulatory effect

Interferon beta 1a - 1

- **SNG001**: inhaled nebulized Interferon beta 1a (INFβ-1a)
- Randomized, double-blind, placebo-controlled, phase 2, multicenter, academic trial, UK (SG016)
- **Inclusion criteria**: age ≥ 18 yo, hospitalized patients, COVID-19 symptoms, positive SARS-CoV-2 RT-PCR
- **Exclusion criteria**: inability to use a nebulizer, pregnant and breastfeeding women,
- **Primary outcome**: clinical condition change (WHO Ordinal Scale for Clinical Improvement)
- **Secondary outcome**: change in Breathlessness, Cough And Sputum Scale score, safety and tolerability
- **101** participants; **50 SNG001** group, **51 placebo** group (1:1)



SoC: standard of care IMV: invasive mechanical ventilation
STR: steroids

Monk PD *et al. Lancet Resp Med* Nov 2020

Immunomodulatory effect

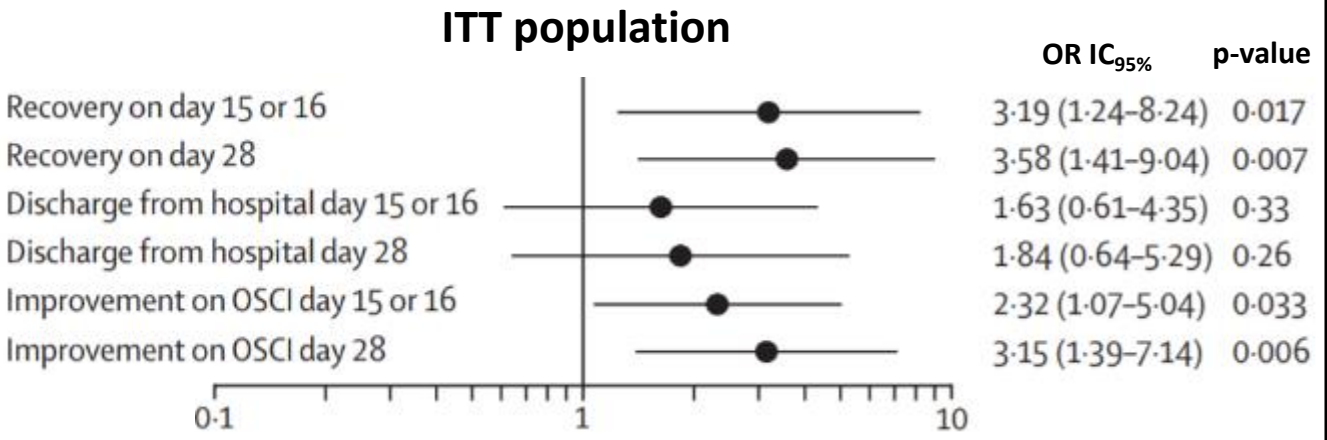
Interferon beta 1a - 1

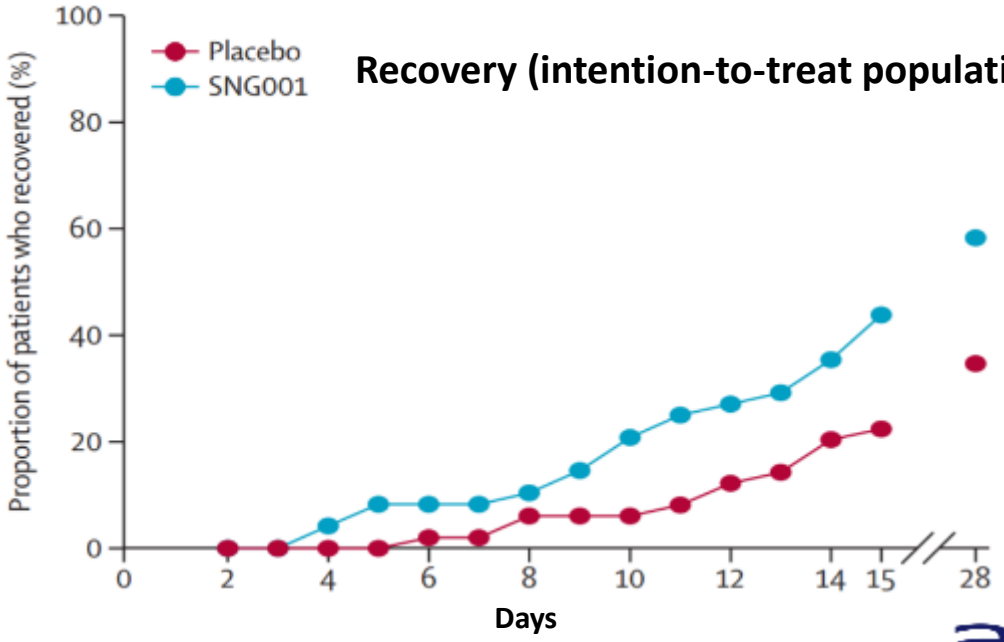
Characteristics	SNG001 (N=50)	Placebo (N=51)
Age (y) – mean (SD)	57,8 (14,6)	56,5 (11,9)
Male sex – no (%)	27 (56)	31 (62)
Coexisting conditions		
Hypertension – no (%)	18/26 (69)	11/27 (41)
Diabetes – no (%)	3/26 (12)	9/27 (33)
Cardiovascular disease – no (%)	5/26 (19)	8/27 (30)
Chronic lung condition – no (%)	11/26 (42)	12/27 (44)
Severity of disease at baseline		
Limitation of activities — no (%)	0	1 (2)
Hospitalised (no oxygen therapy) — no (%)	11 (23)	19 (38)
Oxygen by mask or nasal prongs — no (%)	36 (75)	28 (56)
Non-invasive ventilation or high-flow oxygen — no (%)	1 (2)	1 (2)

Immunomodulatory effect

Interferon beta 1a - 1

- **Clinical condition change (D15 or D16 OSCI improvement):** 36/48 (75,0%) SNG001 group *vs.* 35/50 (70%) placebo group; OR: 2,32; $_{95\%}$CI[1,07-5,04], p=0,033
- **D14 BCSS score:** difference between SNG001 group and placebo group: -0,8; $_{95\%}$CI[-1,5;-0,1], p=0,026
- **Safety**: serious adverse events considered either unlikely be related to study treatment or not related to study treatment
- **Limits:** limited sample size, OSCI: new tool at the time of the study, nebulizer not suitable for ventilated patients, follow-up limited at 28 days



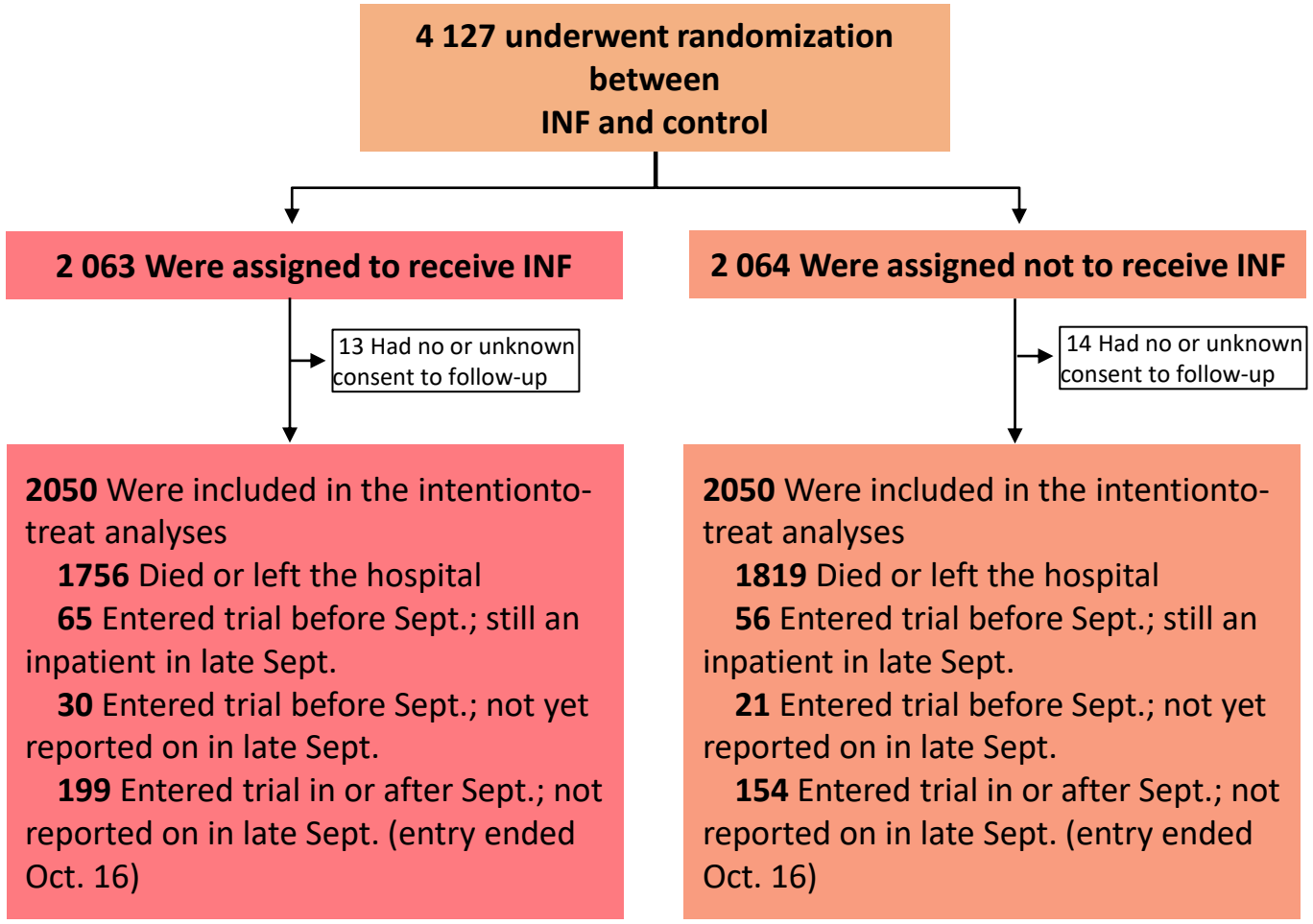


Monk PD *et al. Lancet Resp Med* Nov 2020

Immunomodulatory effect

Interferon beta 1a - 2

- Randomized, open-label, non-placebo-controlled, international trial, WHO, SOLIDARITY
- **Inclusion criteria**: patients aged ≥ 18yo, hospitalized with definite COVID-19, not already receiving any of the study drugs, no allergy nor contra-indications to any of them
- **Exclusion criteria:** significant contraindication to any one of the study drugs
- **Primary outcome**: all-cause mortality
- **Secondary outcome**: initiation of mechanical ventilation and hospitalization duration
- **4127** patients underwent randomization; **2063 INF** group, **2064 control** group (1:1)



Immunomodulatory effect

Interferon beta 1a - 2

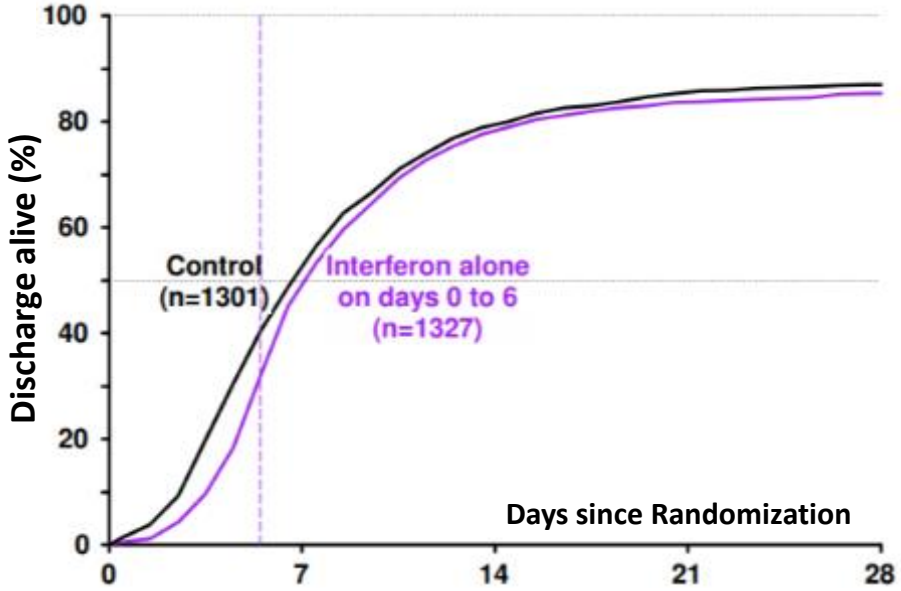
Characteristics		All (N= 11 266)	INF (N= 2 050)	Control (N=2 050)
Age	< 50 yr – no (%)	3995 (35)	720	697
	50-69 yr – no (%)	5125 (45)	934	973
	≥ 70 yr – no (%)	2146 (19)	396	380
Sex	Male sex – no (%)	6985 (62)	1303	1278
Co existing conditions	Diabetes – no(%)	2768 (25)	489	537
	Heart disease – no (%)	2337 (21)	427	456
	Chronic lung disease – no (%)	635 (6)	114	109
Respiratory support	No supplemental O_2 at entry	3204 (28)	482	490
	Supplemental O_2 at entry	7146 (63)	1429	1430
	Already receiving ventilation	916 (8)	139	130

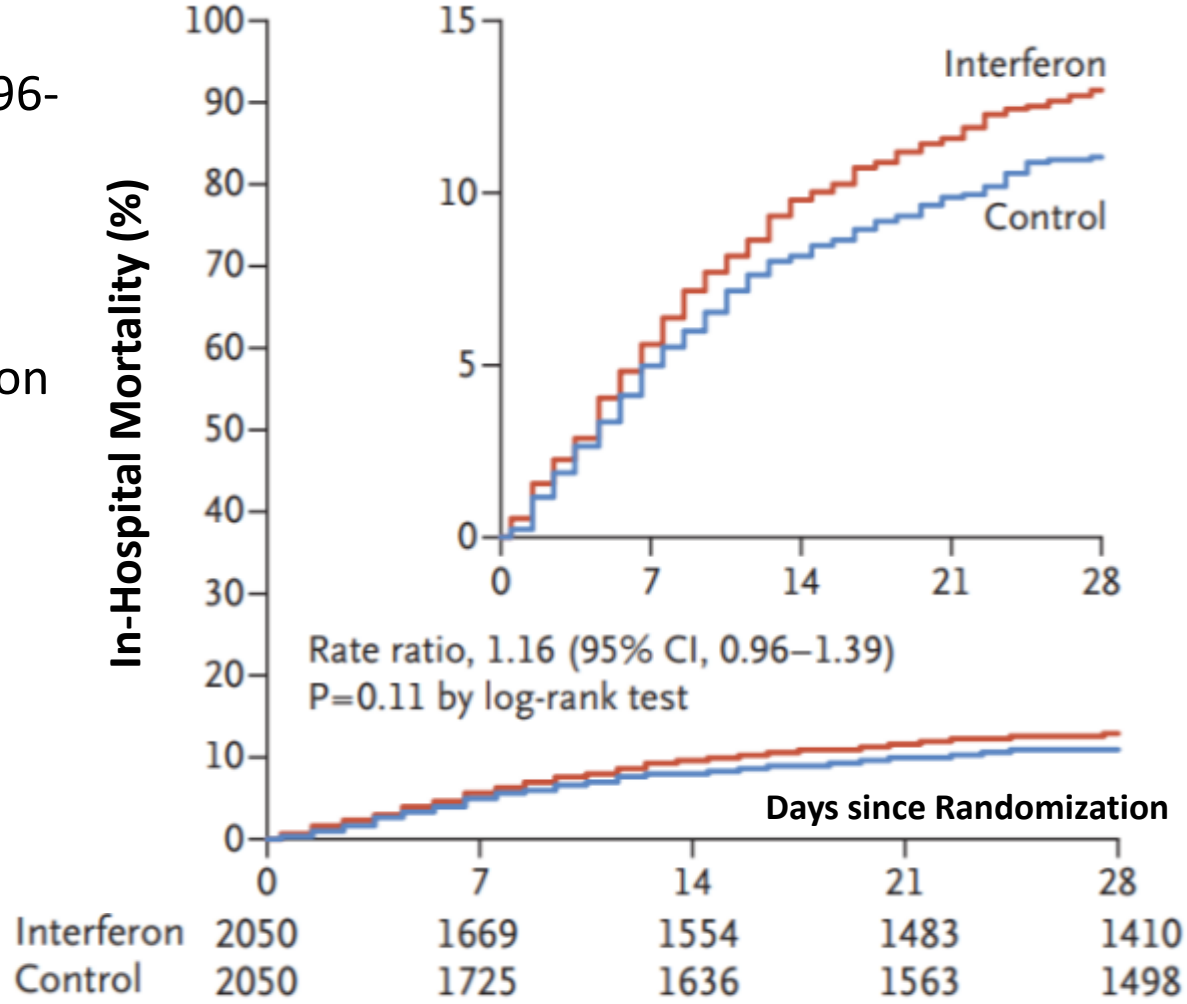
Immunomodulatory effect

Interferon beta 1a - 2

- **All-cause mortality**: 243/2050 (12,9%) INFβ-1a group *vs.* 216/2050 (11%) placebo group; rate ratio: 1,16; $_{95\%}$ CI[0,96-1,39]; p= 0,11
- **Initiation of mechanical ventilation**: INFβ-1a group: 209/1911 (10,9%) *vs*. control group 210/2475 (10,9%)
- **Time to discharge**: INFβ-1a did not reduced hospitalization duration

Study stopped for futility on 16th October



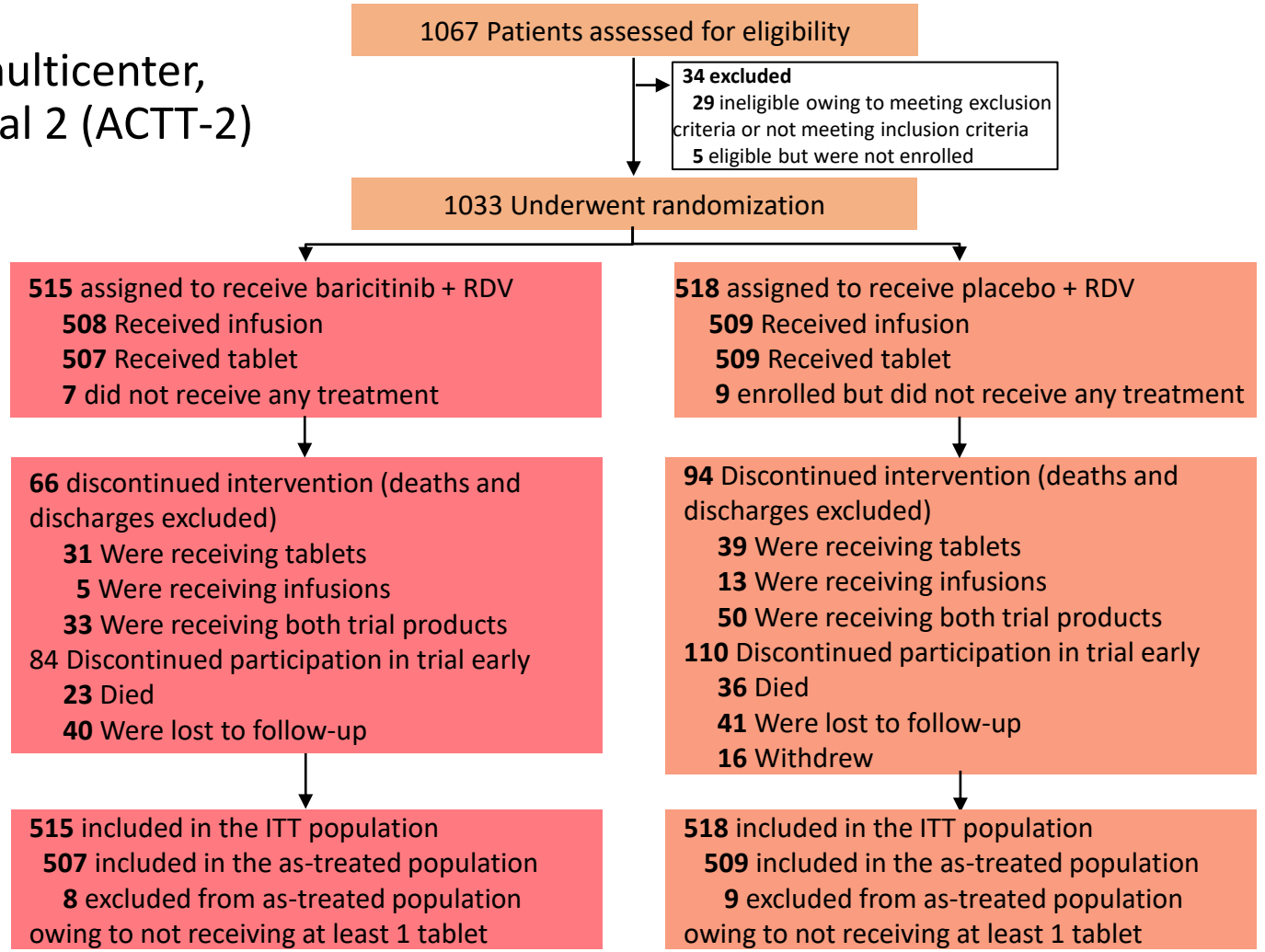


SOLIDARITY *NEJM* Dec 2020

Immunomodulatory effect

Baricitinib (JAK inhibitors)

- Double-blind, randomized, placebo-controlled, multicenter, academic study, Adaptive Covid-19 Treatment Trial 2 (ACTT-2)
- **Inclusion criteria**: hospitalized patients aged ≥ 18yo, positive SARS-CoV-2 RT-PCR test, lower respiratory tract infection (radiographic infiltrates, SpO_2 ≤94% (room air), requiring supplemental O_2, mechanical ventilation, or ECMO)
- **Exclusion criteria:** significant contraindication to any one of the study drugs
- **Primary outcome**: time to recovery
- **Secondary outcome**: clinical status at day 15, D28 mortality, adverse events
- **1033** patients underwent randomization; **515 Baricitinib + RDV** group, **518 control** group (1:1)



RDV: Remdesivir

Kalil AC *et al. NEJM* Dec 2020

Immunomodulatory effect

Baricitinib (JAK inhibitors)

Characteristics	All (N= 1033)	Baricitinib + RDV (N= 515)	Placebo + RDV (N= 518)
Age – Mean – yr (SD)	55,4 (15,7)	55,0 (15,4)	55,8 (16,0)
Male sex – no (%)	652 (63,1)	319 (61,9)	333 (64,3)
BMI – Mean – kg/m^2 (SD)	32,2 (8,3)	32,2 (8,2)	32,3 (8,4)
Time from symptom onset to randomization – Median – days (IQR)	8 (5–10)	8 (5–10)	8 (5–11)
Disease severity			
Moderate – no (%)	706 (68,3)	358 (69,5)	348 (67,2)
Severe – no (%)	327 (31,7)	157 (30,5)	170 (32,8)
Score on ordinal scale – no (%)			
4. Hospitalized, not requiring supplemental O_2, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13,7)	70 (13,6)	72 (13,9)
5. Hospitalized, requiring supplemental O_2	564 (54,6)	288 (55,9)	276 (53,3)
6. Hospitalized, receiving NIV or high-flow O_2 devices	216 (20,9)	103 (20,0)	113 (21,8)
7. Hospitalized, receiving invasive MV or ECMO	111 (10,7)	54 (10,5)	57 (11,0)

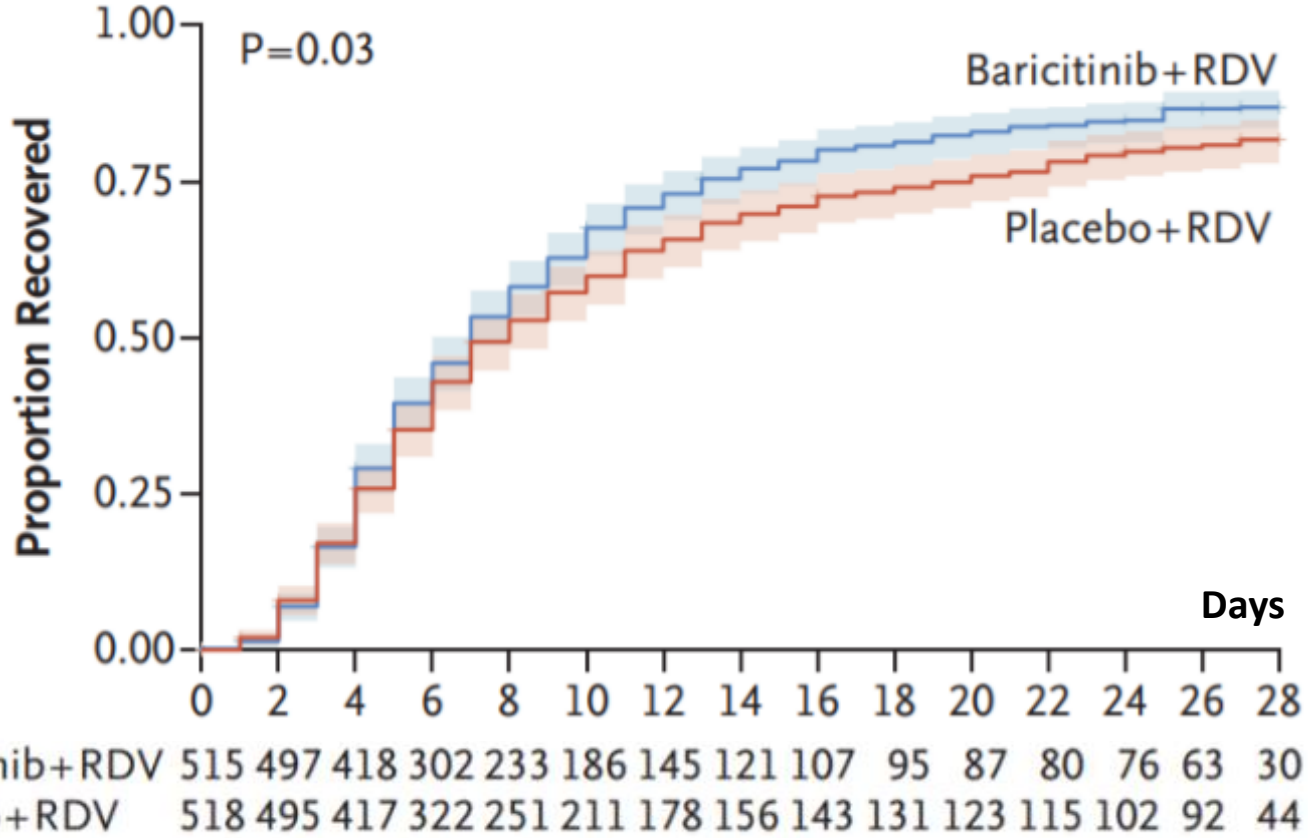
NIV: Non invasive ventilation
MV: mechanical ventilation

Kalil AC *et al. NEJM* Dec 2020

Immunomodulatory effect

Baricitinib (JAK inhibitors)

- **Time to recovery** (median days): 7 days Baricitinib + RDV group *vs.* 8 days RDV group; RR: 1,16 $_{95\%}$ CI[1,01-1,32]; p = 0,03
- **Clinical status at day 15**: Baricitinib + RDV group 30% higher odds of improvement; OR: 1,3 $_{95\%}$CI[1,0-1,6]
- **D28 mortality**: Baricitinib + RDV group: 5,1% $_{95\%}$IC[3,5-7,6] *vs.* RDV group: 7,8% $_{95\%}$IC[5,7-10,6], Hazard ratio: 0,65; $_{95\%}$ CI[0,39-1,09]
- **Serious adverse events:** Baricitinib + RDV group:81/515 (16%) *vs.* RDV group: 107/518 (21%) between-group difference: −5.0; $_{95\%}$CI[-9,8:-0,3]; p=0.03

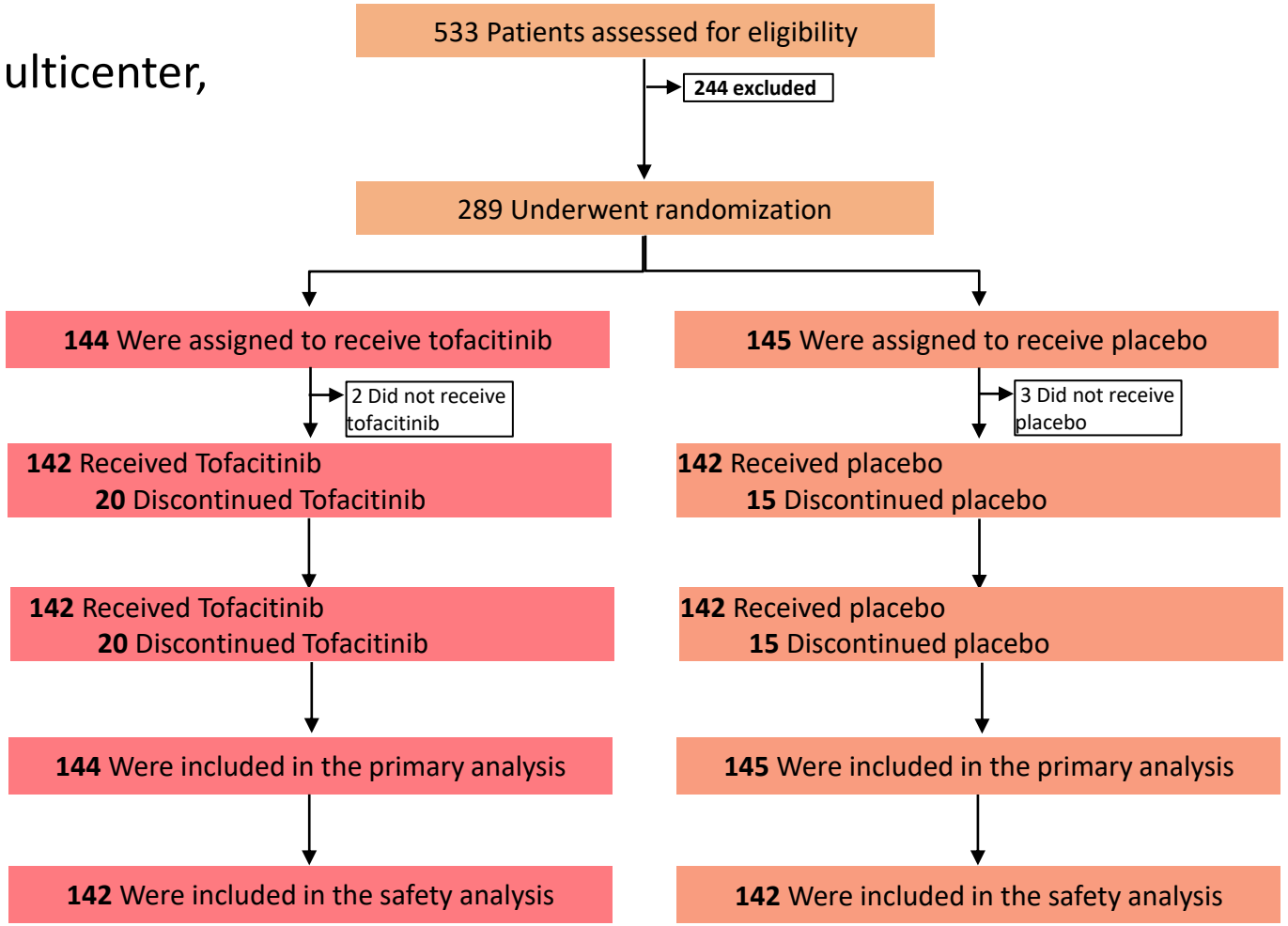


Kalil AC *et al. NEJM* Dec 2020

Immunomodulatory effect

Tofacitinib (JAK inhibitors)

- Double-blind, randomized, placebo-controlled, multicenter, industrial study, Brazil, STOP-COVID
- **Inclusion criteria**: aged ≥ 18yo, positive SARS-CoV-2 RT-PCR test, Covid-19 pneumonia on radiographic imaging, hospitalized patient for less than 72 hours
- **Exclusion criteria:** use of noninvasive or invasive MV or ECMO on the day of randomization
- **Primary outcome**: D28 occurrence of death or respiratory failure
- **Secondary outcome**: All-cause mortality
- **289** patients underwent randomization; **144 tofacitinib** group, **145 placebo** group (1:1)



MV: Mechanical Ventilation

Guimarães PO *et al. NEJM* Jul 2021

Immunomodulatory effect

Tofacitinib (JAK inhibitors)

Characteristics	Total (N= 289)	Tofacitinib (N= 144)	Placebo (N= 145)
Age – Mean – yr (SD)	56 (14)	54 (14)	57 (14)
Female sex – no (%)	101 (34,9)	50 (34,7)	51 (35,2)
BMI – Median – kg/m^2 (IQR)	29,7 (26,7-32,9)	29,4 (26,8-33,2)	29,7 (26,4-32,7)
Time from symptom onset to randomization – Median – days (IQR)	10 (7–11)	10 (7–12)	9 (7–11)
Time from Covid-19 diagnosis to randomization – Median – days (IQR)	5 (2–8)	5 (2–8)	4 (2–8)
Hospitalization in the ICU at randomization — no (%)	54 (18,7)	28 (19,4)	26 (17,9)
Score on ordinal scale – no (%)			
4. Hospitalized, not requiring supplemental O_2, requiring ongoing medical care (Covid-19–related or otherwise)	71 (24,6)	34 (23,6)	37 (25,5)
5. Hospitalized, requiring supplemental O_2	181 (62,6)	91 (63,2)	90 (62,1)
6. Hospitalized, receiving NIV or high-flow O_2 devices	37 (12,8)	19 (13,2)	18 (12,4)

NIV: Non invasive ventilation
MV: mechanical ventilation

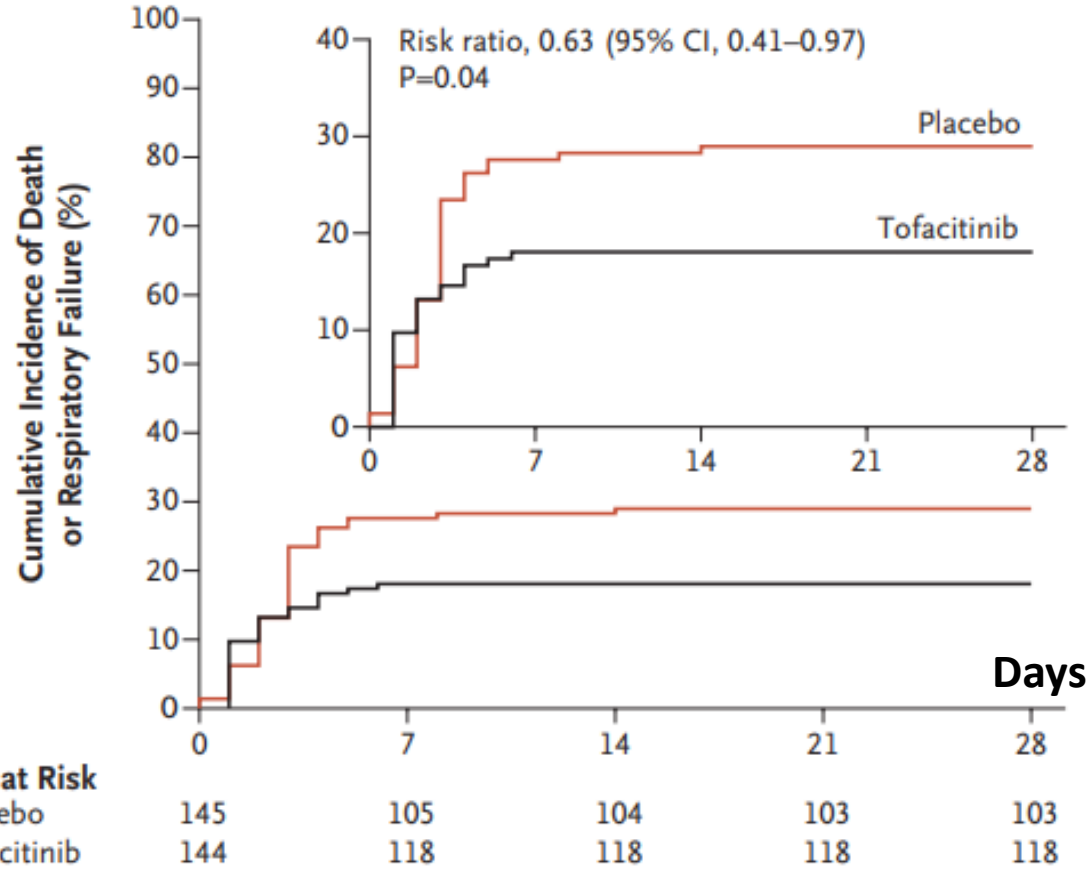
Guimarães PO *et al. NEJM* Jul 2021

Immunomodulatory effect

Tofacitinib (JAK inhibitors)

- **D28 cumulative of death or respiratory failure:** 26/144 (18,1%) Tofacitinib group *vs*. 42/145 (29%) placebo group; RR: 0,63 $_{95\%}$ CI[0,41-0,97]; p = 0,04
- **D28 all causes mortality**: 4/144 (2,8%) Tofacitinib group *vs*. 8/145 (5,5%) placebo group; HR: 0,49 $_{95\%}$CI[0,15-1,63]
- **Proportional odds of having a worse score on the eight-level ordinal scale with Tofacitinib *vs.* control**; D14: 0,60 $_{95\%}$ CI[0,36-1,00], D28: 0,54 $_{95\%}$ CI[0,27-1,06]

Cumulative Incidence of death or respiratory failure through day 28

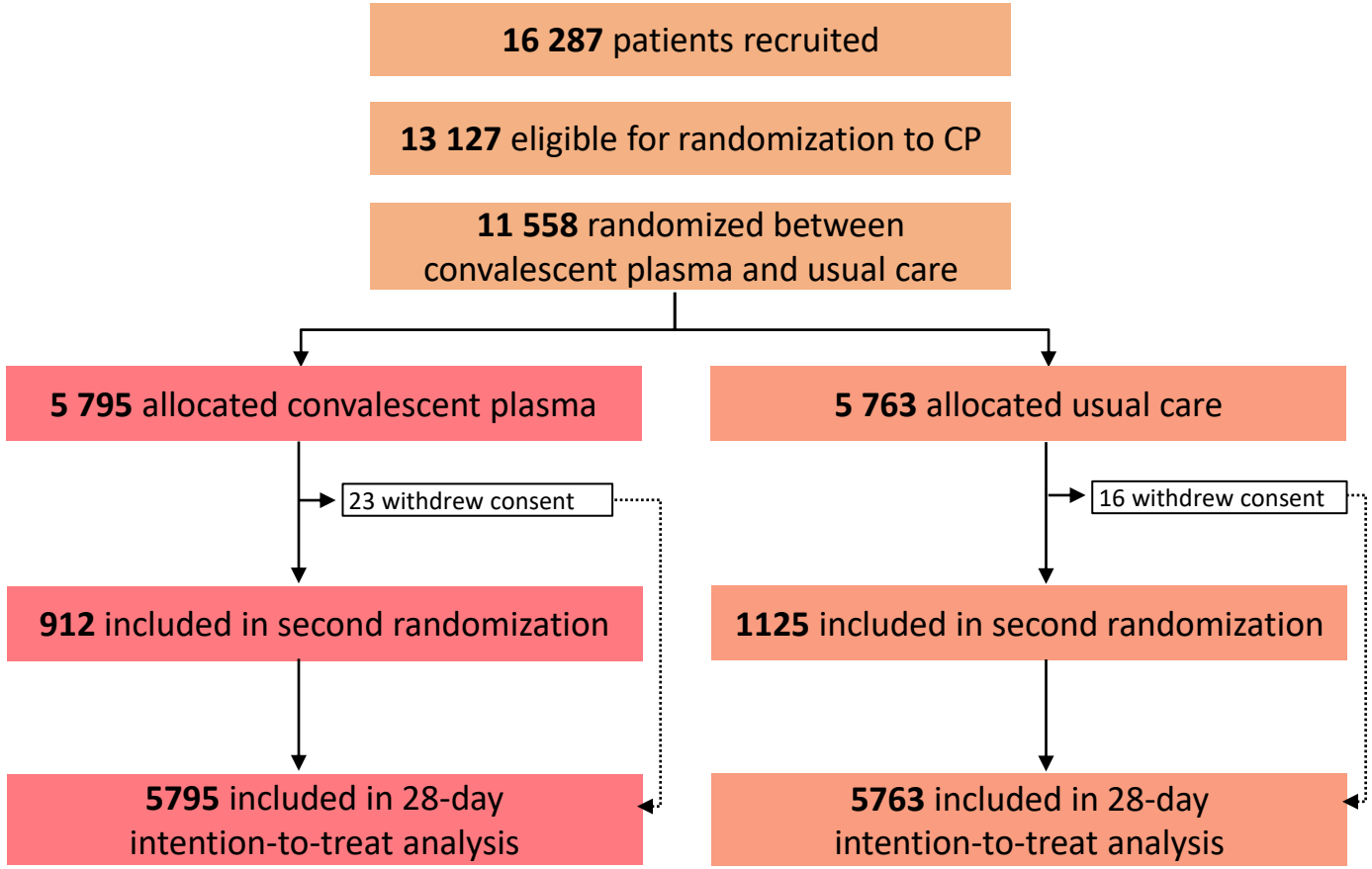


Guimarães PO *et al. NEJM* Jul 2021

Passive immunity

Convalescent plasma (CP) - 1

- Randomized, controlled, open-label, multicenter trial, academic study, UK, (Randomized Evaluation of COVID-19 Therapy) RECOVERY
- **Inclusion criteria**: Hospitalized patients of any age, clinically suspected or laboratory confirmed SARS-CoV-2 infection, no medical contraindications to join the trial
- **Primary outcome**: all-cause mortality
- **Secondary outcome**: time to discharge from hospital, in patients not receiving MV at randomization; receipt of invasive MV (including ECMO) or death
- **11 558** patients underwent randomization; **5795 CP** group, **5763 usual care** group (1:1)



Passive immunity

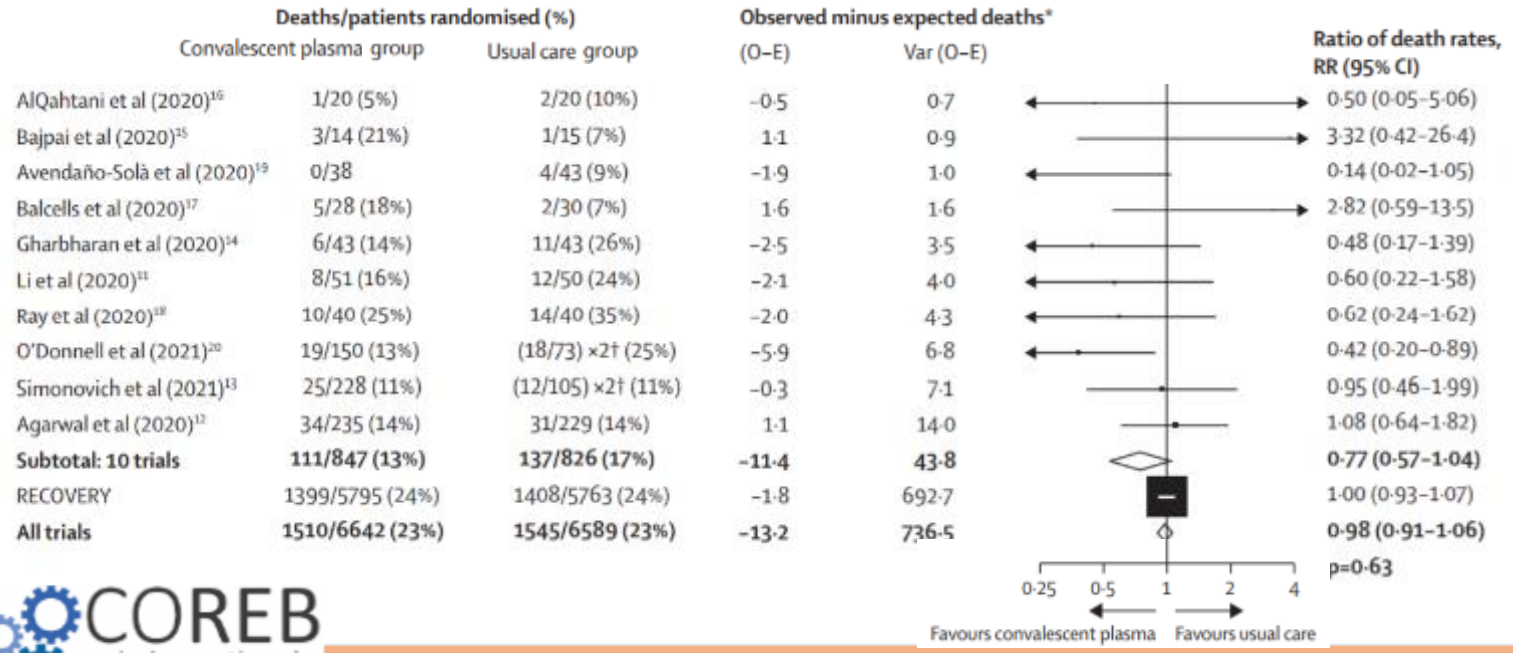
Convalescent plasma (CP) - 1

Characteristics		CP (N= 5 795)	Usual care (N=5 763)
Age	< 70 yr – no (%)	3 705 (64)	3 748 (65)
	70-79 yr – no (%)	1 310 (23)	1 281 (22)
	≥ 80 yr – no (%)	780 (13)	734 (13)
Sex	Male sex – no (%)	3 643 (63)	3 787 (66)
Co existing conditions	Diabetes – no(%)	1 535 (26)	1 569 (27)
	Heart disease – no (%)	1 267 (22)	1 309 (23)
	Chronic lung disease – no (%)	1 385 (24)	1 328 (23)
	Median number of days since symptom onset	9 (6–12)	9 (6–12)
	Median number of days since admission to hospital	2 (1–3)	2 (1–4)
Respiratory support received	Oxygen only – no (%)	5 051 (87)	4 993 (87)
	Invasive mechanical ventilation – no (%)	302 (5)	315 (5)

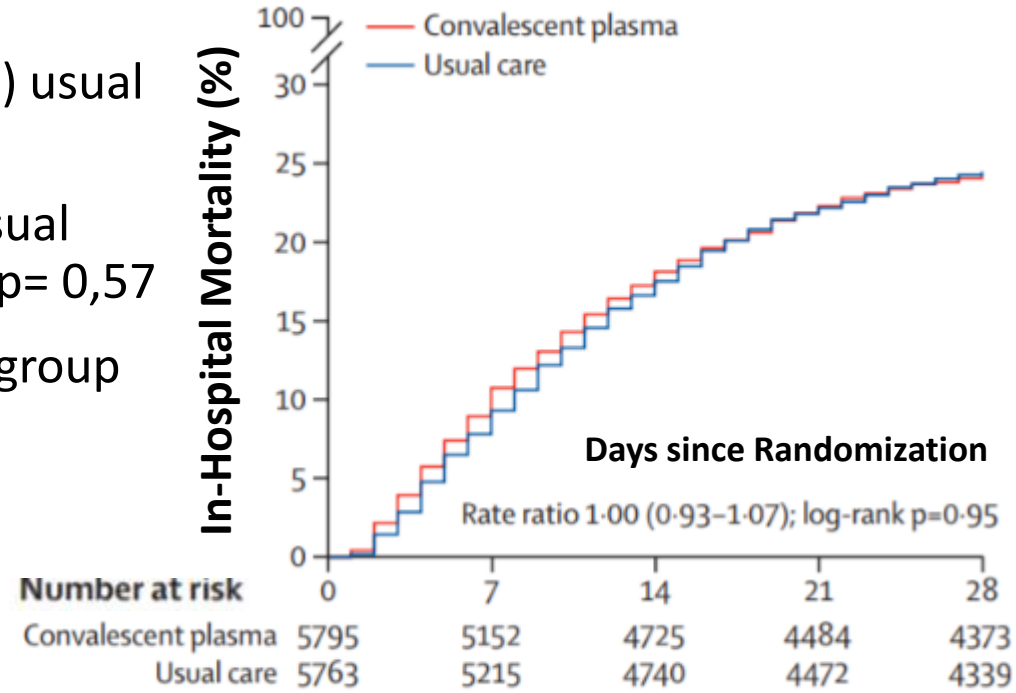
Passive immunity

Convalescent plasma (CP) - 1

- **28-day mortality**: 1388/5795 (24%) CP group *vs.* 1408/5763 (24%) usual care group; rate ratio: 1,00; $_{95\%}$ CI[0,93-1,07]; p= 0,95
- **Discharge alive within 28 days**: CP group: 3822/5795 (66%) *vs*. usual care group 3822/5763 (10,9%); rate ratio: 0,99; $_{95\%}$ CI[0,94-1,03]; p= 0,57
- **Invasive MV or death:** CP group: 1568/5493 (29%) *vs*. usual care group 1568/5448 (29%); rate ratio: 0,99; $_{95\%}$ CI[0,93-1,05]; p= 0,79



	Deaths/patients randomised (%)		Observed minus expected deaths*		Ratio of death rates, RR (95% CI)
	Convalescent plasma group	Usual care group	(O–E)	Var (O–E)	
AlQahtani et al (2020)[16]	1/20 (5%)	2/20 (10%)	-0·5	0·7	0·50 (0·05–5·06)
Bajpai et al (2020)[15]	3/14 (21%)	1/15 (7%)	1·1	0·9	3·32 (0·42–26·4)
Avendaño-Solà et al (2020)[19]	0/38	4/43 (9%)	-1·9	1·0	0·14 (0·02–1·05)
Balcells et al (2020)[17]	5/28 (18%)	2/30 (7%)	1·6	1·6	2·82 (0·59–13·5)
Gharbharan et al (2020)[14]	6/43 (14%)	11/43 (26%)	-2·5	3·5	0·48 (0·17–1·39)
Li et al (2020)[11]	8/51 (16%)	12/50 (24%)	-2·1	4·0	0·60 (0·22–1·58)
Ray et al (2020)[18]	10/40 (25%)	14/40 (35%)	-2·0	4·3	0·62 (0·24–1·62)
O'Donnell et al (2021)[20]	19/150 (13%)	(18/73) ×2† (25%)	-5·9	6·8	0·42 (0·20–0·89)
Simonovich et al (2021)[13]	25/228 (11%)	(12/105) ×2† (11%)	-0·3	7·1	0·95 (0·46–1·99)
Agarwal et al (2020)[12]	34/235 (14%)	31/229 (14%)	1·1	14·0	1·08 (0·64–1·82)
Subtotal: 10 trials	**111/847 (13%)**	**137/826 (17%)**	**-11·4**	**43·8**	**0·77 (0·57–1·04)**
RECOVERY	1399/5795 (24%)	1408/5763 (24%)	-1·8	692·7	1·00 (0·93–1·07)
All trials	**1510/6642 (23%)**	**1545/6589 (23%)**	**-13·2**	**736·5**	**0·98 (0·91–1·06)**
					p=0·63



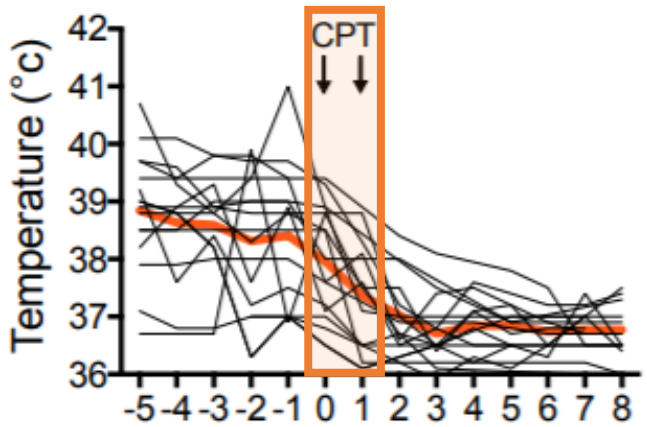
- **Meta–analysis of mortality in RECOVERY and other trials:** mortality rate ratio: 0,98 ; $_{95\%}$ CI[0,91-1,06]; p= 0,63

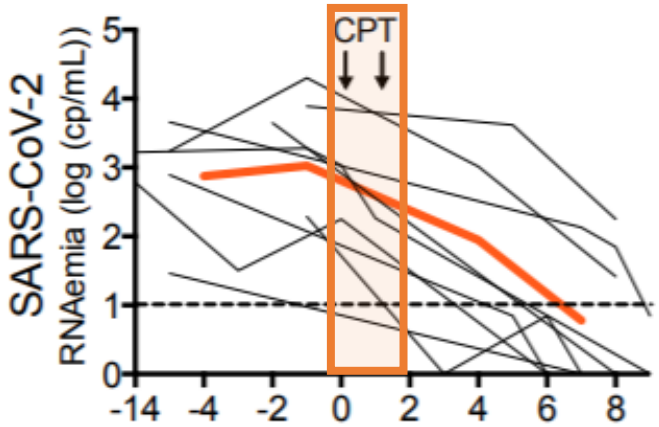
RECOVERY *Lancet* May 2021

Passive immunity

Convalescent plasma (CP) - 2

- Observational, multicenter, academic study, France
- **Inclusion criteria:** B-cell immunodeficiency with prolonged COVID-19 symptoms, positive SARS-CoV-2 RT-PCR from respiratory samples, no SARS-CoV-2 seroconversion
- 17 patients treated with 4 units of COVID-19 convalescent plasma





Characteristics (N=17)		CP
Age, median [range] - yr		58 [35-77]
Male sex – no (%)		12 (71)
Hematological malignancies		15 (88)
Non - Hematological malignancies		2 (12)
COVID -19 severity (WHO score), n (%)	4 – no (%)	5 (29)
	5-6 – no (%)	10 (59)
	7 – no (%)	2 (12)
Time between COVID -19 symptoms onset and CPT (days), median [range]		56 [7-83]
Time for oxygen weaning after CPT (days), median [range]		5 [1-45]
Overall survival, n (%)		16 (94)

- **Clinical symptoms**: 16/17 patients experienced amelioration of SARS-CoV-2 within 48 hours CP
- **SARS-CoV-2 RNAemia**: 9/9 patients witnessed a decreased below sensitivity threshold

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

Hueso T *et al. Blood* Sep 2020

anrs MALADIES INFECTIEUSES ÉMERGENTES

THERAPEUTIC (July 22nd 2021)

1. What drug showed clinical efficacy?

- Dexamethasone is the first drug to show life-saving efficacy in patients infected with COVID-19

2. What drugs did not show proven benefits?

- No proven benefits have been reported with (hydroxy)chloroquine, ivermectin nor lopinavir/ritonavir treatment

COREB
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