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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Boris Lacarra – *ANRS MIE*

F-Xavier Lescure – *Inserm, AP-HP Bichat, COREB*

Guillaume Mellon – *AP-HP Bichat, COREB*

Inmaculada Ortega Perez – *ANRS MIE*

Éric D'Ortenzio – *Inserm, AP-HP, ANRS MIE*

Erica Telford – *ANRS MIE*

Reviewing committee

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Flavie Chatel – *COREB*

Hélène Coignard – *HCL, COREB*

Dominique Costagliola – *Inserm, ANRS MIE*

Marie-Paule Kieny – *Inserm, ANRS MIE*

Quentin Le Hingrat – *Inserm, AP-HP Bichat*

Jean-Christophe Lucet – *Inserm, AP-HP Bichat*

Claire Madelaine – *Inserm, ANRS MIE*

Matthieu Mahevas – *Inserm, AP-HP Henri-Mondor*

Emmanuelle Vidal Petiot – *Inserm, AP-HP Bichat*

Benoit Visseaux – *Inserm, AP-HP Bichat*

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

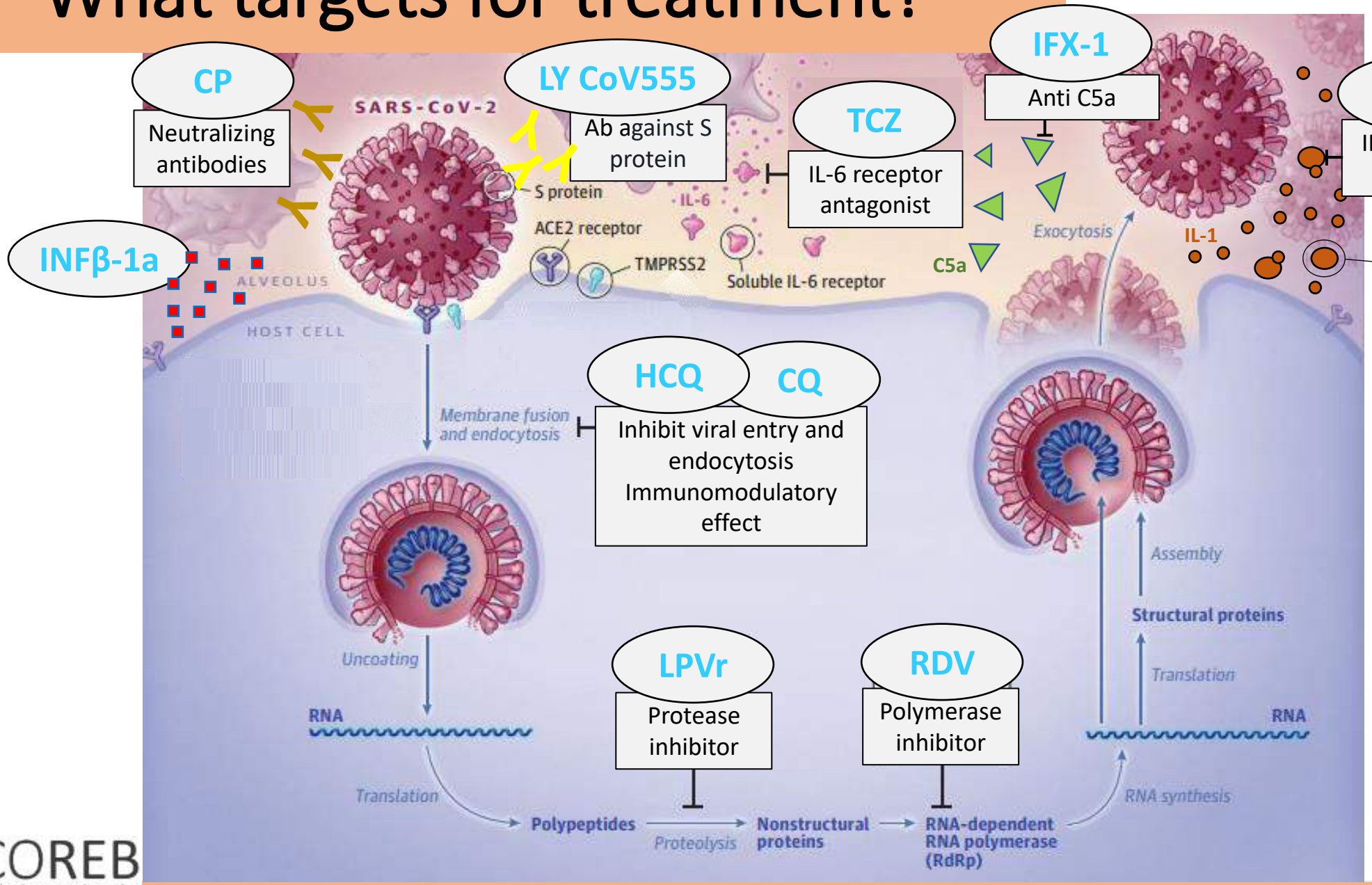
Immunomodulatory effect

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

Passive immunity

- Convalescent plasma

What targets for treatment?



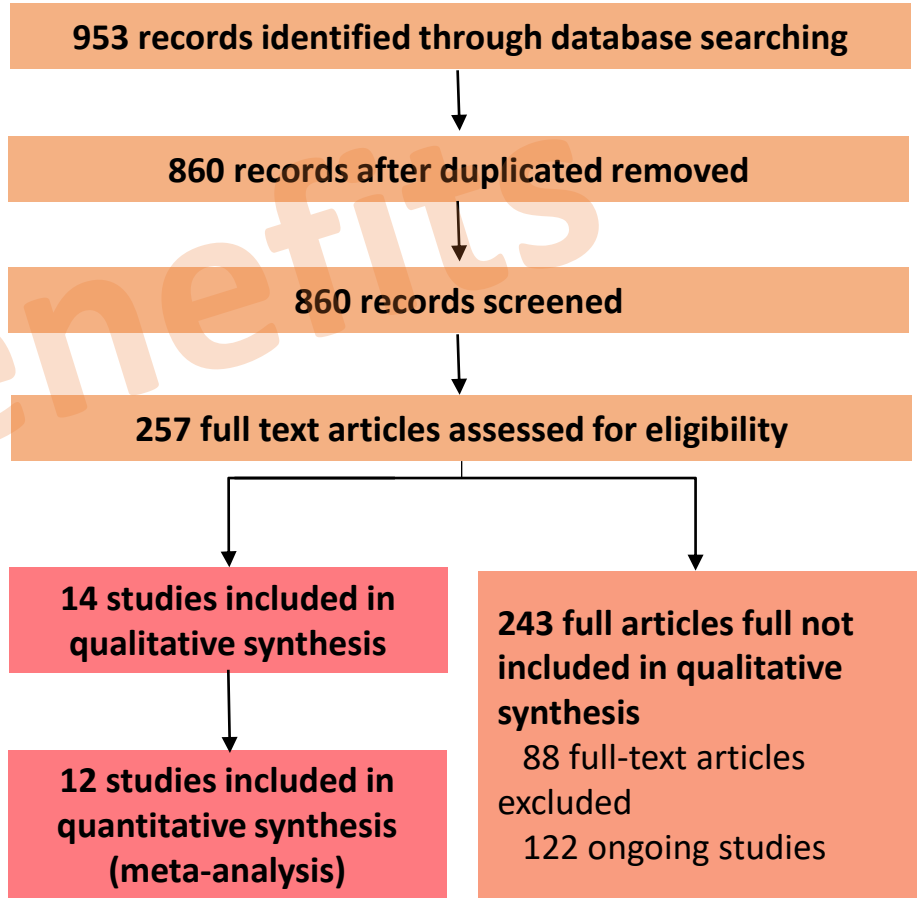
ANK: anakinra
CT: corticosteroids
CP: convalescent plasma
CQ: chloroquine
HCQ: hydroxychloroquine
IFX-1: vilobelimab
INFβ-1a: interferon beta
LPVr: lopinavir/ritonavir
RDV: remdesivir
TCZ: tocilizumab

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

anRS MALADIES INFECTIEUSES ÉMERGENTES

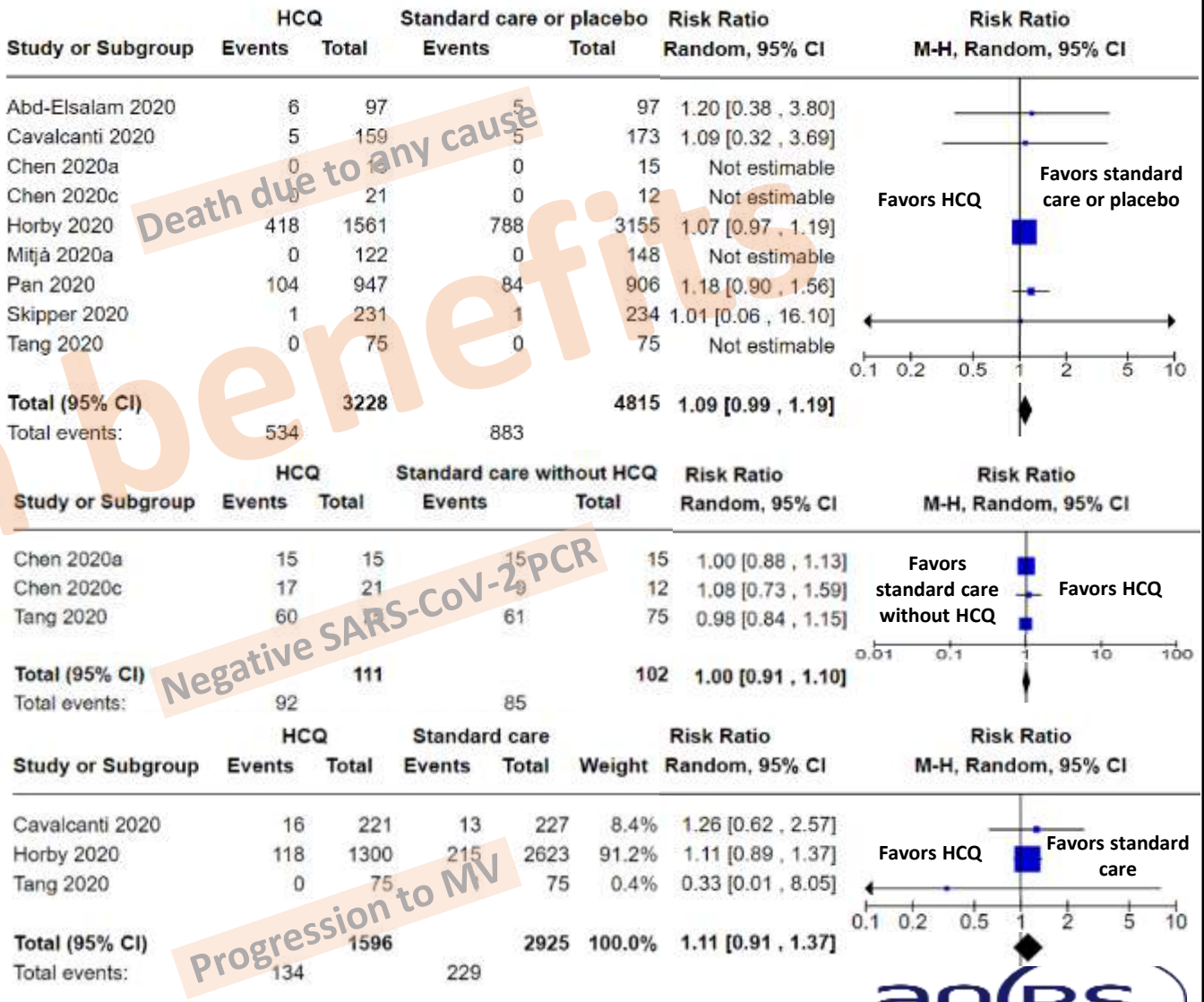
Anti viral effect

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



MV: mechanical ventilation

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

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

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

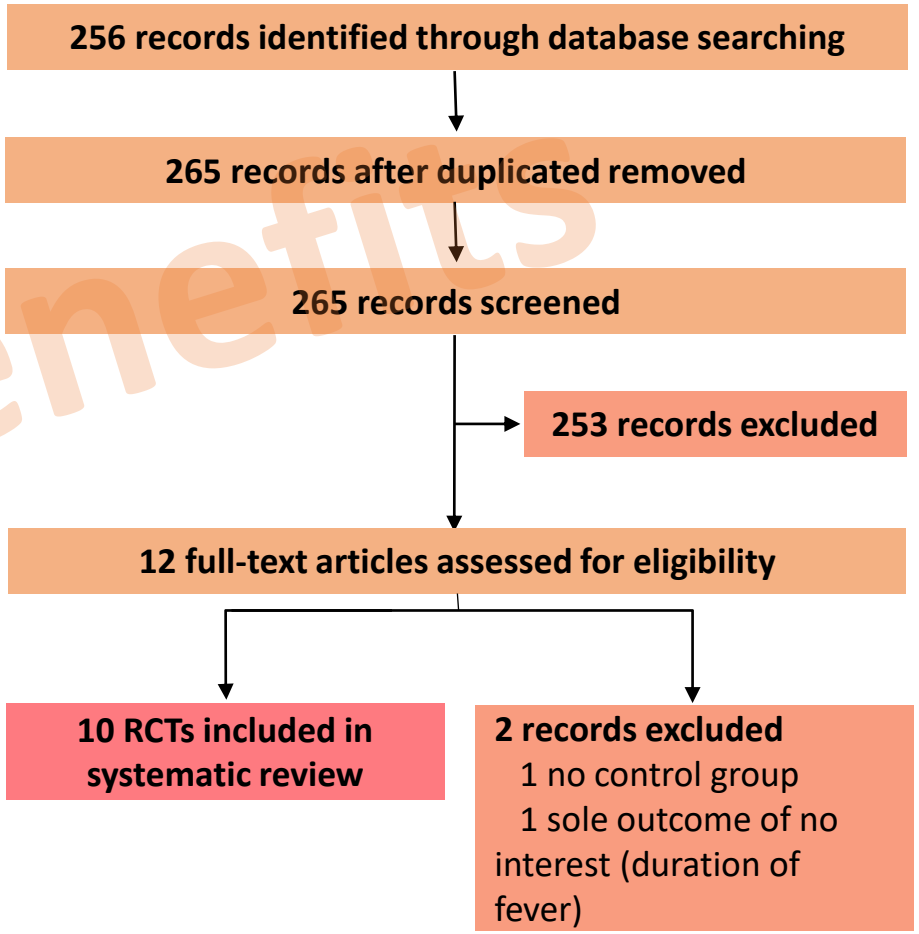
* Discovery study is included in Solidarity study

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)

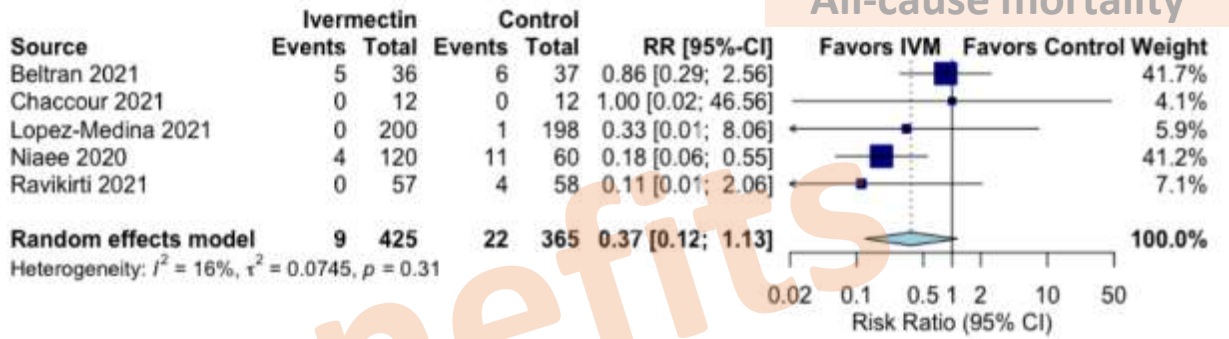
- IVM did not have effect on **all-cause mortality** compared with controls; RR: 0,37, $_{95\%}$CI [0,12:1,13]; 425 participants; 5 trials

- 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

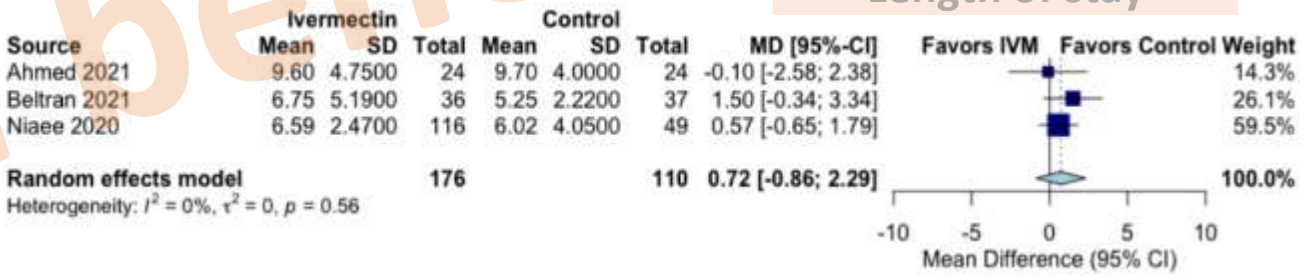
- IVM did not have effect on **adverse events** compared with controls; RR: 0,95, $_{95\%}$CI [0,79:1,07]; 425 participants; 5 trials

- 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

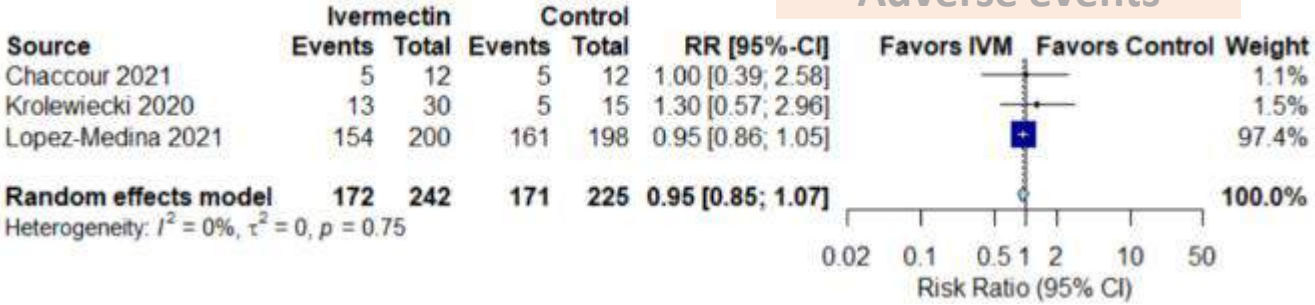
All-cause mortality



Length of stay



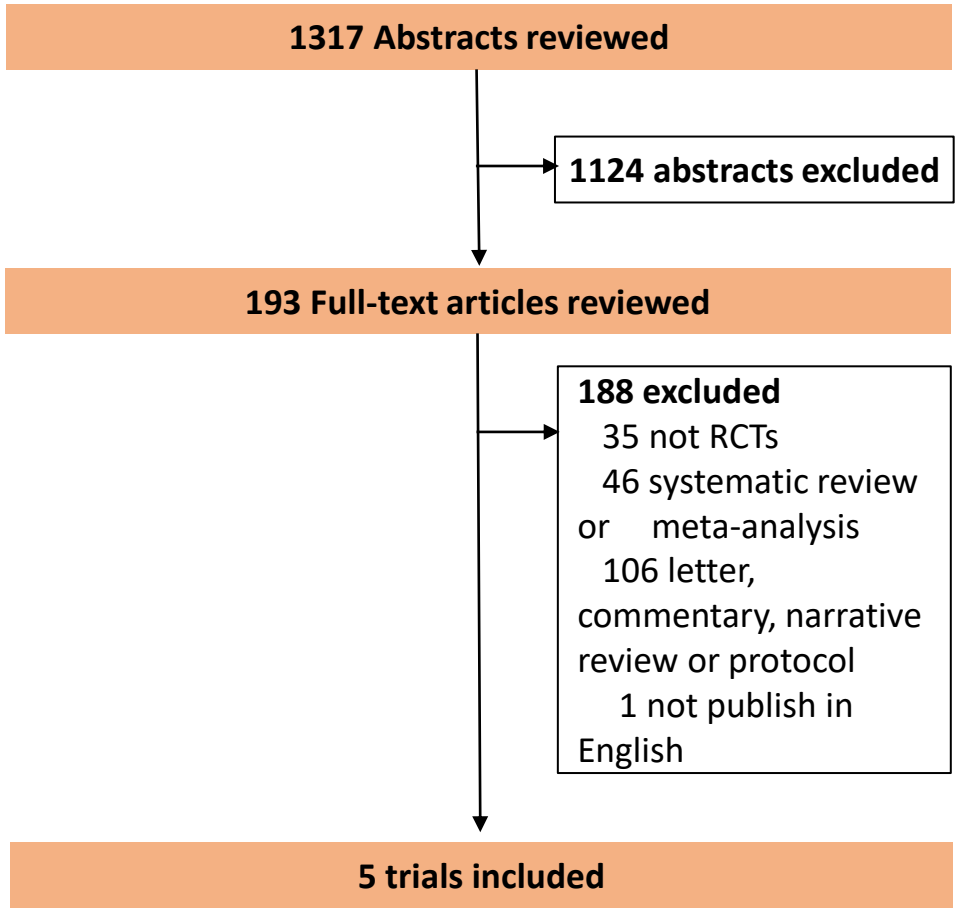
Adverse events



Anti viral effect

Remdesivir (RDV)

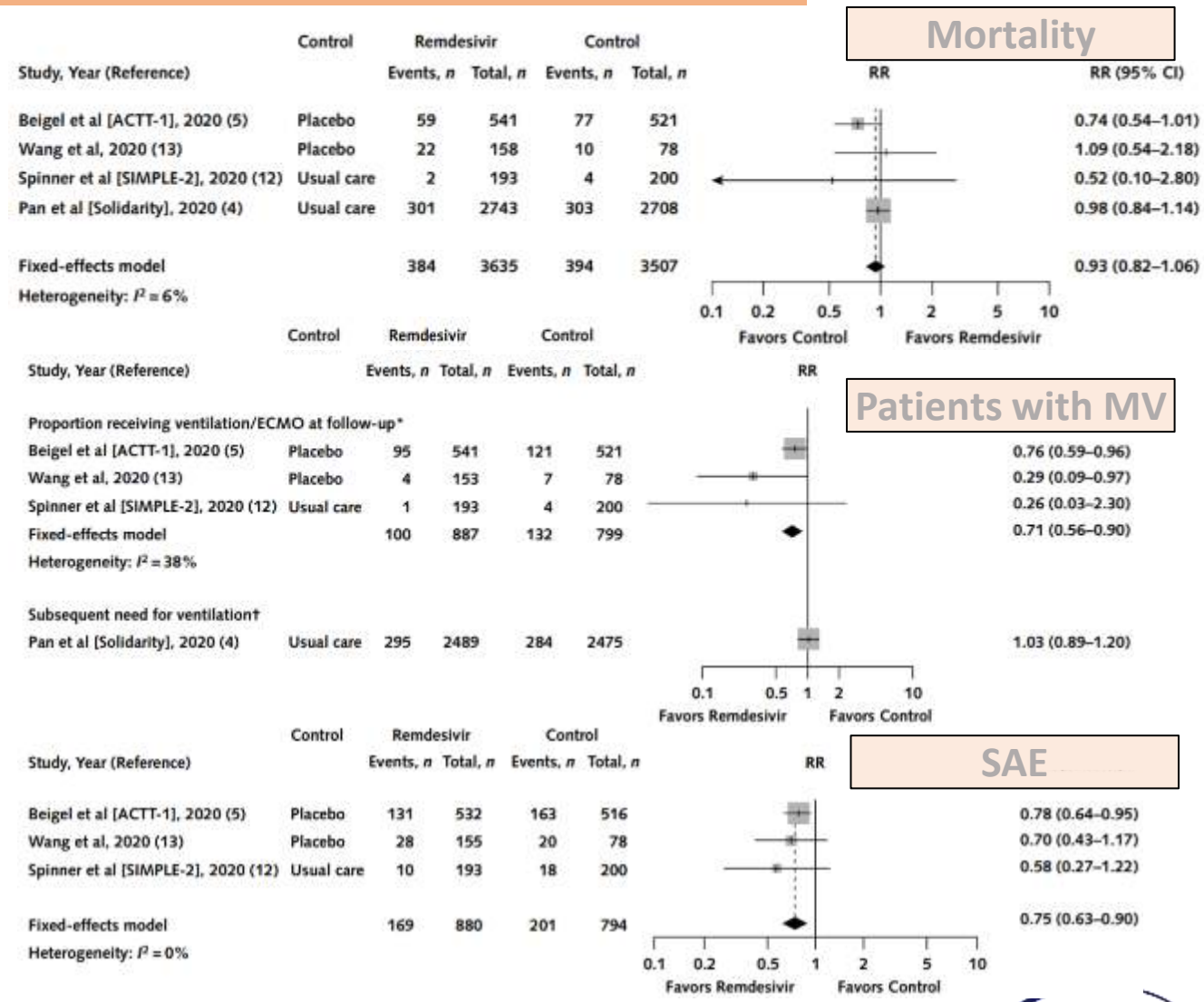
- Systematic review and meta-analysis of randomized controlled trials (RCTs), academic study, USA
- **Inclusion criteria:** English-language, RCTs reporting on remdesivir for treatment of adults with confirmed or suspected COVID-19. Studies were eligible if they compared remdesivir *versus* placebo, 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

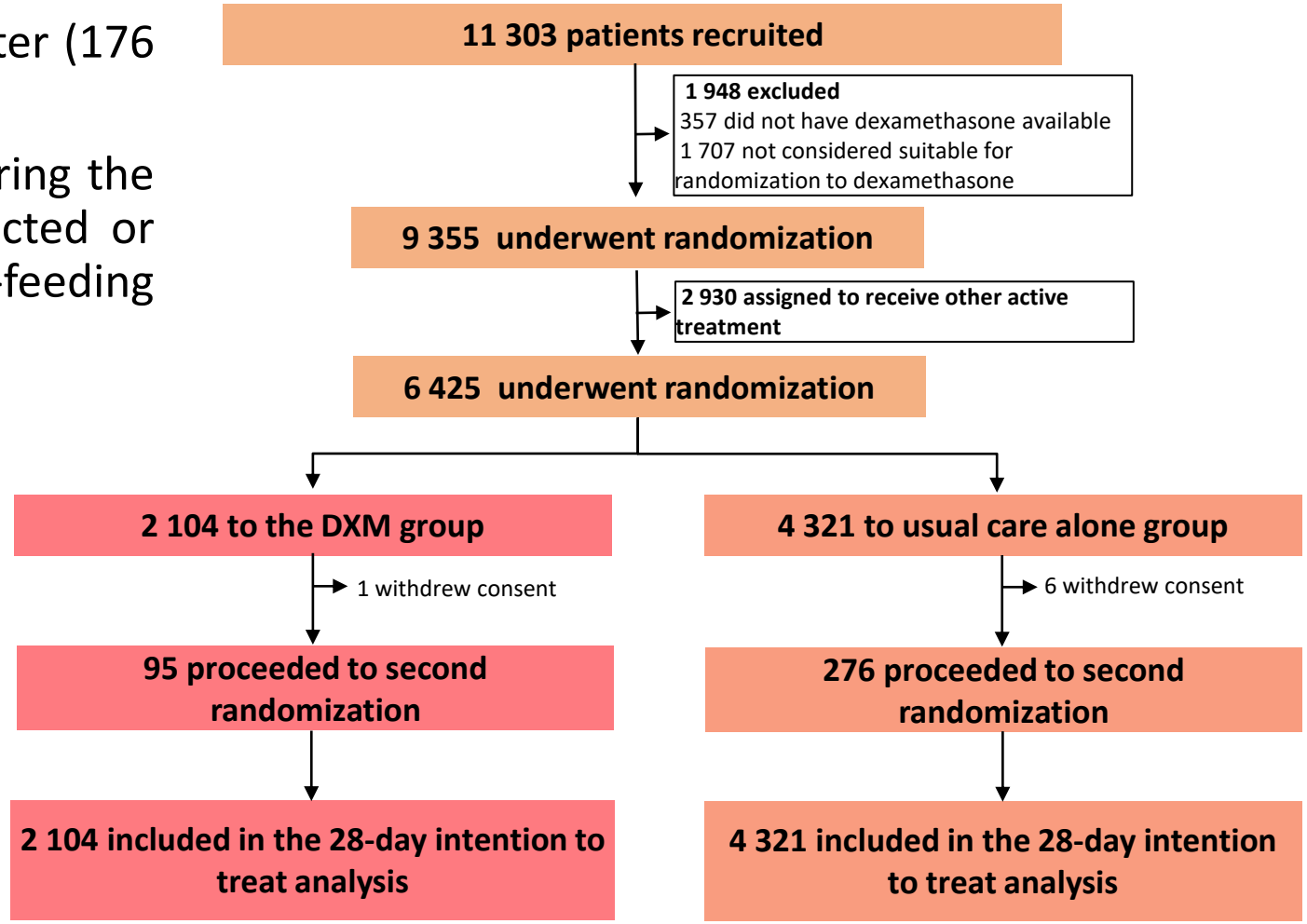


Kaka SA *et al*. Ann Intern Med *May* 2021

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

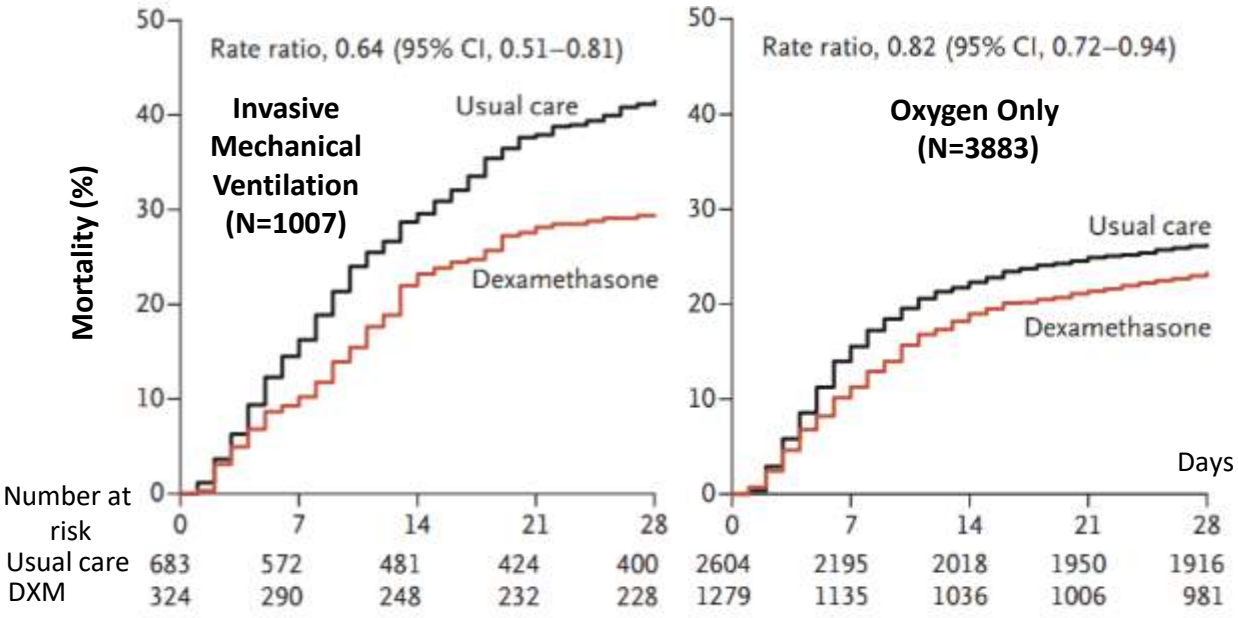
Corticosteroids (CT) - 1

	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

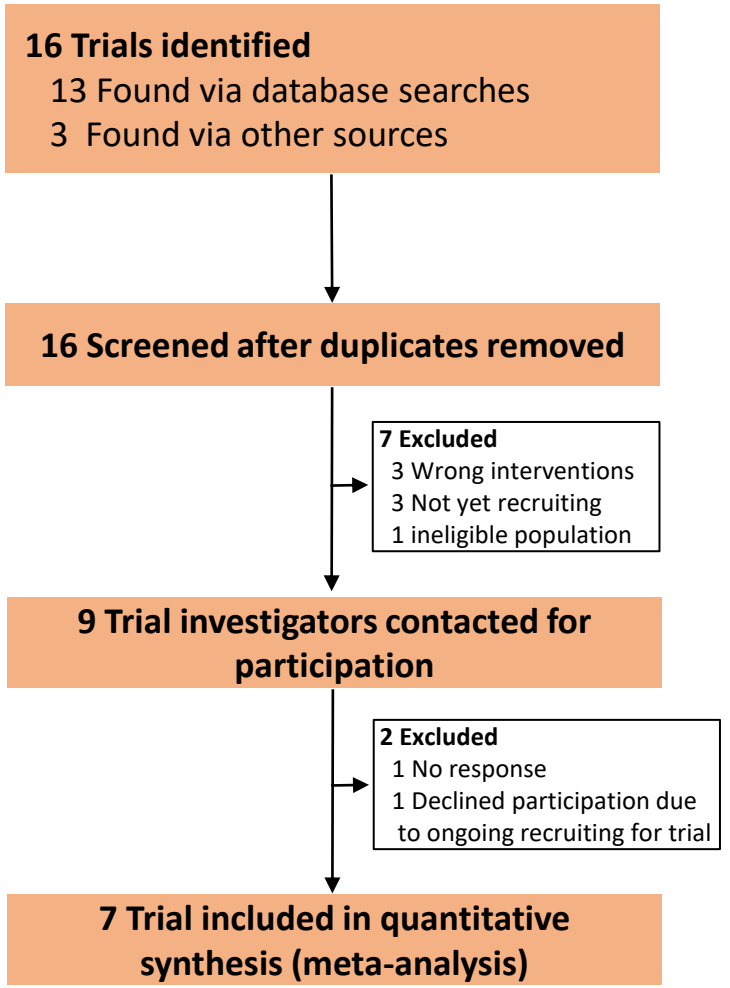
categories: 11.5

0.50 0.75 1.00 1.50 2.00

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**

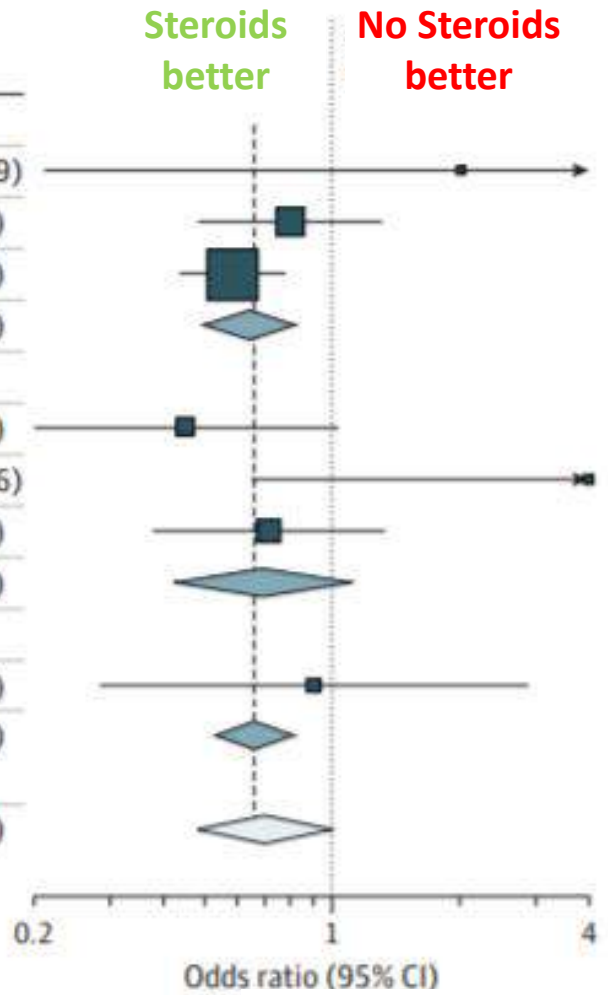


Immunomodulatory effect

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

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

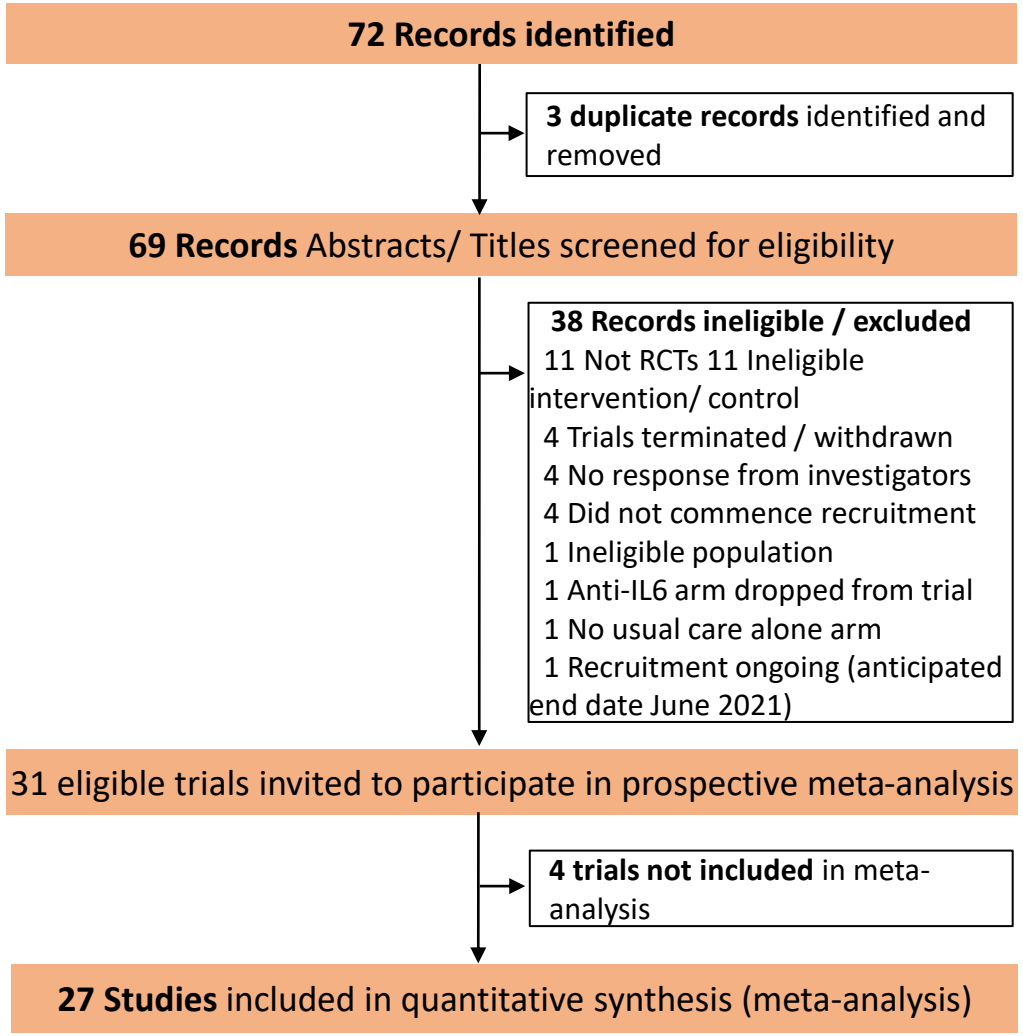
HC: hydrocortisone

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

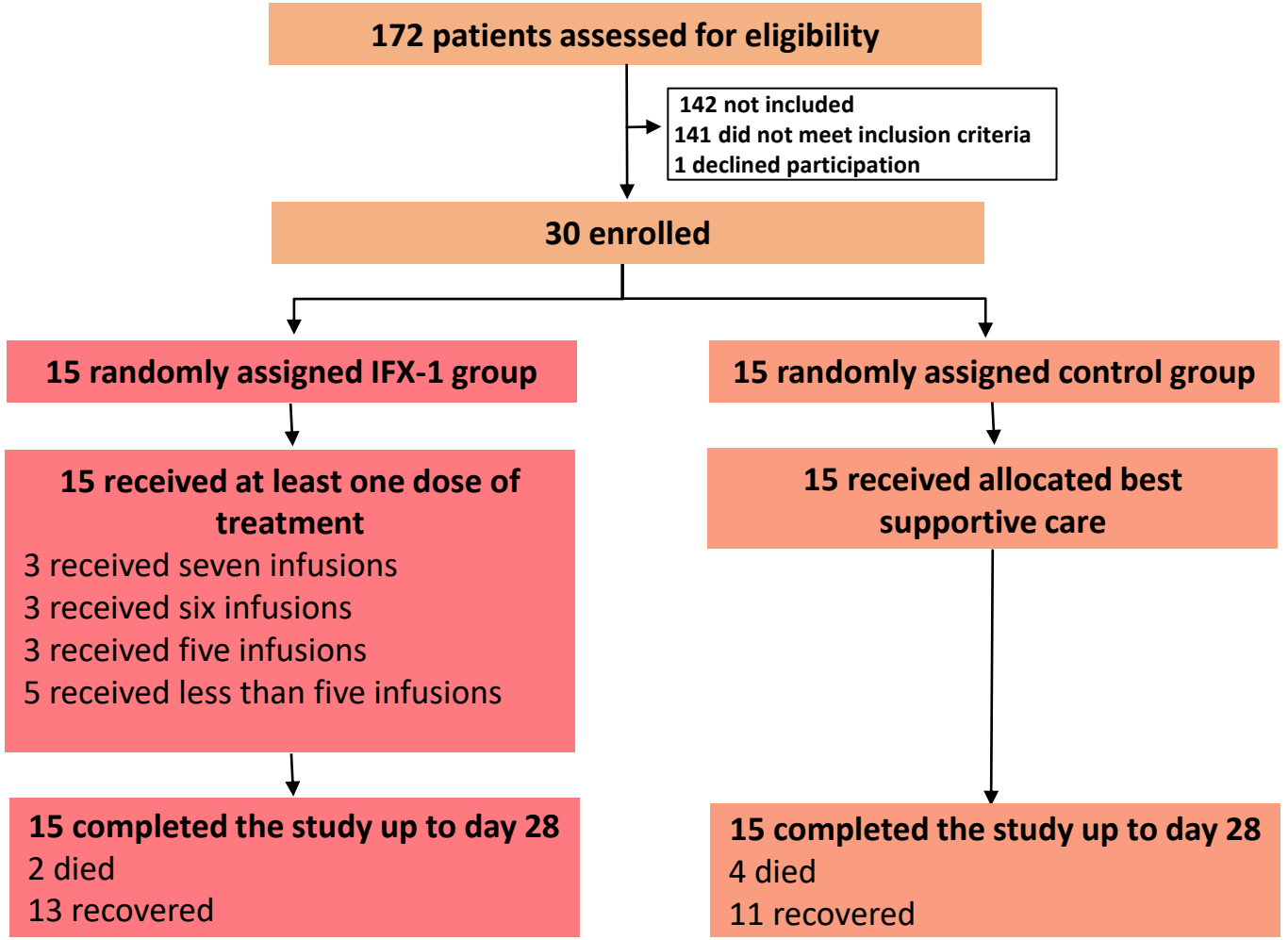
Odds ratio (95% CI)

- **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)

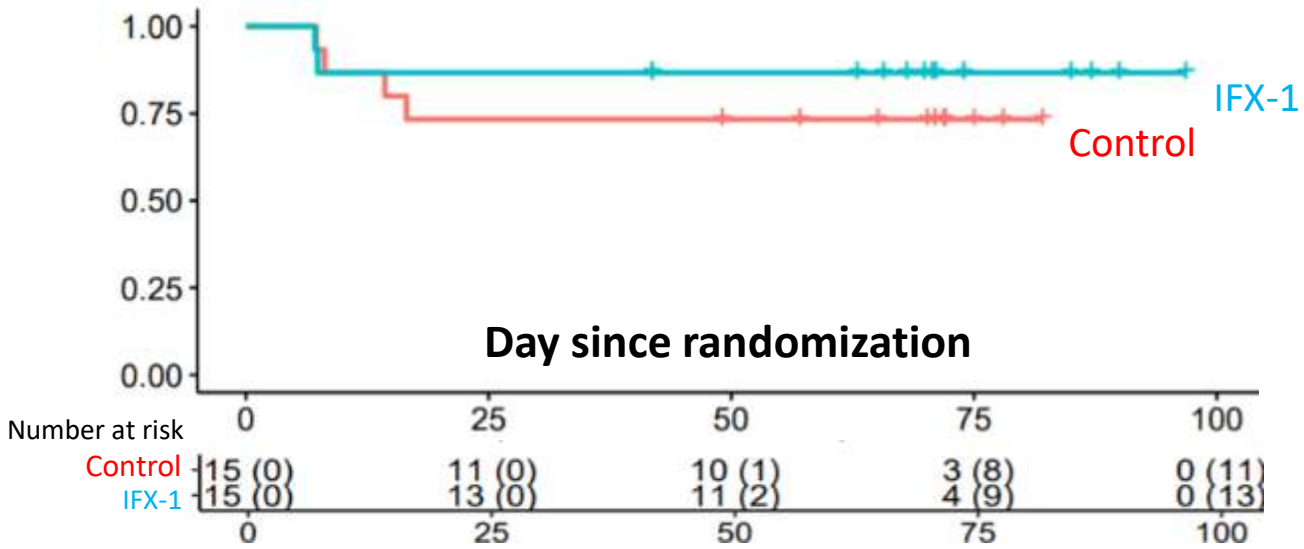
- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria** : age ≥ 18yo, severe pneumonia (PaO_2/FiO_2 between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive 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]



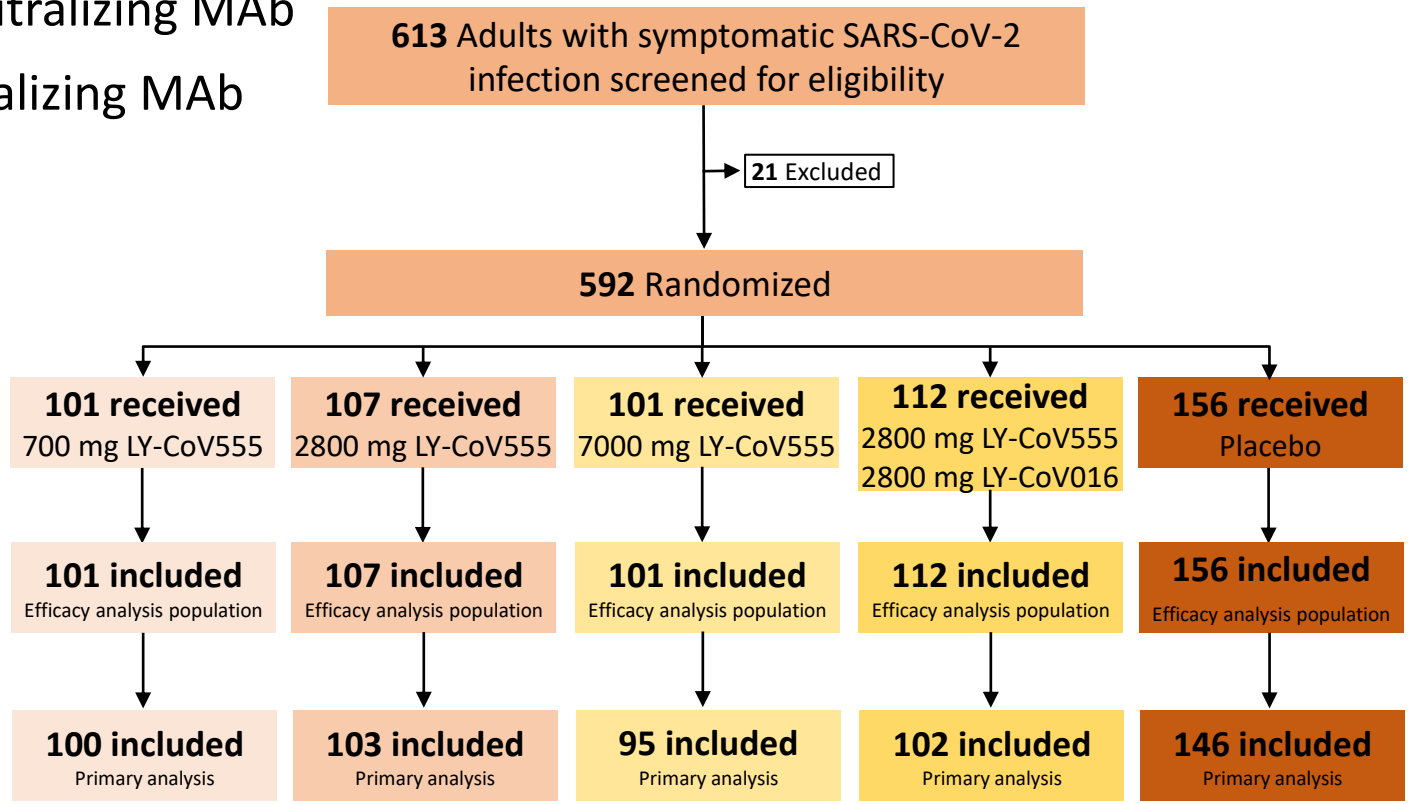
- **Limits**: patient heterogeneity, open label study, very low number of participants (15 in each group)

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

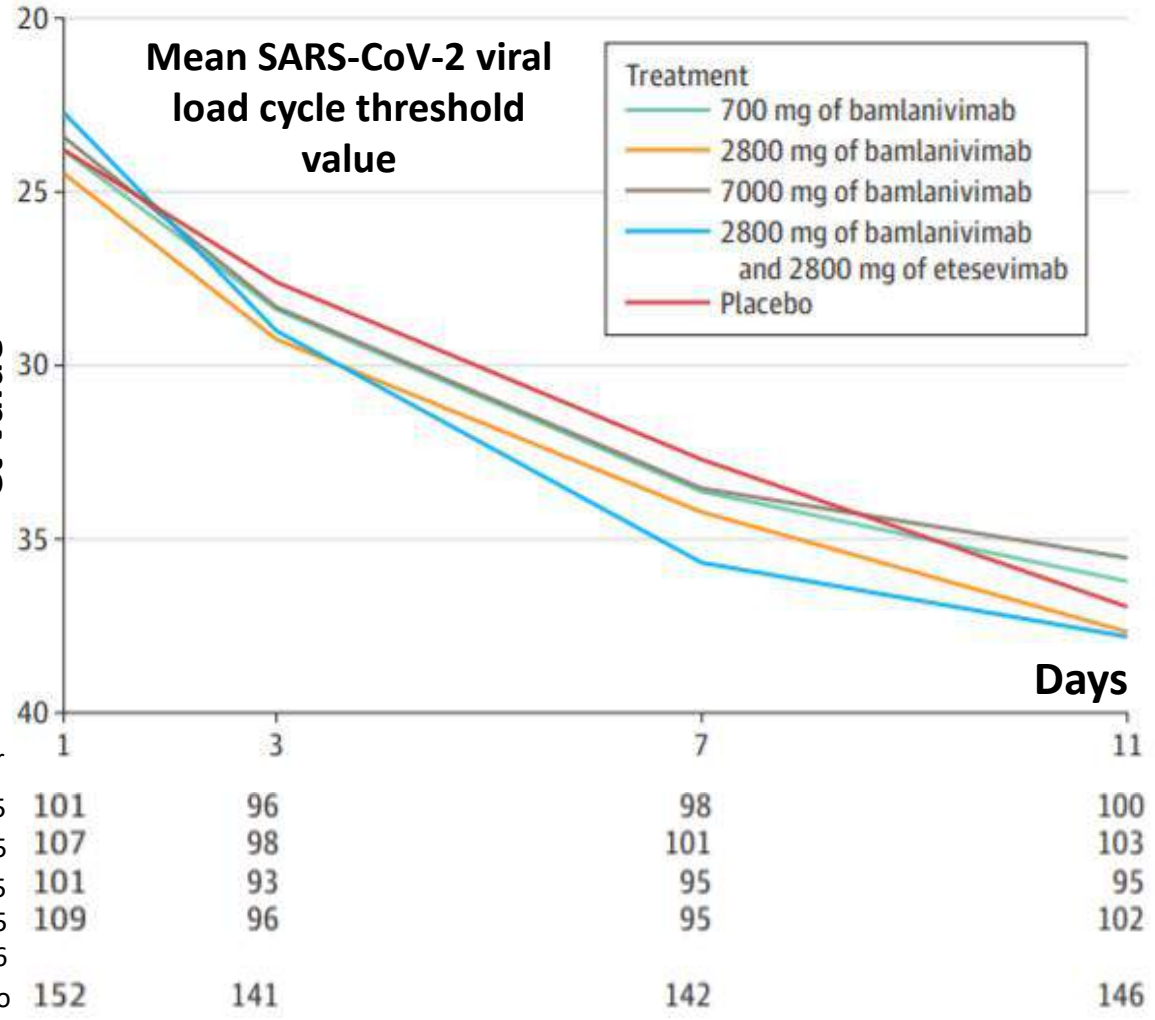
Characteristics	LY-CoV555			LY-CoV555 + LY-CoV016	Placebo
	700 mg N=101	2800 mg N=107	7000 mg N=101	2800 mg + 2800 mg N= 112	N= 156
Age (y) – median (IQR)	39 (31-58)	45 (31-56)	46 (34-55)	44 (30-60)	46 (35-57)
Female sex – no (%)	63 (62.4)	51 (47.7)	58 (57.4)	58 (51.8)	85 (54.5)
BMI (kg/m²) – median (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)

Gottlieb RL *et al. JAMA* Jan 2021

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**

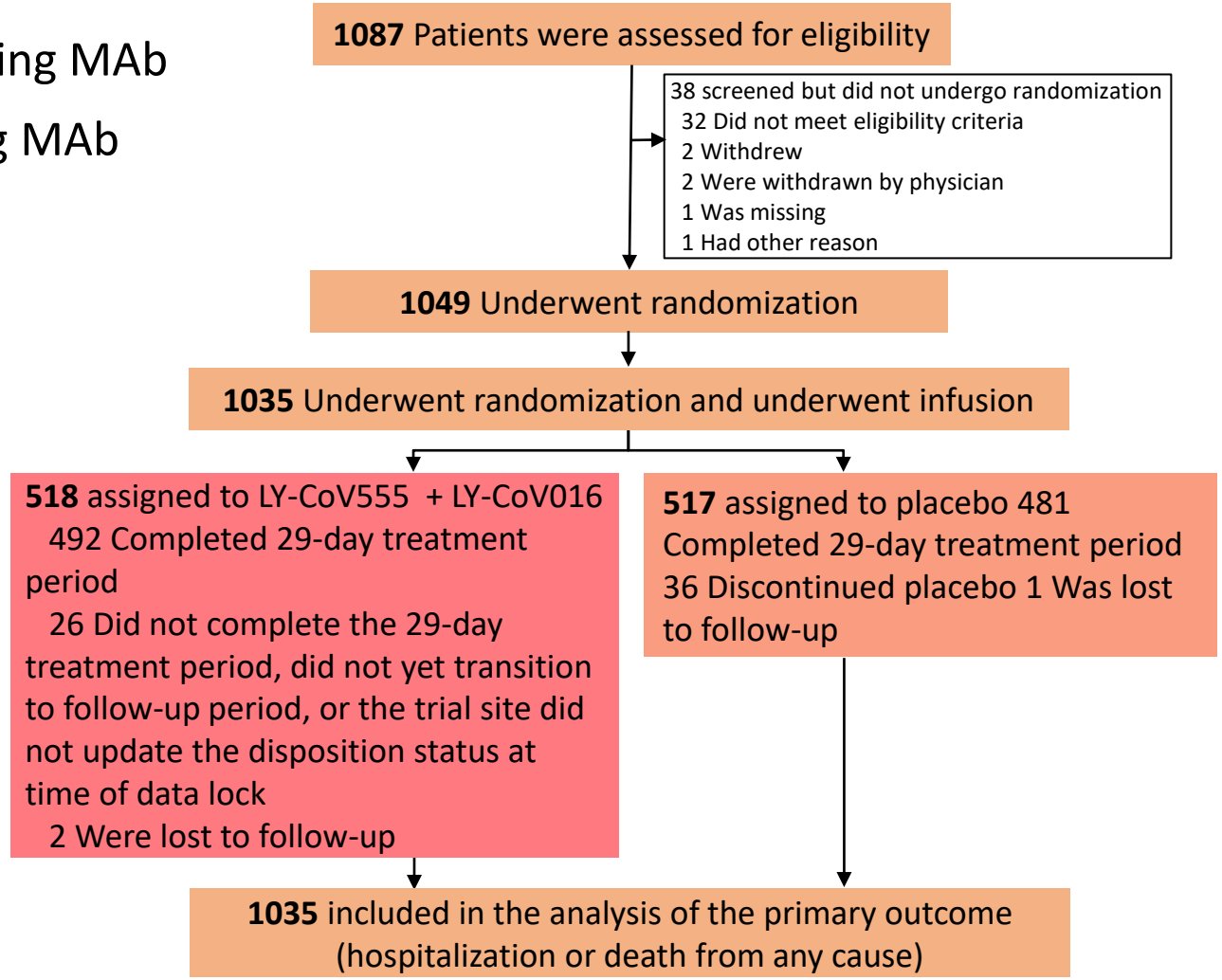


Gottlieb RL *et al. JAMA* Jan 2021

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

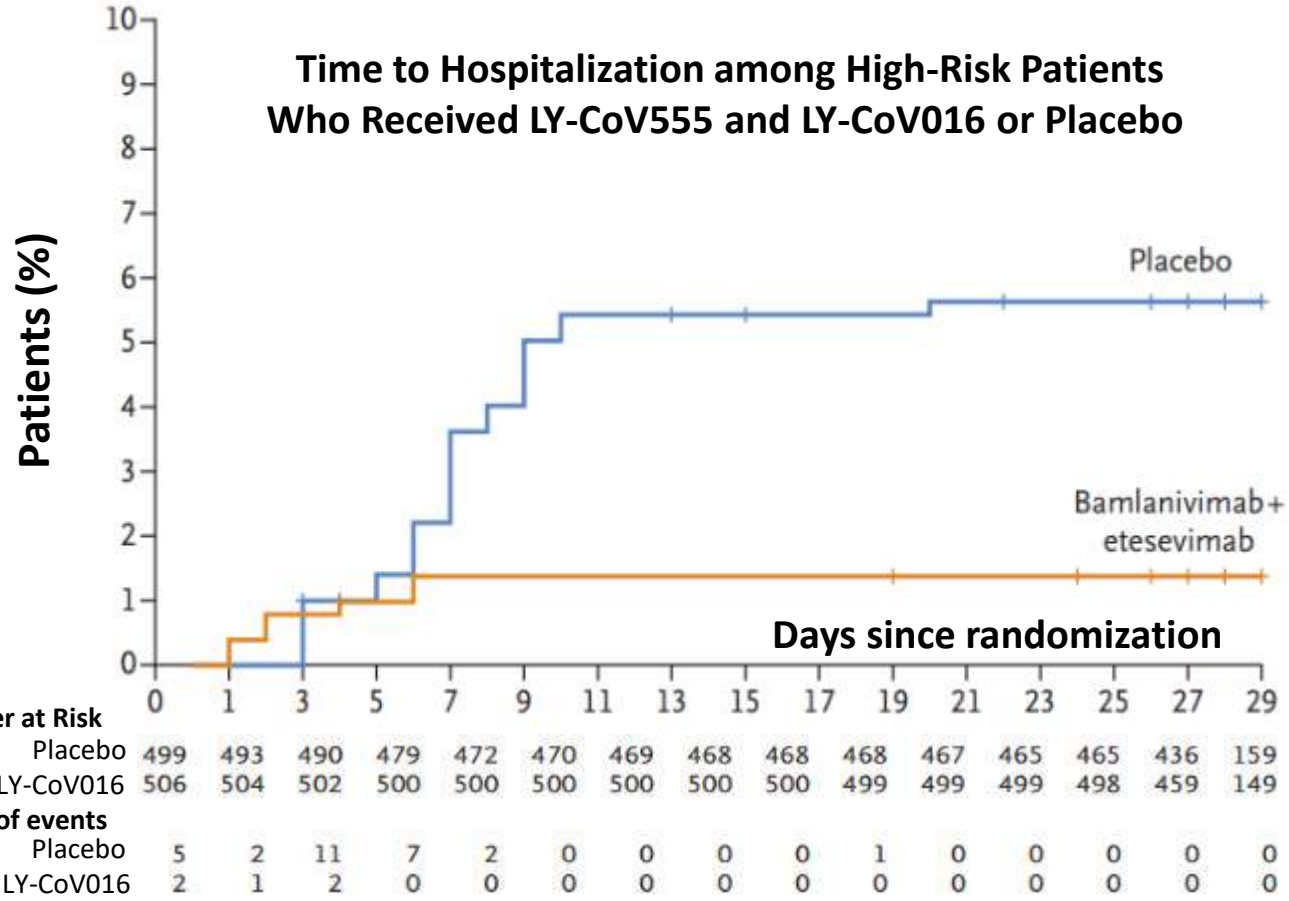
LY-CoV555 and LY-CoV016 - 2

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**

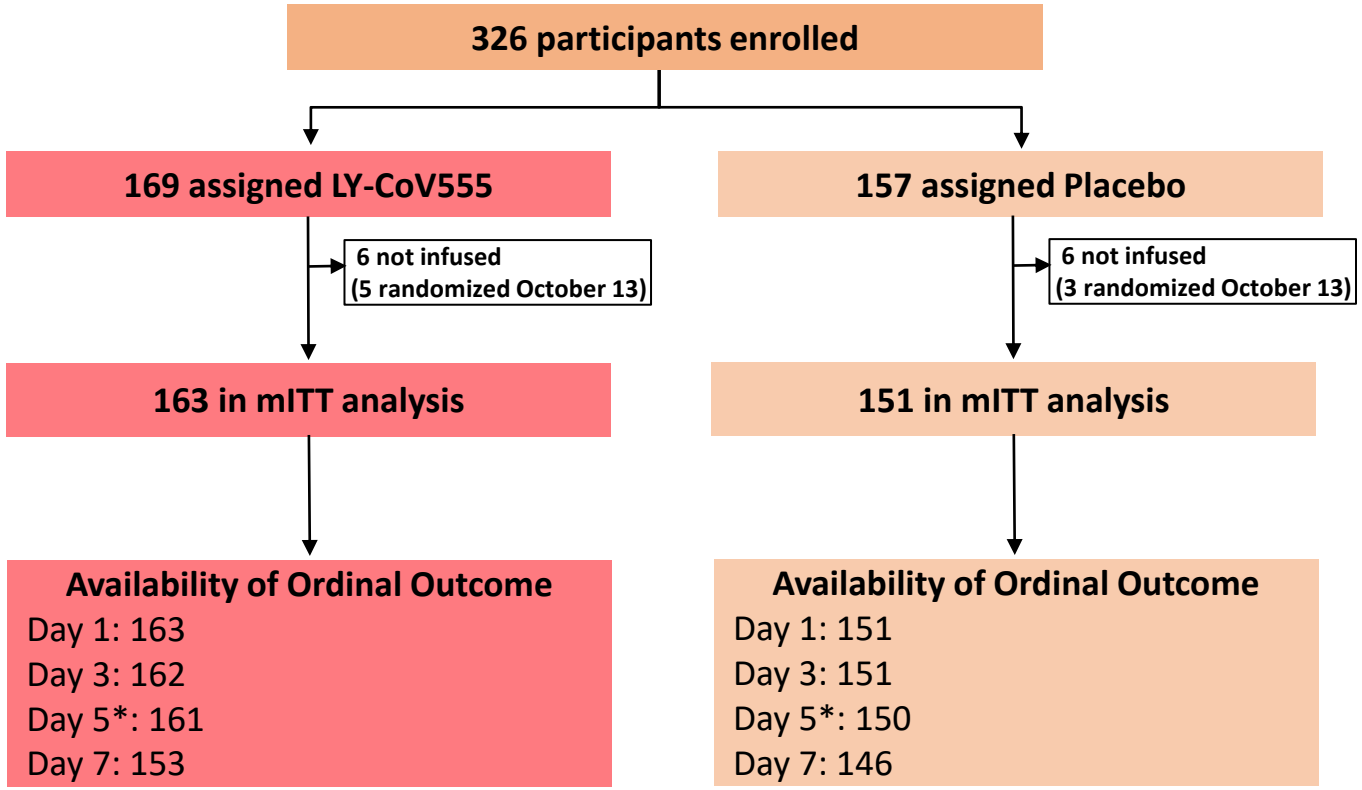


Dougan M *et al. NEJM* Jul 2021

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

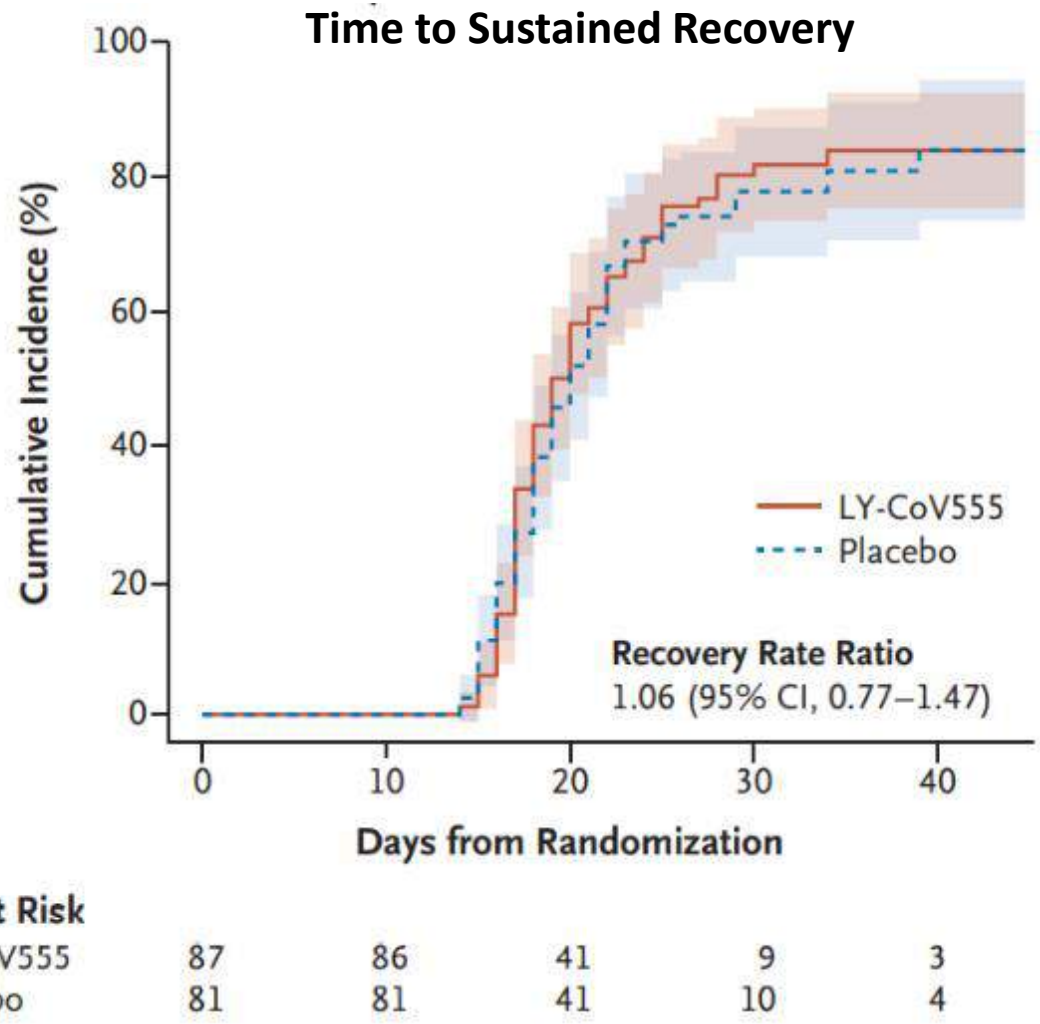
LY-CoV555

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)

ER: emergency room
NmAb: Neutralizing monoclonal antibody

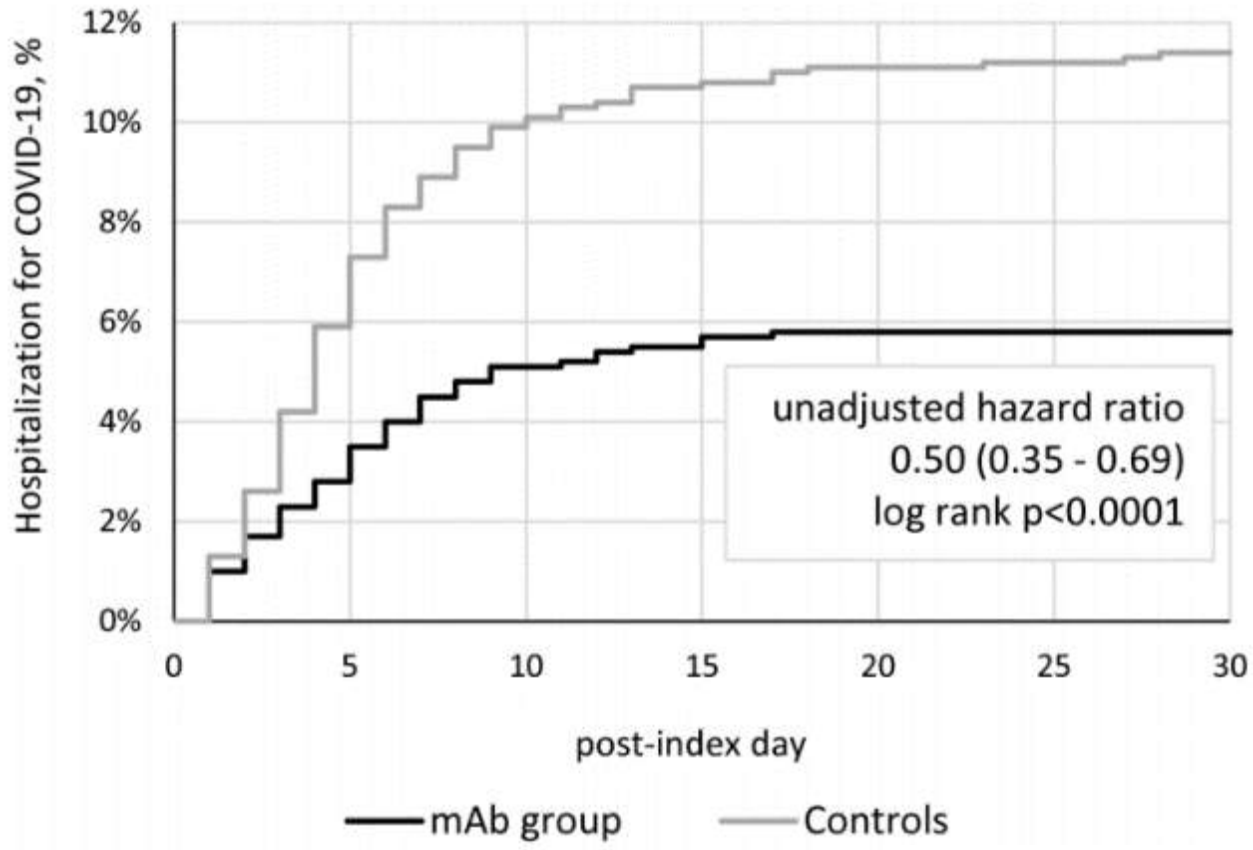
Verderese JP *et al. CID* Jun 2021

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**

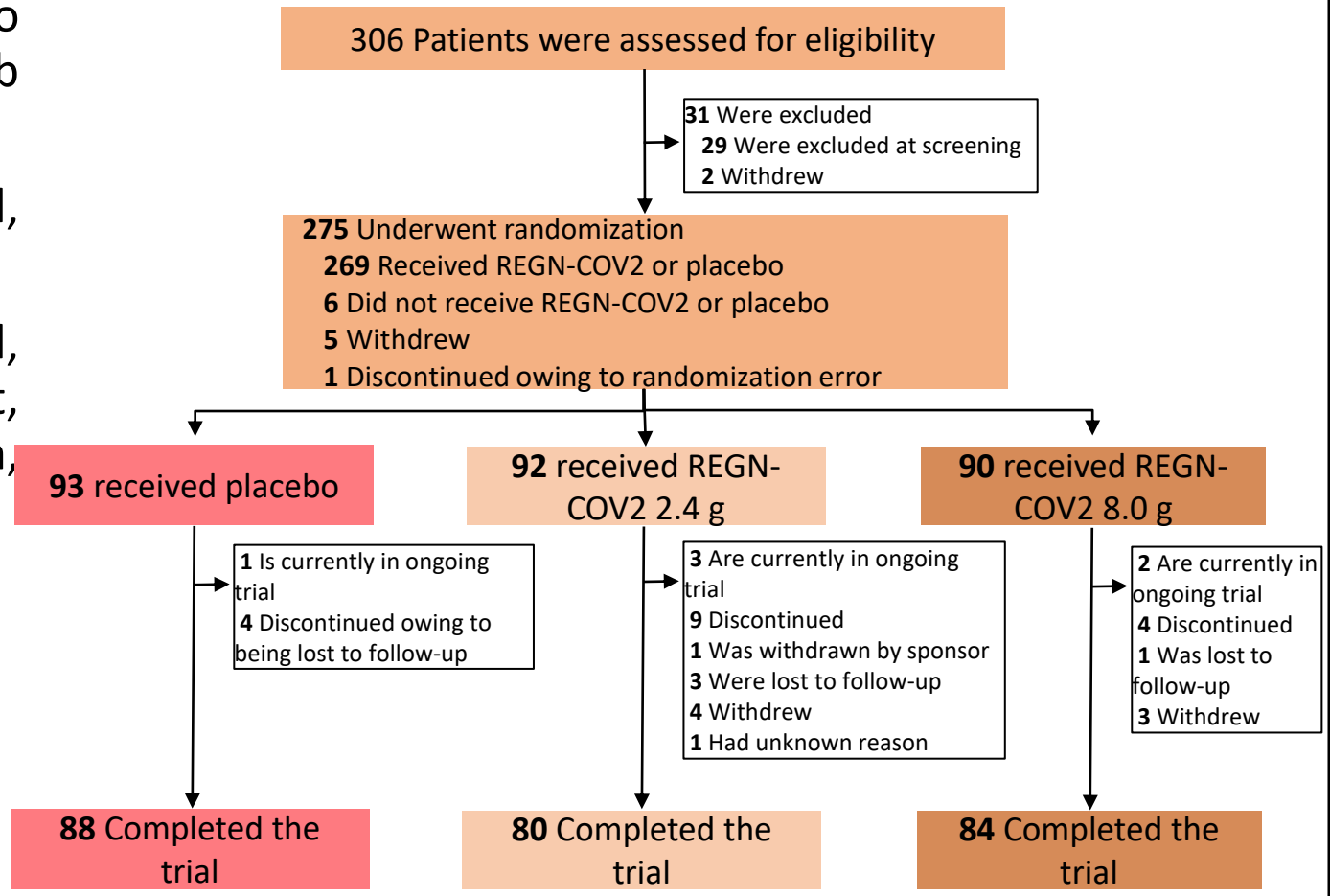
Hospitalizations for COVID-19 in patients who received a NmAb infusion and controls (censored at 30 days)



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)

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Weinreich DM *et al. NEJM* Dec 2020

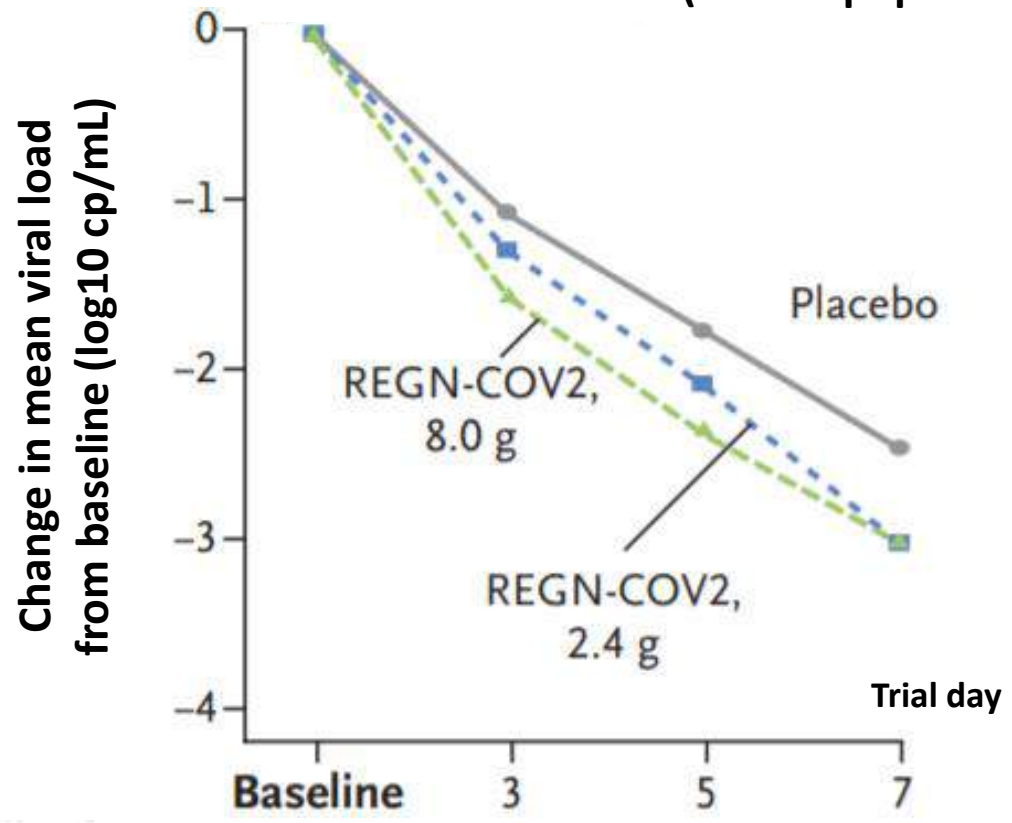
anrs MALADIES INFECTIEUSES ÉMERGENTES

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)



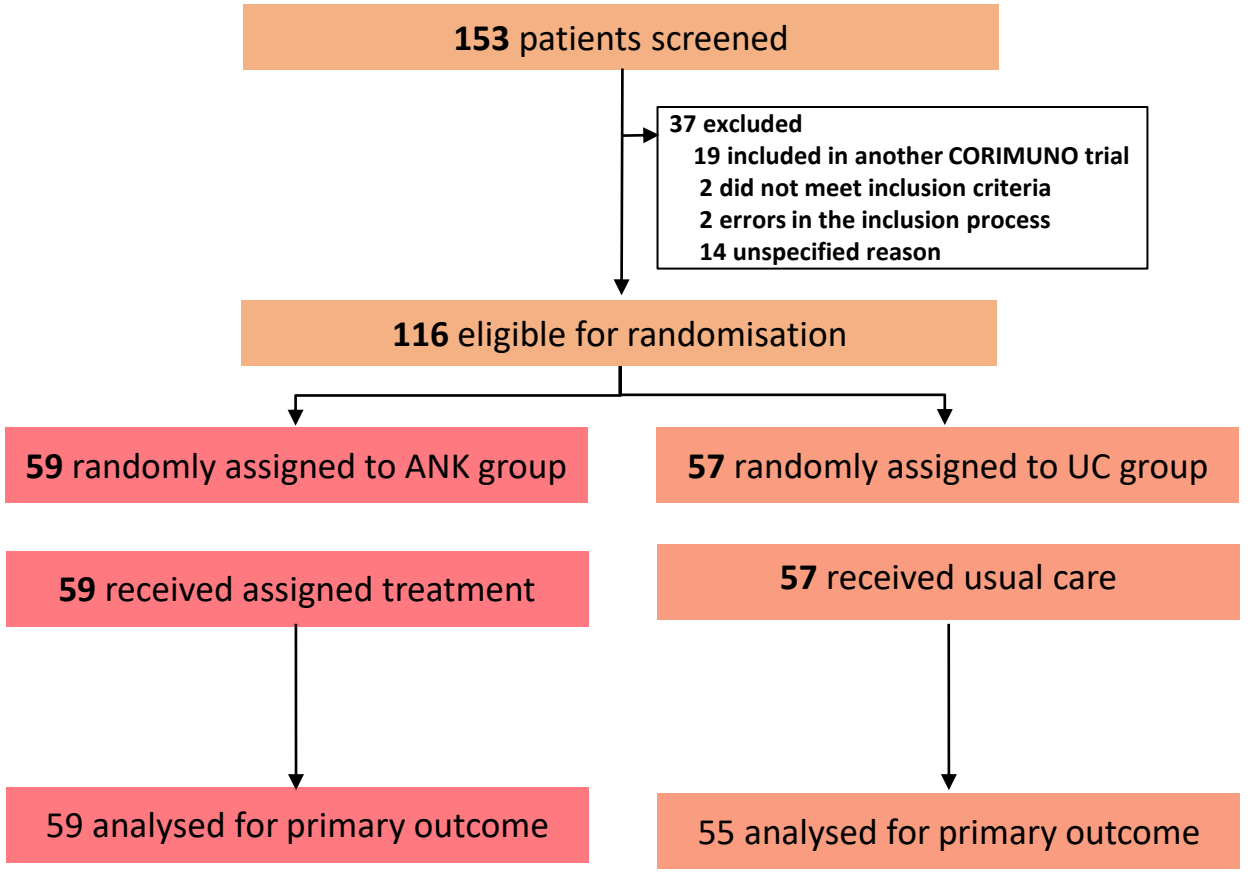
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

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

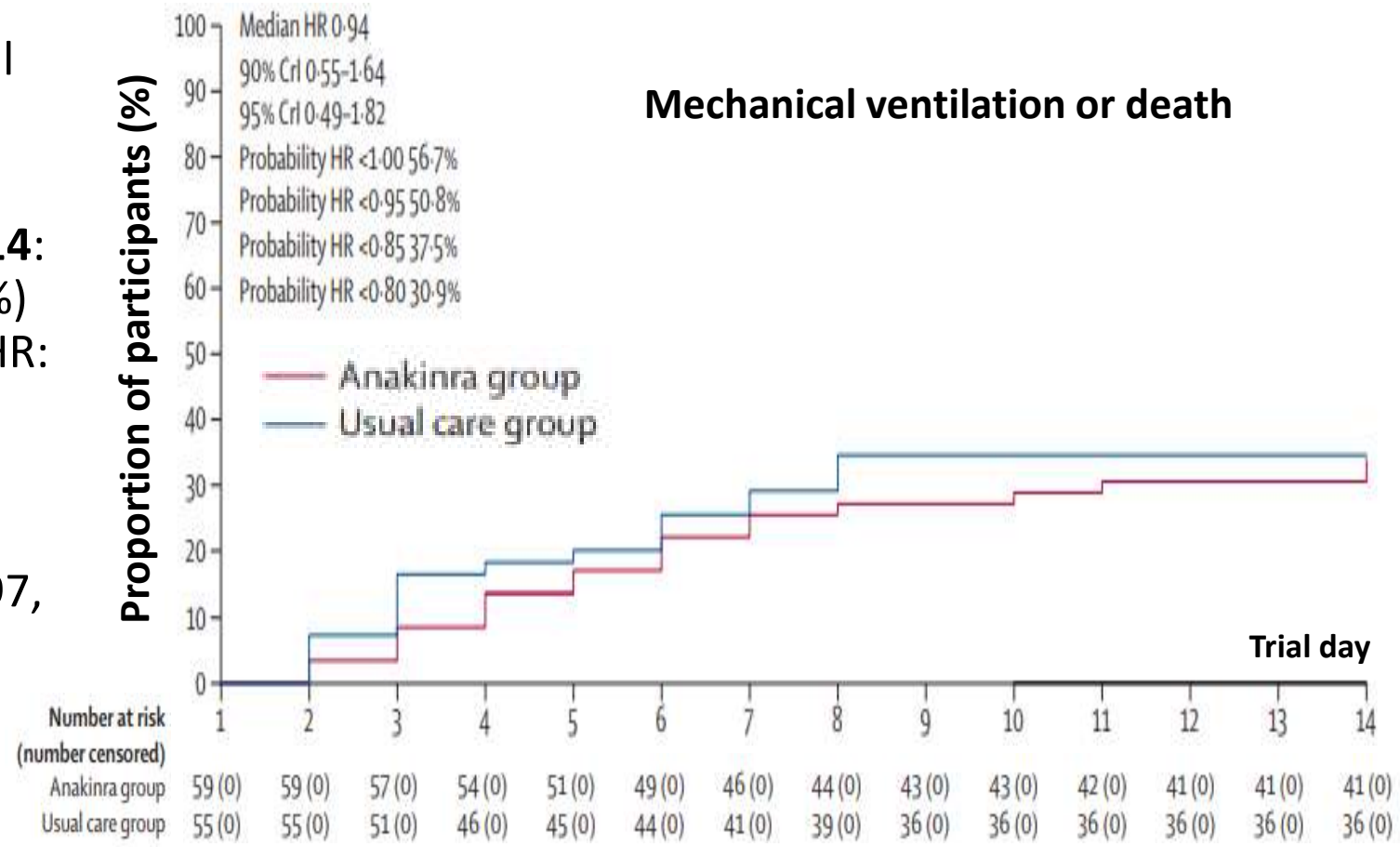
Anakinra (ANK)

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>**

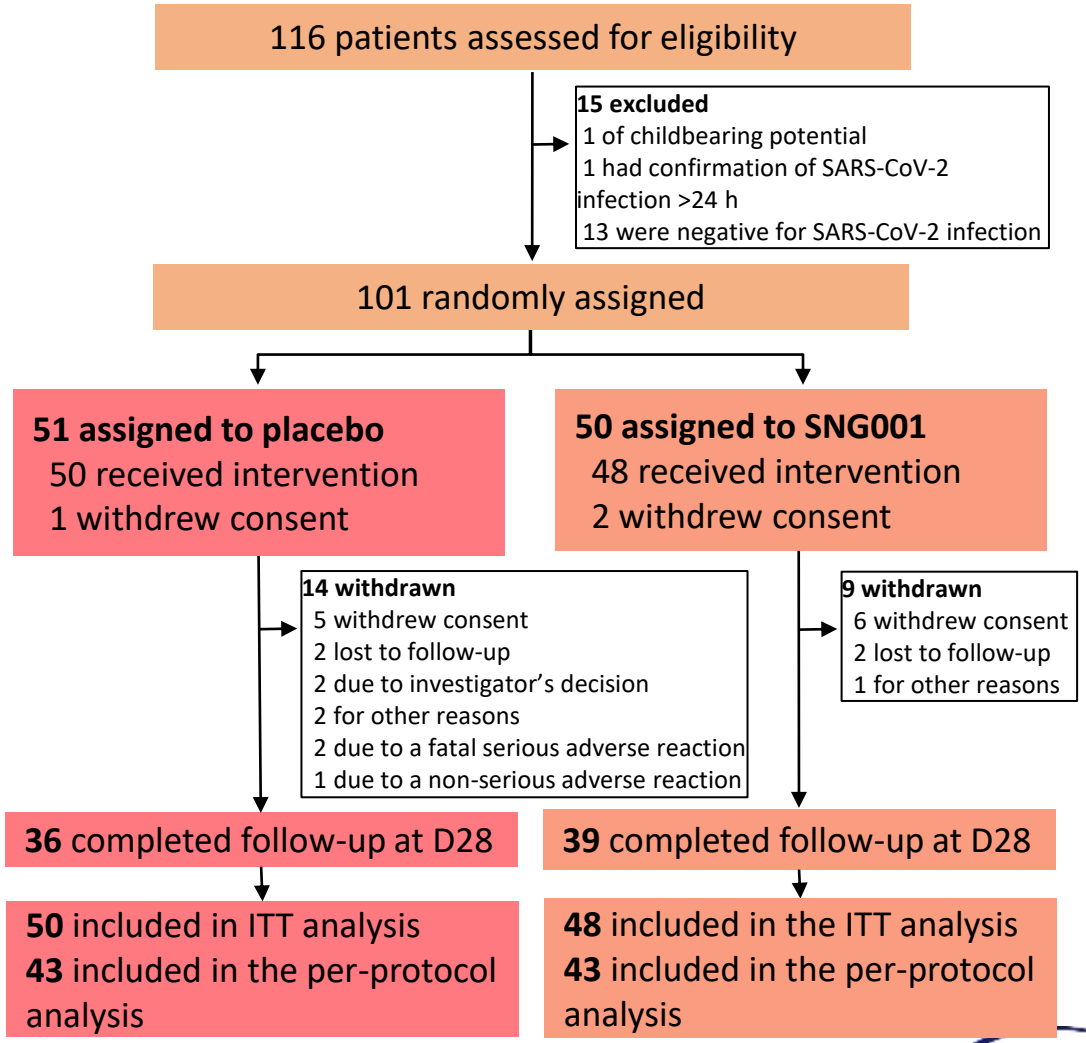


The CORIMUNO-19 Collaborative group. *Lancet Resp Med* Jan 2021

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

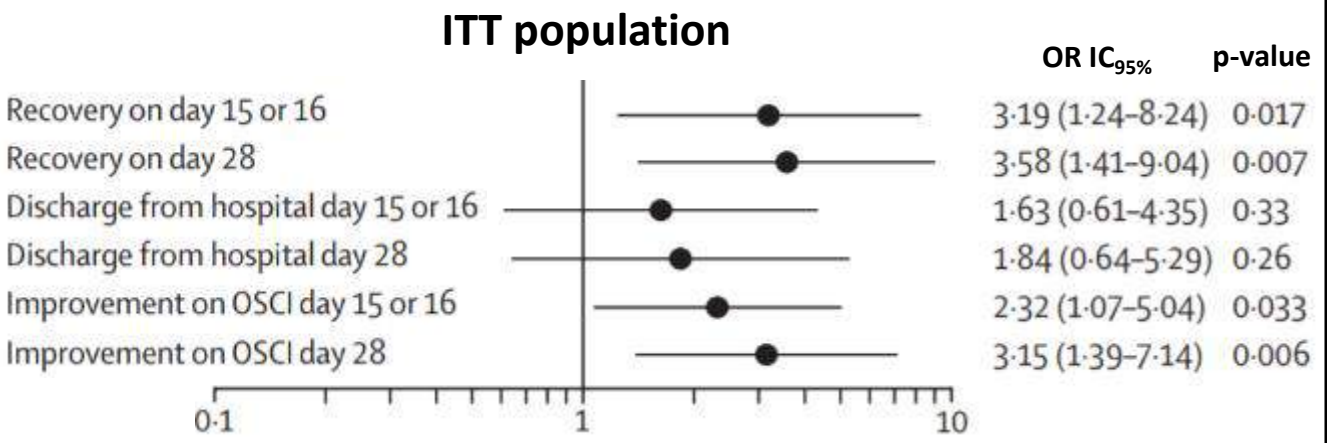
Interferon beta 1a - 1

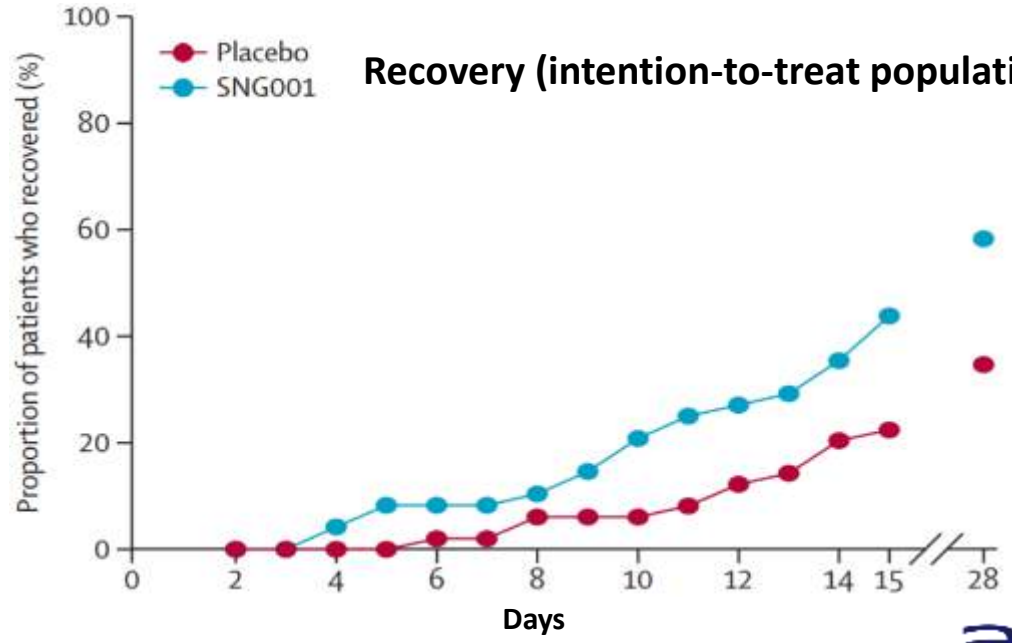
Characteristics	SNG001 (N=50)	Placebo (N=51)
Age (y) – mean (SD)	57,8 (14,6)	56,5 (11,9)
Male sex – no (%)	27 (56)	31 (62)
Coexisting conditions		
Hypertension – no (%)	18/26 (69)	11/27 (41)
Diabetes – no (%)	3/26 (12)	9/27 (33)
Cardiovascular disease – no (%)	5/26 (19)	8/27 (30)
Chronic lung condition – 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



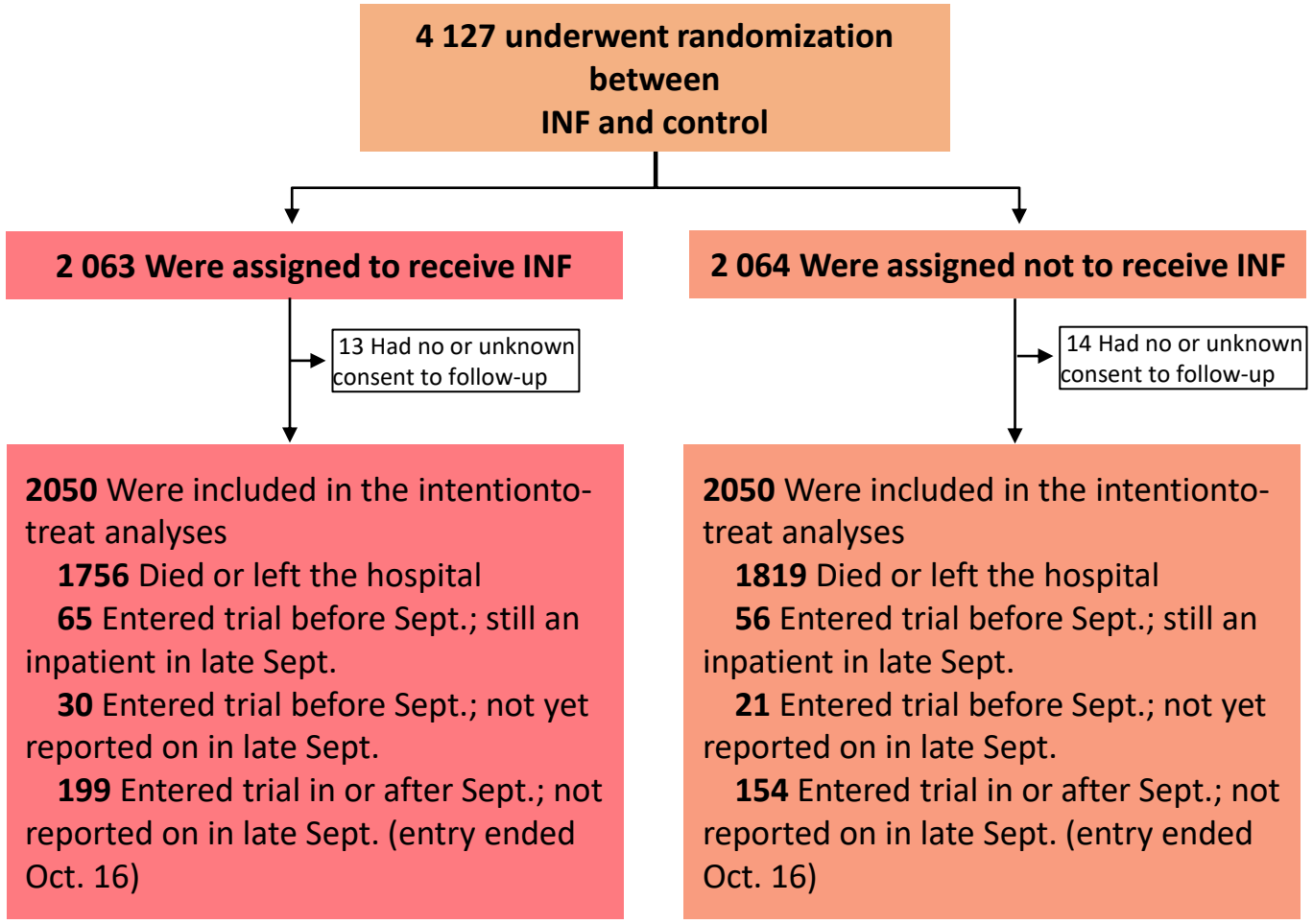


Monk PD *et al. Lancet Resp Med* Nov 2020

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

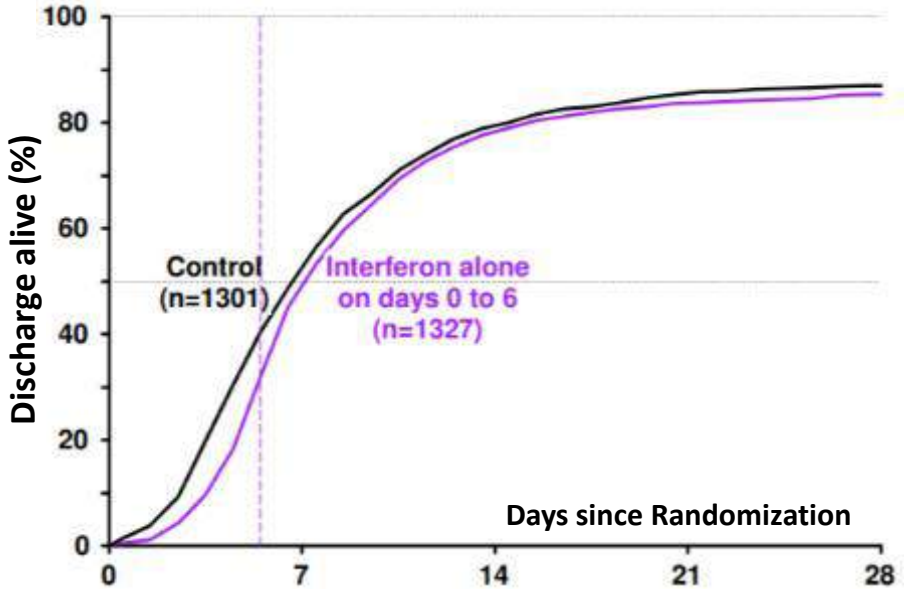
Characteristics		All (N= 11 266)	INF (N= 2 050)	Control (N=2 050)
Age	< 50 yr – no (%)	3995 (35)	720	697
	50-69 yr – no (%)	5125 (45)	934	973
	≥ 70 yr – no (%)	2146 (19)	396	380
Sex	Male sex – no (%)	6985 (62)	1303	1278
Co existing conditions	Diabetes – no(%)	2768 (25)	489	537
	Heart disease – no (%)	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

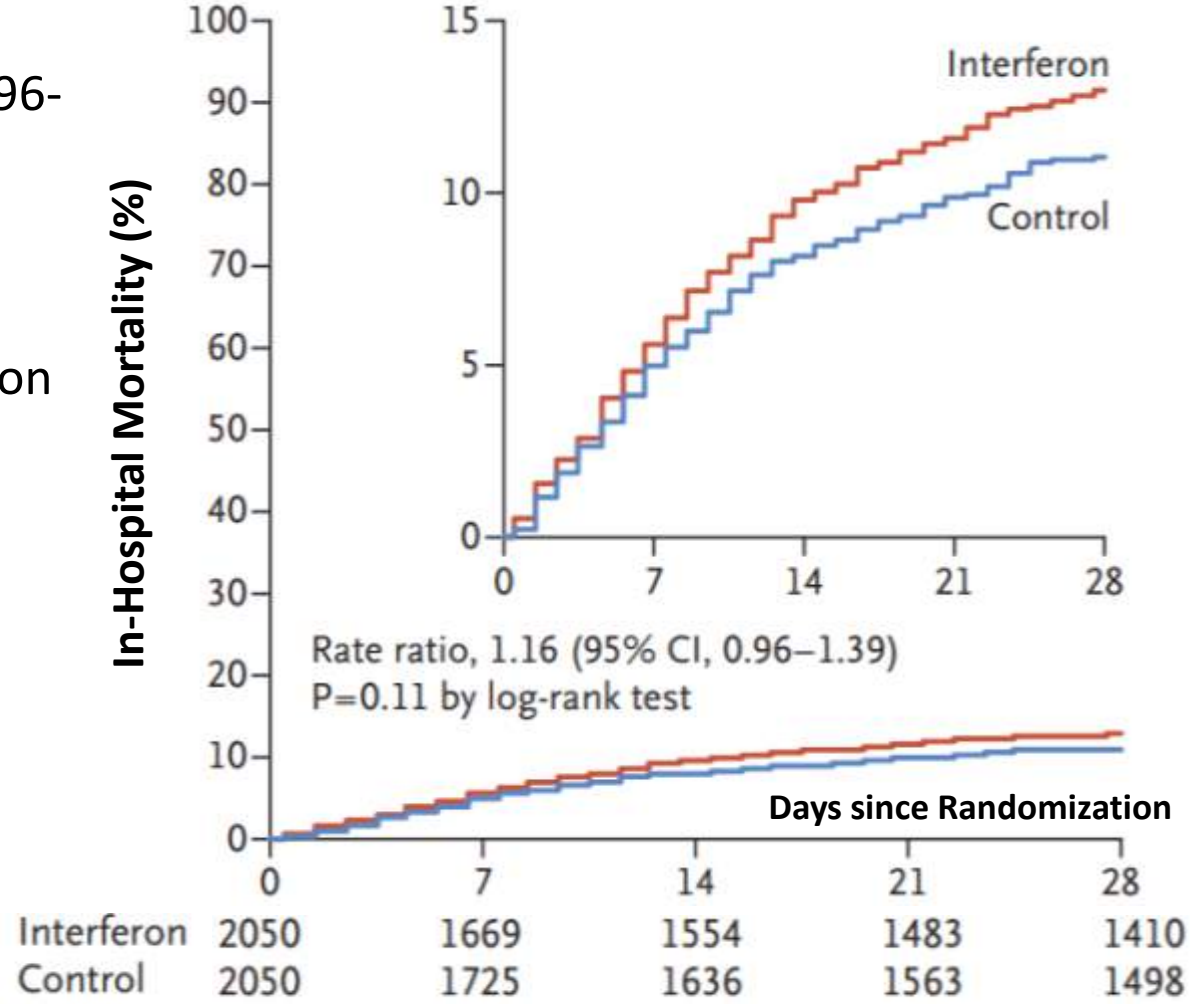
Immunomodulatory effect

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



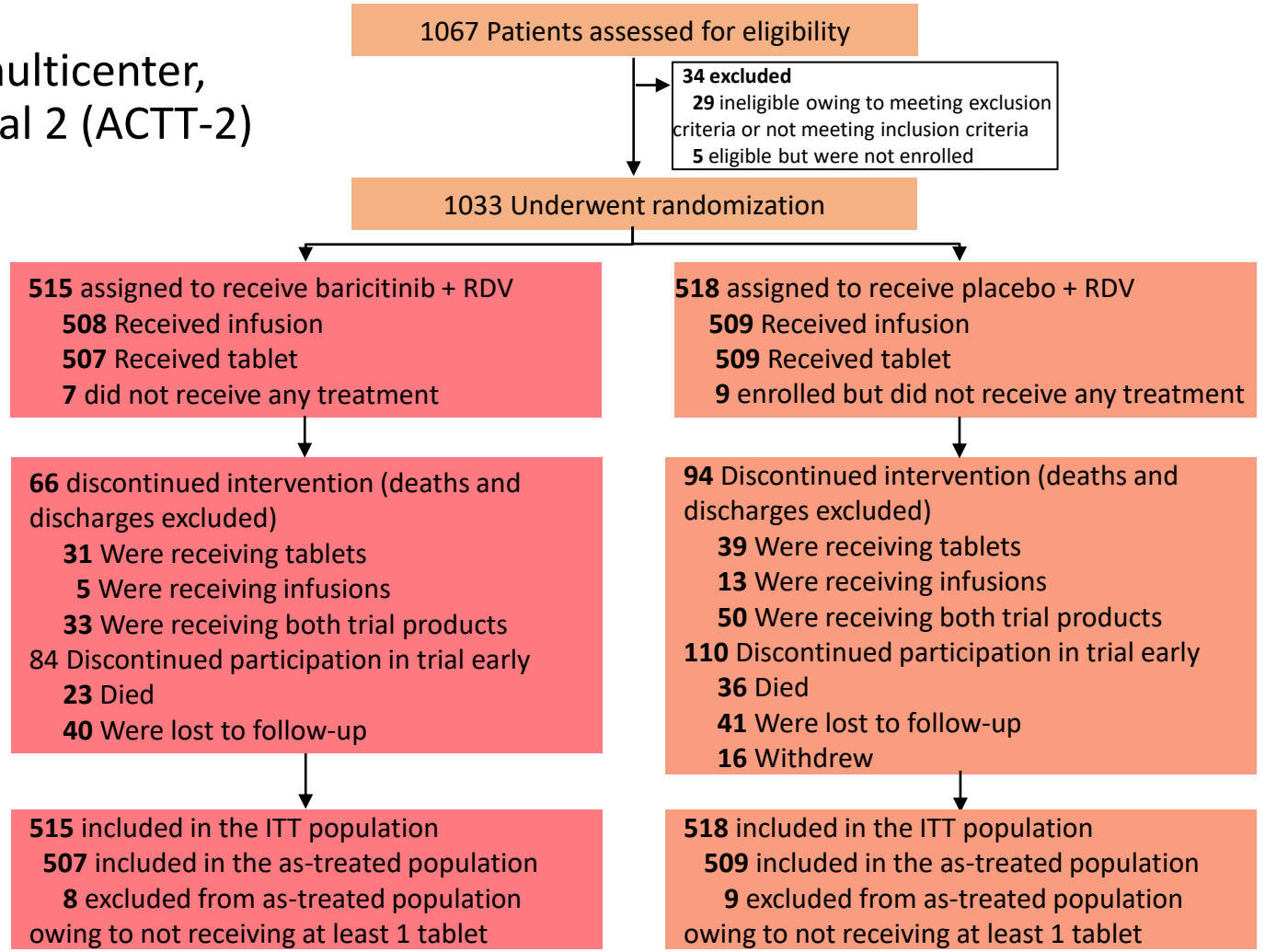


SOLIDARITY *NEJM* Dec 2020

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)

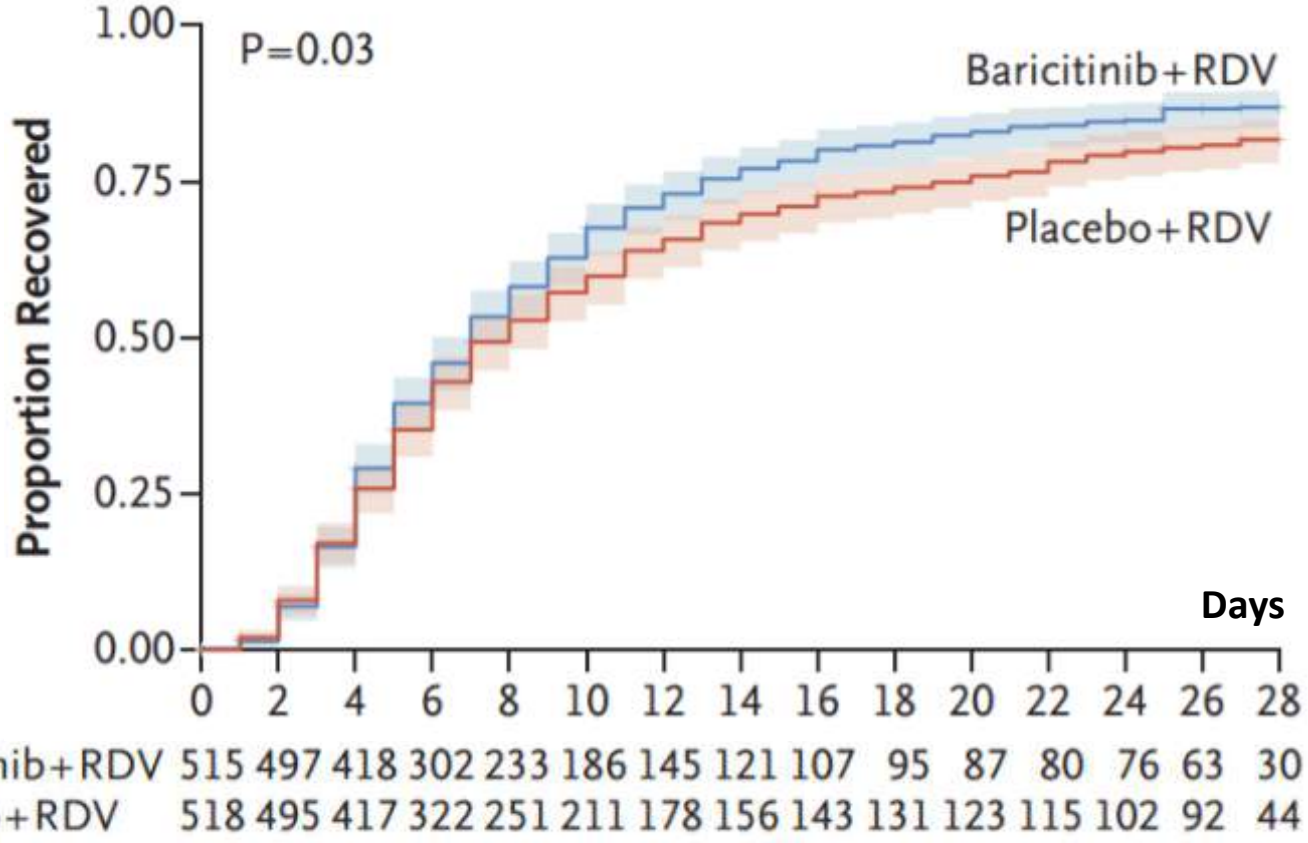
NIV: Non invasive ventilation
MV: mechanical ventilation

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

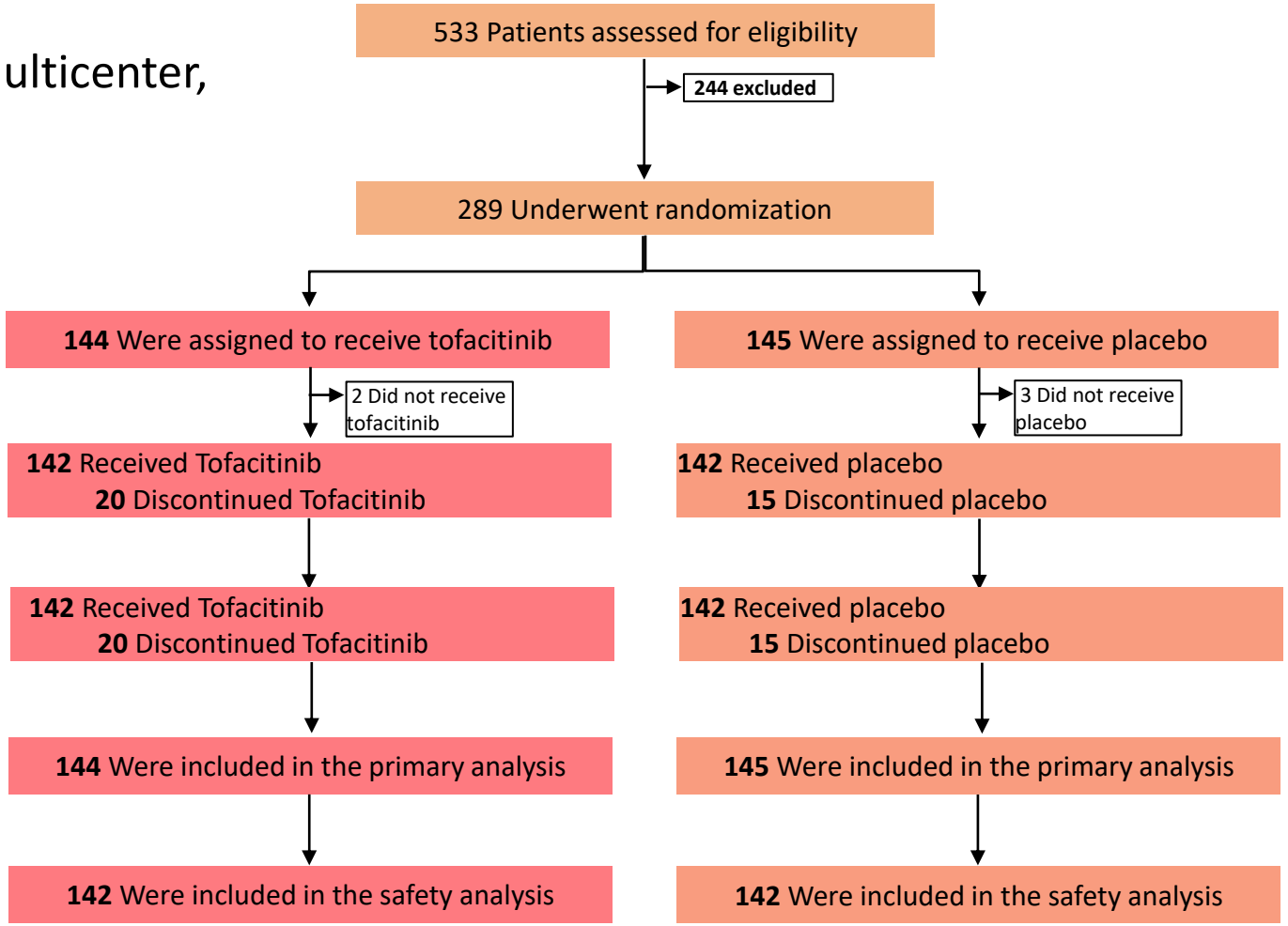


Kalil AC *et al. NEJM* Dec 2020

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

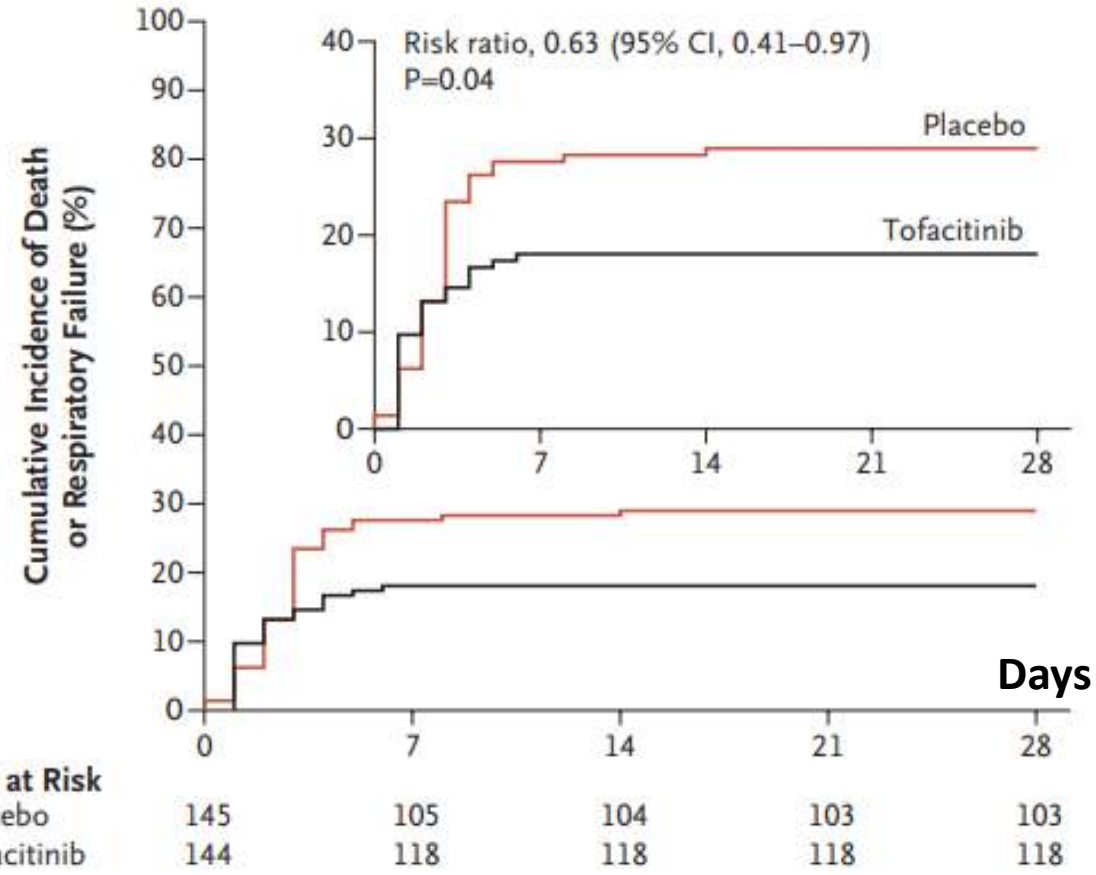
Guimarães PO *et al. NEJM* Jul 2021

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

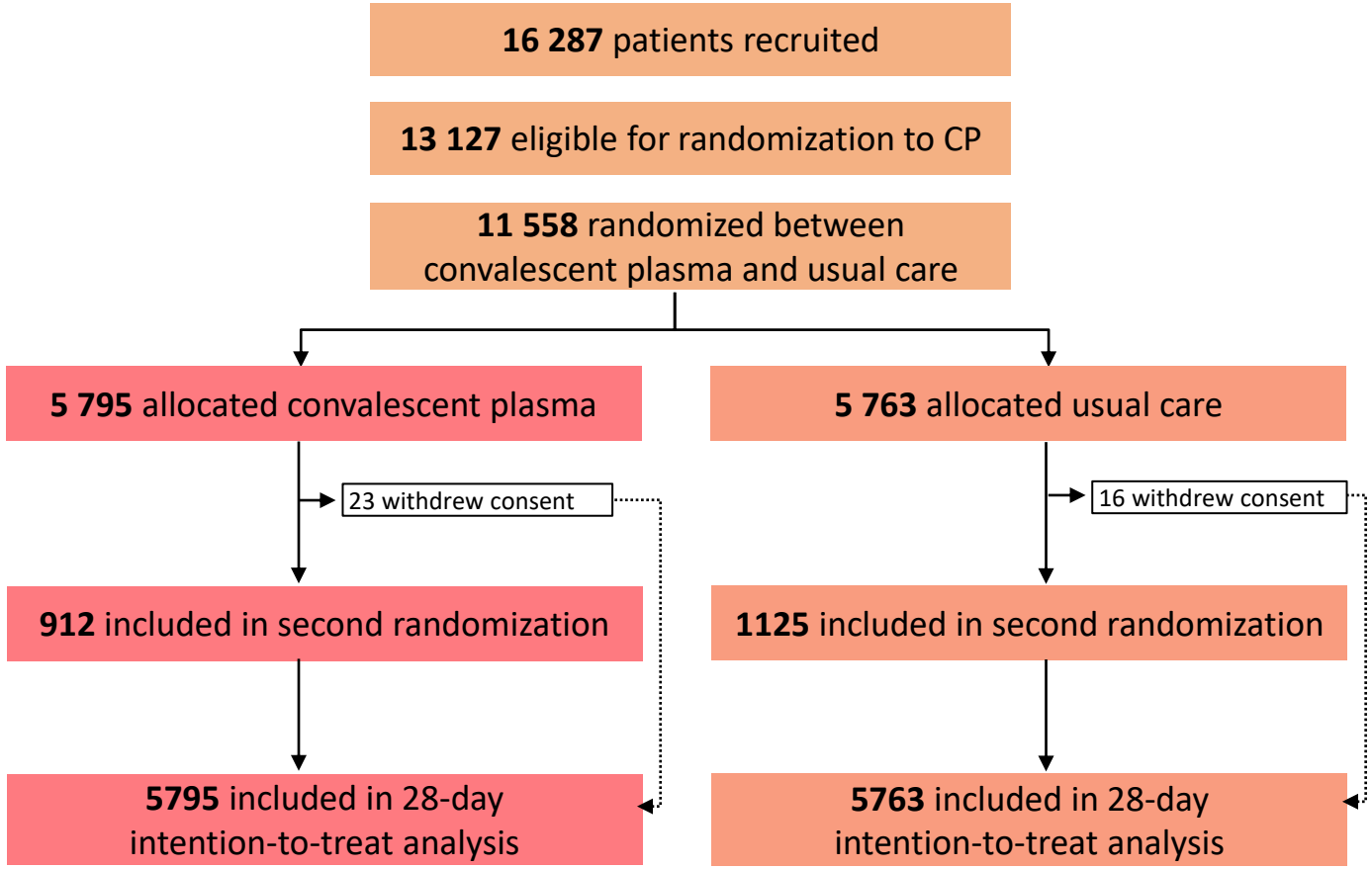


Guimarães PO *et al. NEJM* Jul 2021

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

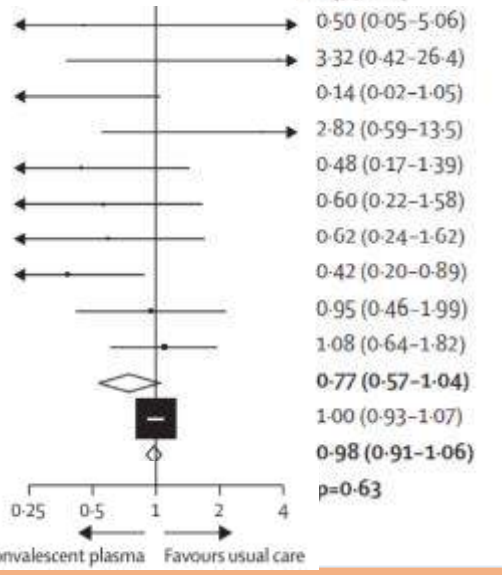
Characteristics		CP (N= 5 795)	Usual care (N=5 763)
Age	< 70 yr – no (%)	3 705 (64)	3 748 (65)
	70-79 yr – no (%)	1 310 (23)	1 281 (22)
	≥ 80 yr – no (%)	780 (13)	734 (13)
Sex	Male sex – no (%)	3 643 (63)	3 787 (66)
Co existing conditions	Diabetes – no(%)	1 535 (26)	1 569 (27)
	Heart disease – no (%)	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)

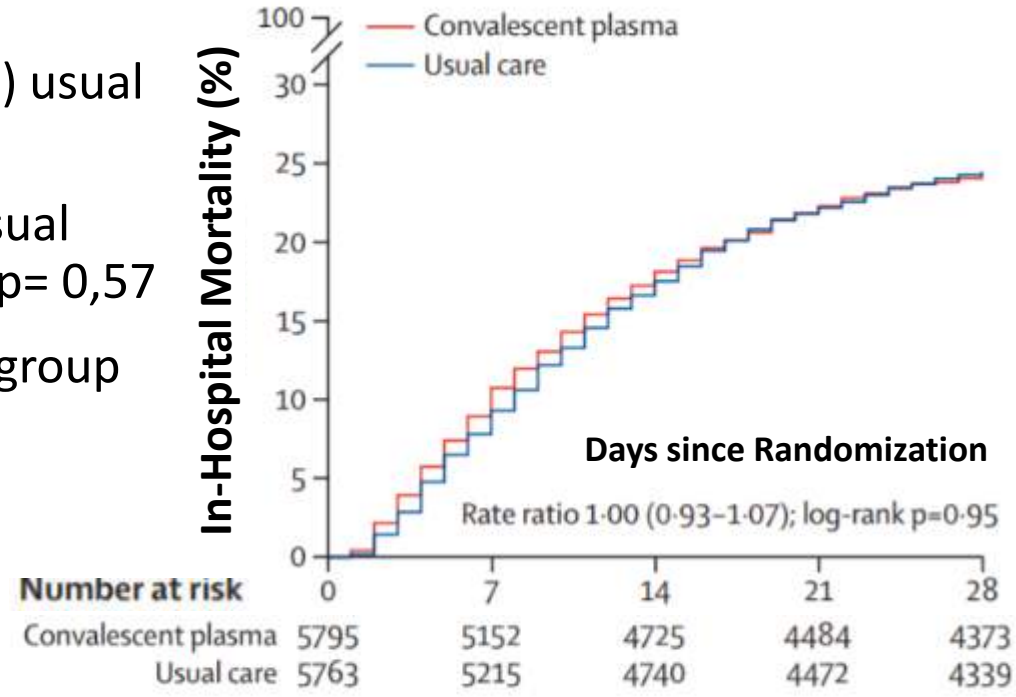
Passive immunity

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





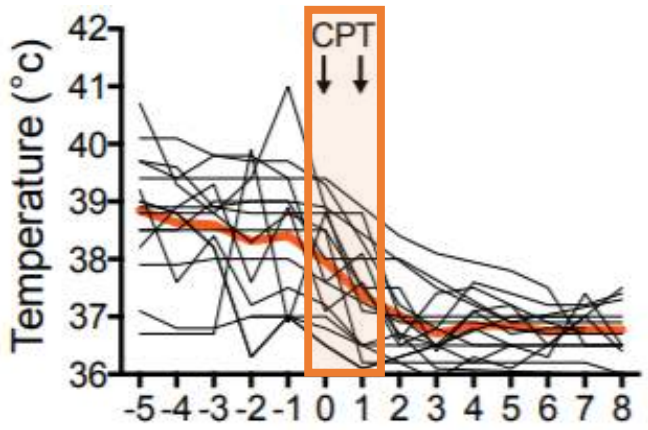
- **Meta–analysis of mortality in RECOVERY and other trials:** mortality rate ratio: 0,98 ; $_{95\%}$ CI[0,91-1,06]; p= 0,63

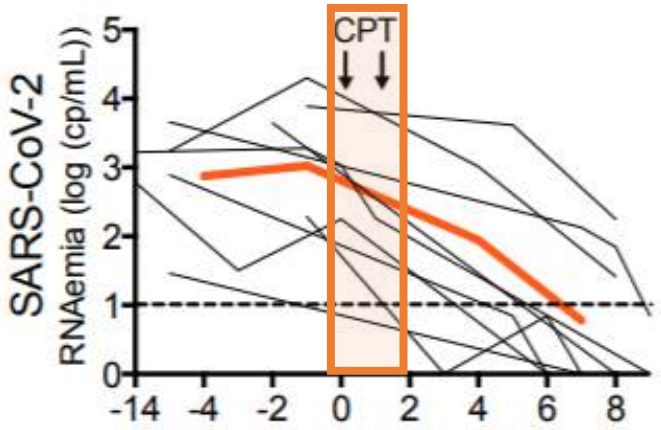
RECOVERY *Lancet* May 2021

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

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Contacts

Dr Guillaume Mellon
guillaume.mellon@aphp.fr

Dr Eric D'Ortenzio
eric.dortenzio@inserm.fr