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Coordination Opérationnelle
Risque Epidémique et Biologique

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THERAPEUTIC

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MALADIES INFECTIEUSES ÉMERGENTES

Scientific update on COVID-19

Updated on April 19th 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

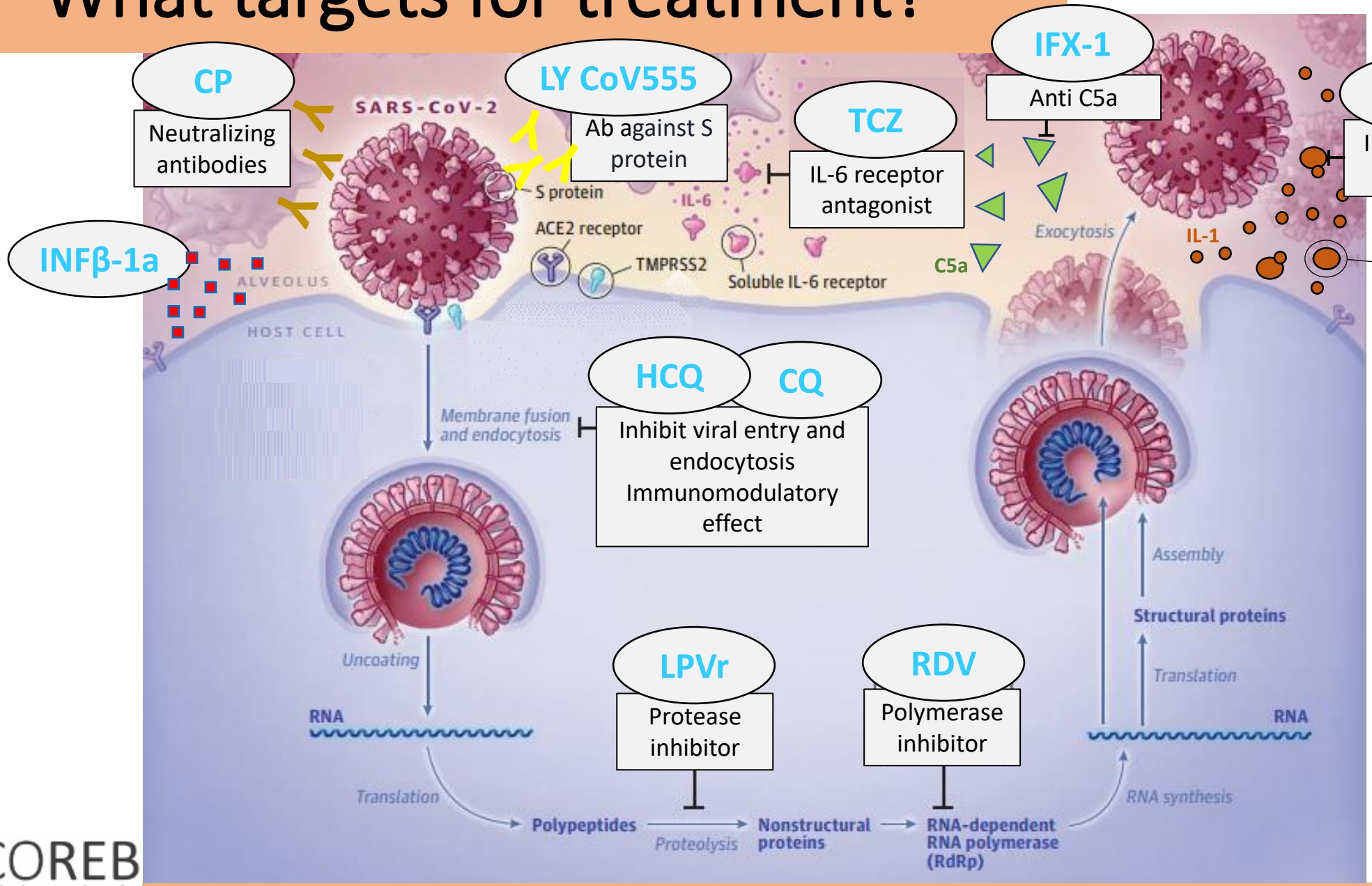
Immunomodulatory effect

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

Passive immunity

- Convalescent plasma

What targets for treatment?



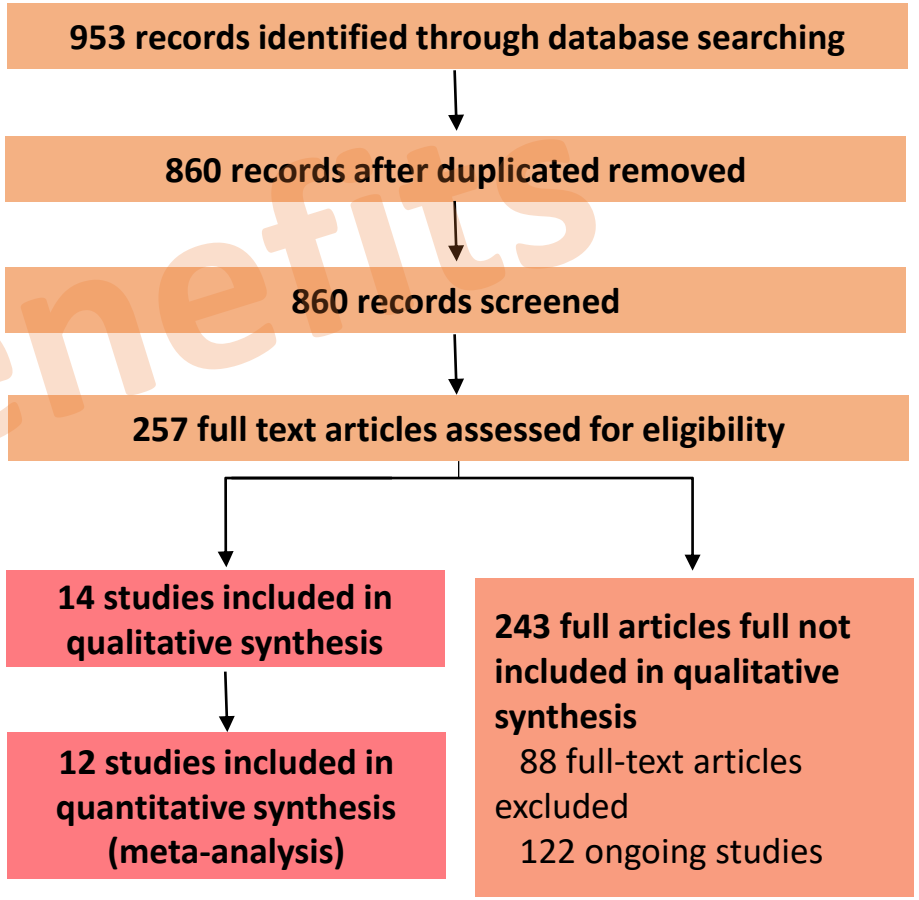
ANK: anakinra
CT: corticosteroids
CP: convalescent plasma
CQ: chloroquine
HCQ: hydroxychloroquine
IFX-1: vilobelimab
INFβ-1a: interferon beta
LPVr: lopinavir/ritonavir
RDV: remdesivir
TCZ: tocilizumab

Sanders JM *et al. JAMA* May 2020

Anti viral effect

Hydroxychloroquine (HCQ)

- Systematic review of randomized controlled trials, using standard Cochrane methods, academic study, UK
- **Inclusion criteria:** randomized controlled trials (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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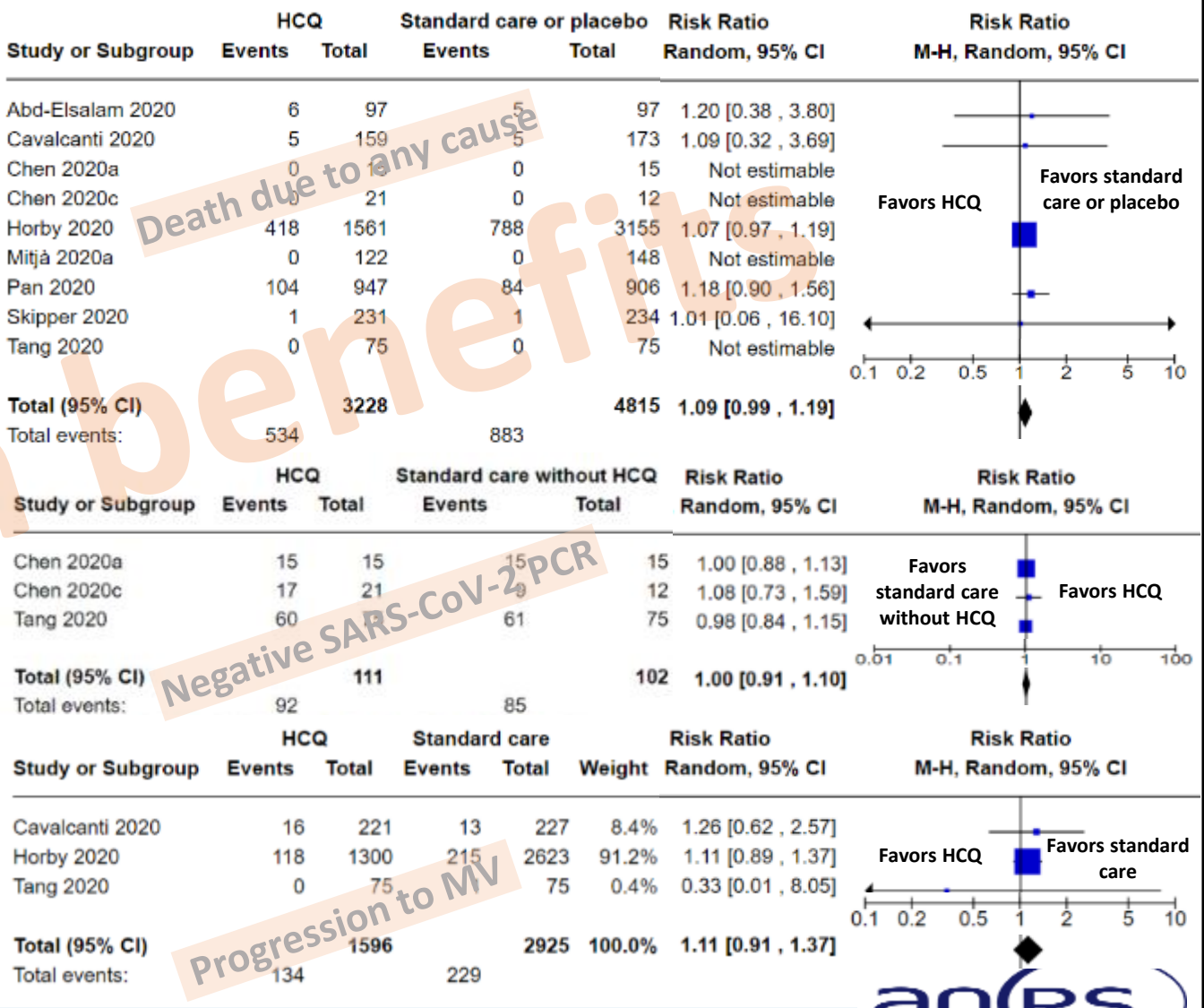
Anti viral effect

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]; 8208 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

No virological data on some studies

LPVr : Lopinavir/ritonavir

Zhang J et *al. CID* May 2020
SOLIDARITY *NEJM* Dec 2020

Anti viral effect

Ivermectin (IVM)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Ahmed	Randomized, double-blind, placebo-controlled	Oral IVM alone *vs.* IVM + doxycycline *vs.* placebo (**Hospitalized**)	**N= 72**	Virological clearance (days)	Oral IVM group: 9,7 $_{95\%}$CI [7,8-11,8], IVM + doxycycline group: 11,5 $_{95\%}$CI [9,8-13,2], placebo group: 12,7 $_{95\%}$CI [11,3-14,2] Oral IVM group *vs.* placebo p=0,02; Oral IVM group *vs.* IVM + doxycycline p=0,27
Camprubí	Retrospective study	IVM *vs.* non-IVM (**Hospitalized**)	**N= 26** All patients received HCQ and azithromycin Severe patients	D3-D5 SARS-CoV-2 PCR and clinical improvement	D3-D5 SARS-CoV-2 PCR: IVM group : 5/13 (38,5%) *vs.* non-IVM group : 4/13 (30,8%); p>0,99 Clinical improvement: IVM group : 9/13 (69,2%) *vs.* non-IVM group : 10/13 (76,9%); p>0,99

Anti viral effect

Ivermectin (IVM)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Cepelowicz Rajter	Retrospective study	IVM *vs.* usual care (**Hospitalized**)	**N= 280**	All-cause in-hospital mortality	IVM group: 15,0% *vs.* usual care group: 25,2%; OR, 0,52; $_{95\%}$ CI [0,29-0,96]; p= 0,03 ▲ non-randomized treatment allocation, unmeasured confounding factors, timing bias
Chaccour	Double-blind, placebo-controlled, parallel-arm, superiority, randomized	IVM *vs.* placebo	**N= 24** Non-severe patients without risk factors	D7 proportion of patients with detectable SARS-CoV-2 RNA (PCR)	IVM group: 11/12 (91%) *vs.* placebo group: 12/12 (100%) RR 0,92 $_{95\%}$CI [0,77-10,09]; p=1,0

Anti viral effect

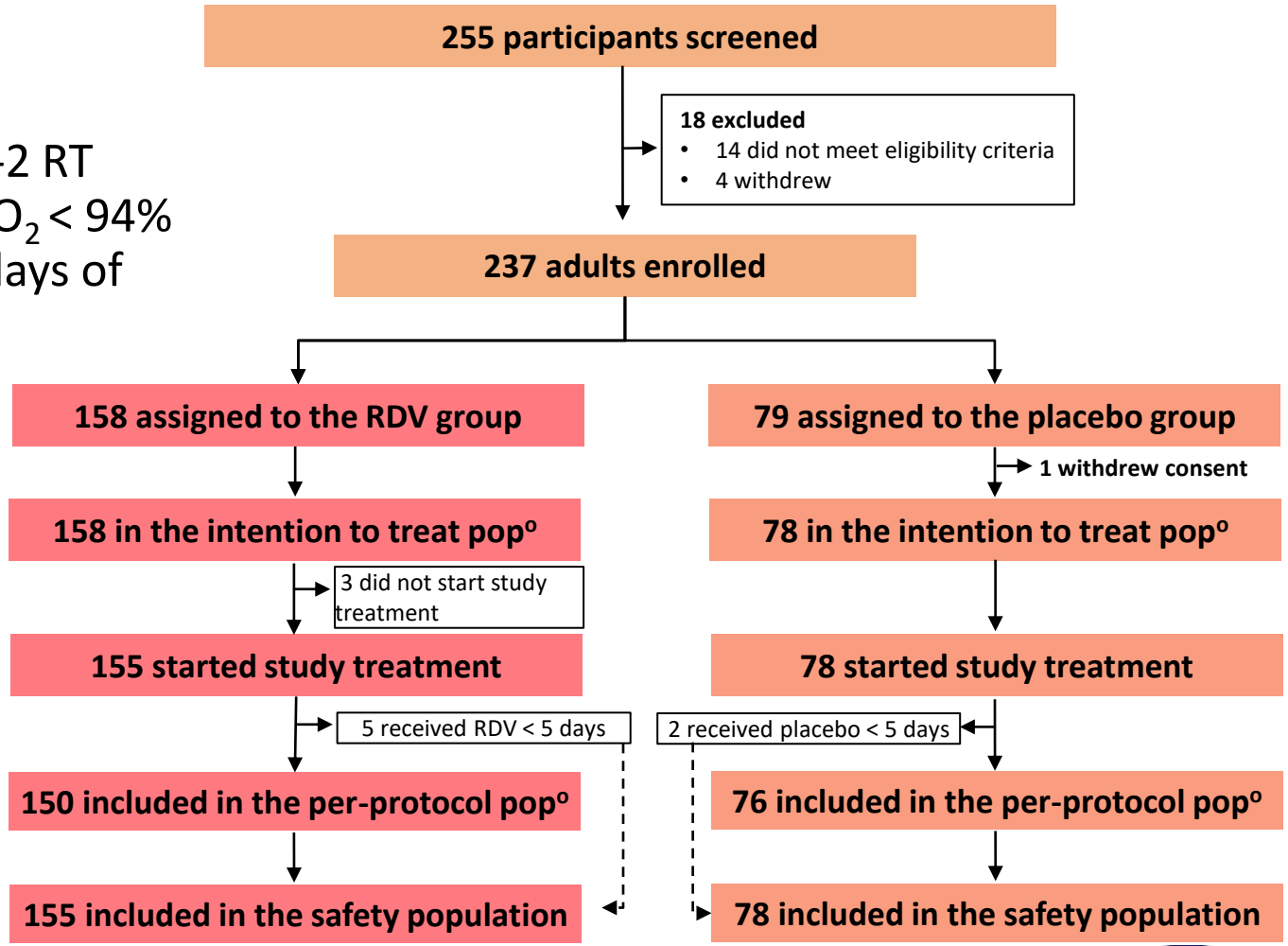
Ivermectin (IVM)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Chachar	Randomized, controlled, open-label	IVM *vs.* usual care	**N= 50** Mild cases of COVID-19 patients	D7 improvement symptoms	IVM group : 16/25 (64%) vs. non-IVM group : 15/25 (60%); p= 0,5
Lopez-Medina	Double-blind, randomized trial, single center	IVM *vs.* placebo **(At home or hospitalized)**	**N= 398** Mild disease and symptoms for ≤ 7 days	Median time to resolution of symptoms within a 21-day follow-up period (days)	IVM group : 10 (IQR, 9-13) *vs.* control group : 12 (IQR, 9-13); HR: 1,07 $_{95\%}$CI [0,87-1,32]; p= 0,53

Anti viral effect

Remdesivir (RDV) - 1

- Randomized, double-blind, placebo-controlled, multicenter, academic study, China
- **Inclusion criteria:** age ≥ 18yo, positive SARS-CoV-2 RT PCR, pneumonia confirmed by chest Imaging, $SpO_2 < 94\%$ (room air) or $PaO_2/FiO_2 \leq 300$ mmHg, within 12 days of symptom onset
- **Exclusion criteria:** pregnant women, renal impairment, hepatic cirrhosis
- **Primary outcome**: time to clinical improvement within 28 days after randomization
- **Secondary outcome** : D28 mortality, SARS-CoV-2 viral load
- 237 eligible patients, 158 received **RDV**, 79 **placebo** (2:1)



Wang Y *et al*. *Lancet* Apr 2020

Anti viral effect

Remdesivir (RDV) - 1

Characteristics	RDV (N=158)	Placebo (N=78)
Age, median (IQR) – yr	66 (57-73)	64 (53-70)
Male sex – no (%)	89 (56)	51 (65)
Baseline viral load of NP and OP swabs median (IQR) – (log_{10} copies/mL)	4,7 (0,3)	4,7 (0,4)
Coexisting conditions		
Diabetes – no (%)	40 (25)	16 (21)
Hypertension – no (%)	72 (46)	30 (38)
Coronary heart disease – no (%)	15 (9)	2 (3)
Vital sign		
Respiratory rate > 24/min – no (%)	36 (23)	11 (14)
Time from symptom onset to starting study treatment, median (IQR) – days	11 (9–12)	10 (9–12)
Early (≤10 days from symptom onset) – no (%)	71/155 (46%)	47 (60%)
Late (>10 days from symptom onset) – no (%)	84/155 (54%)	31 (40%)

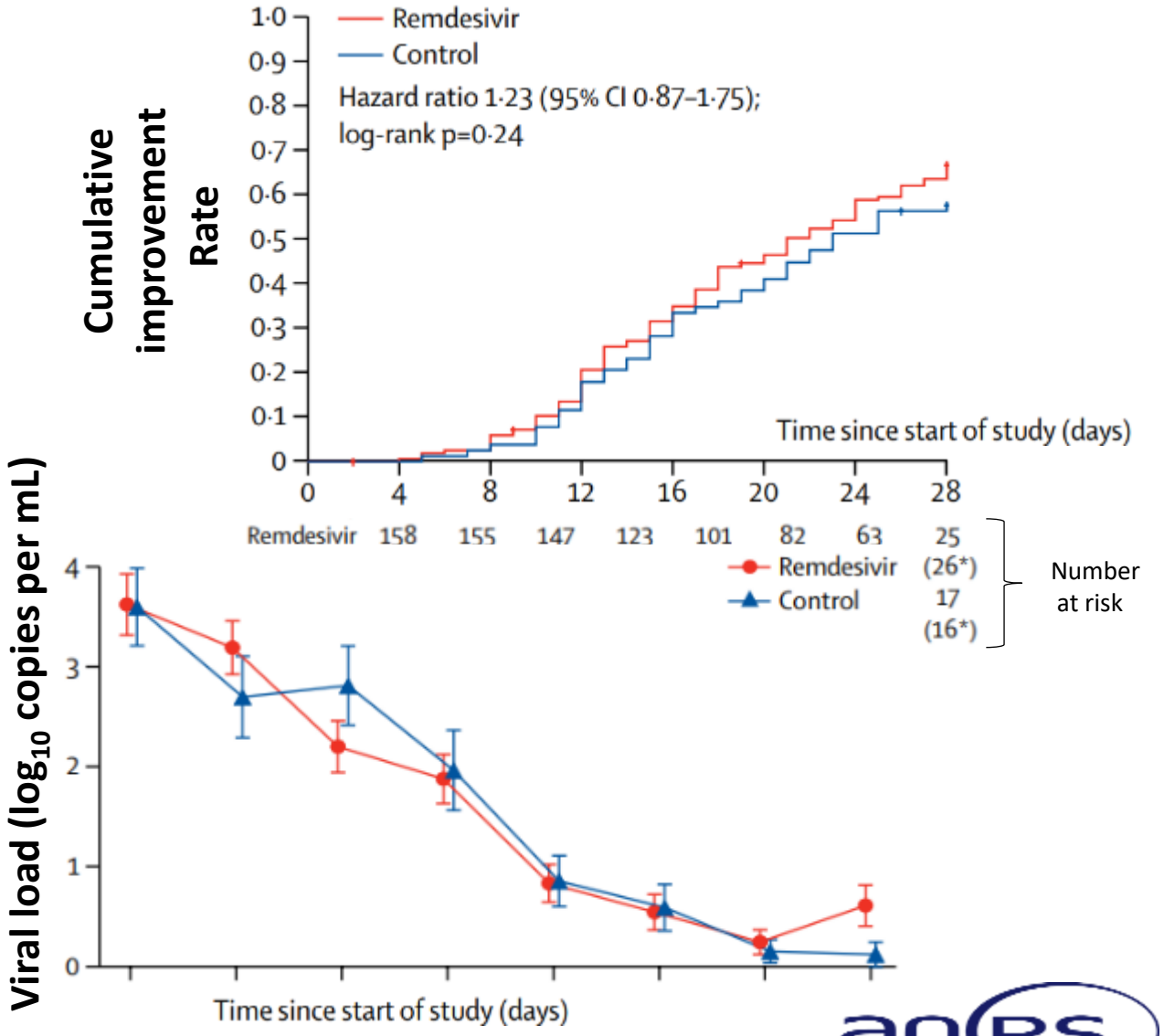
NP: nasopharyngeal
OP: oropharyngeal

Wang Y *et al*. *Lancet* Apr 2020

Anti viral effect

Remdesivir (RDV) - 1

- **Time to clinical improvement**: median 21,0 days [IQR 13,0–28,0] RDV group *vs.* 23,0 days [15,0–28,0] placebo group; no significant difference HR 1,23 $IC_{95\%}$[0,87-1,75]
- **D28 mortality**: 22/158 (14%) RDV group *vs.* 10/78 (13%) placebo group; **similar**
- **Viral load**: decreased over time similarly in both groups
- Adverse events: 102 (66%) RDV group *vs*. 50 (64%) placebo group
- **<u>Limits:</u>** target enrolment not reached; insufficient power to detect assumed differences in clinical outcomes, late treatment initiation (within 12 days of symptom onset), no virological data

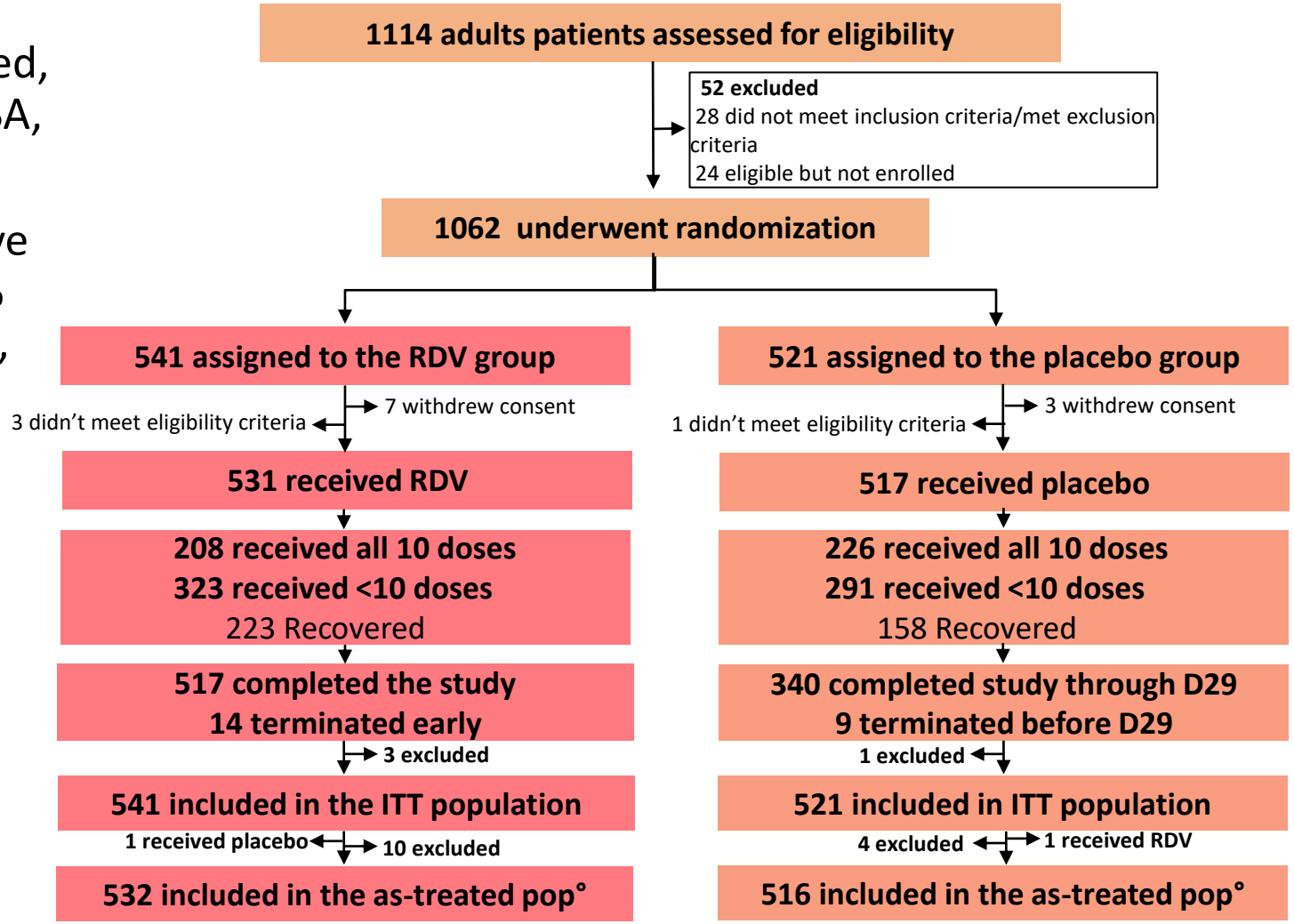


Wang Y *et al*. *Lancet* Apr 2020

Anti viral effect

Remdesivir (RDV) - 2

- Randomized, double-blind, placebo-controlled, multicenter (73 centers), academic study, USA, Adaptive Covid-19 treatment trial (ACTT-1)
- **Inclusion criteria**: SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, SpO_2 < 94% (room air) or requiring supplemental oxygen, mechanical ventilation, or ECMO
- **Exclusion criteria:** pregnant women, allergy to study product
- **Primary outcome**: time to recovery
- 1062 patients underwent randomization; 541 **RDV** group, 521 **placebo** group (1:1)



Beigel JH *et al*. *NEJM* Nov 2020

Anti viral effect

Remdesivir (RDV) - 2

Characteristics	All (N=1062)	RDV (N=541)	Placebo (N=521)
Age, mean (SD) – yo	58,9 (15)	58,6 (14,6)	59,2 (15,4)
Male sex – no (%)	684 (64,4)	352 (65,1)	332 (63,6)
Time from symptom onset to randomization, median (IQR) — days	9 (6–12)	9 (6–12)	9 (7–13)
Co existing conditions			
Type 2 Diabetes – no (%)	322/1051 (30,6)	164/532 (30,8)	158/519 (30,4)
Hypertension – no (%)	533/1051 (50,7)	269/532 (50,6)	264/519 (50,9)
Obesity – no (%)	476/1049 (45,4)	242/531 (45,6)	234/518 (45,2)
Score on ordinal scale			
4. Hospitalized, not requiring supplemental O_2, requiring ongoing medical care – no (%)	133 (13,0)	75 (13,9)	63 (12,1)
5. Hospitalized, requiring supplemental O_2 – no (%)	435 (41,0)	232 (41)	203 (39,0)
6. Hospitalized, receiving noninvasive ventilation/high flow O_2 device – no (%)	193 (18,2)	95 (17,6)	98 (18,8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%)	285 (26,8)	131 (24,2)	154 (29,6)

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Beigel JH *et al*. *NEJM* Nov 2020

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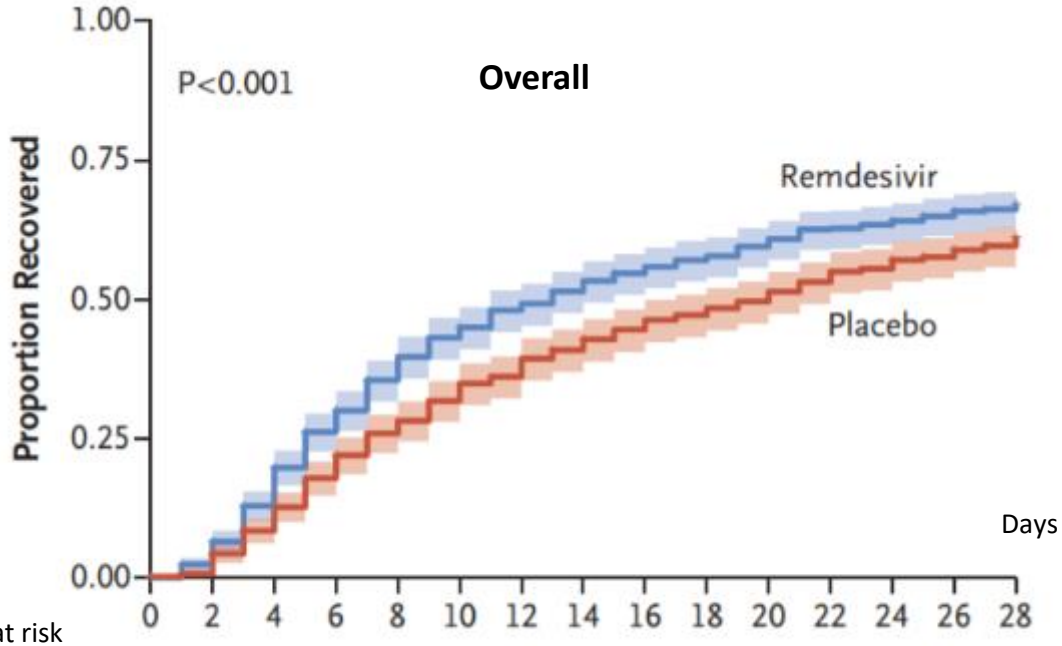
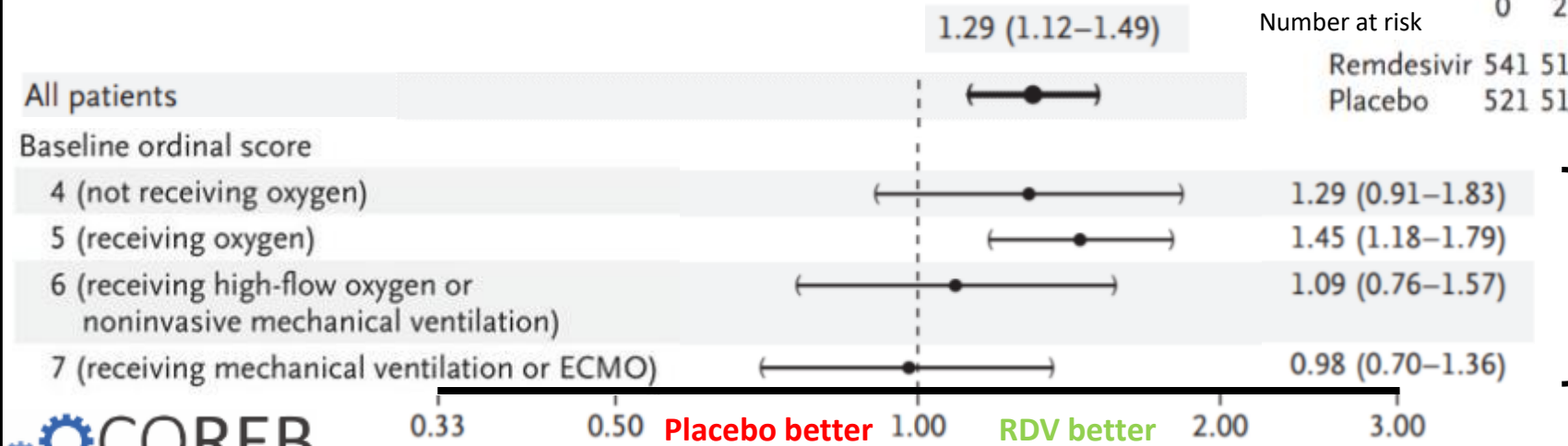
Anti viral effect

Remdesivir (RDV) - 2

- **Time to recovery (median)**: RDV group: 10 days *vs.* placebo group: 15 days; recovery rate ratio 1,29 $CI_{95\%}$[1,12-1,49]
- **D29 mortality**: RDV group: 11,4% *vs.* placebo group: 15,2%; HR 0,73 $CI_{95\%}$[0,52-1,03]
- **Adverse events**: RDV group: 131/532 (24,6%) *vs.* placebo group: 163/516 (31,6%)
- **<u>Limits:</u>** primary outcome changed during the study, uncompleted follow up, no virological data





Recovery rate ratio $CI_{95\%}$

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Beigel JH *et al*. *NEJM* Nov 2020

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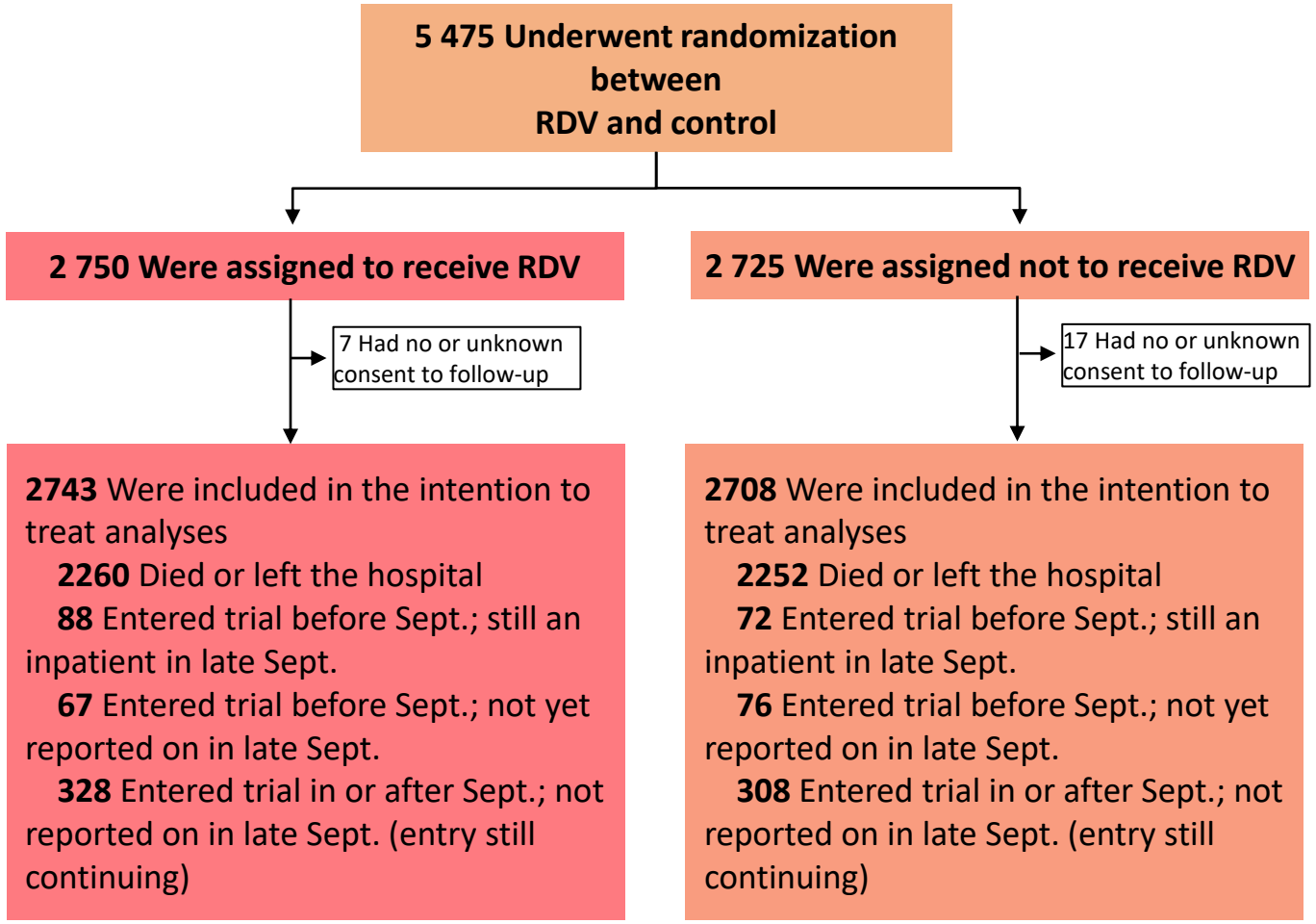
Anti viral effect

Remdesivir (RDV) - 3

- 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
- 5475 patients underwent randomization; 2750 **RDV** group, 2725 **control** group (1:1)



Anti viral effect

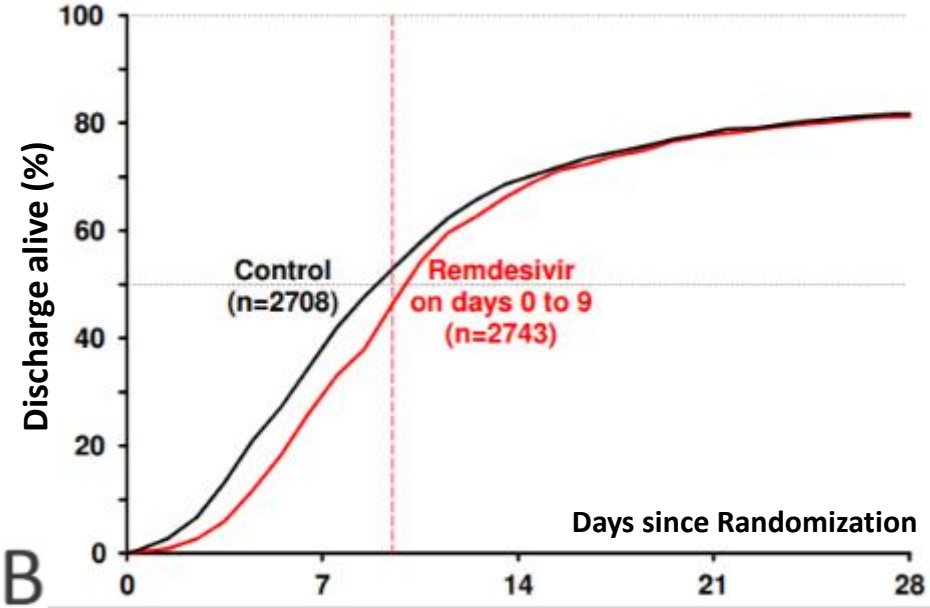
Remdesivir (RDV) - 3

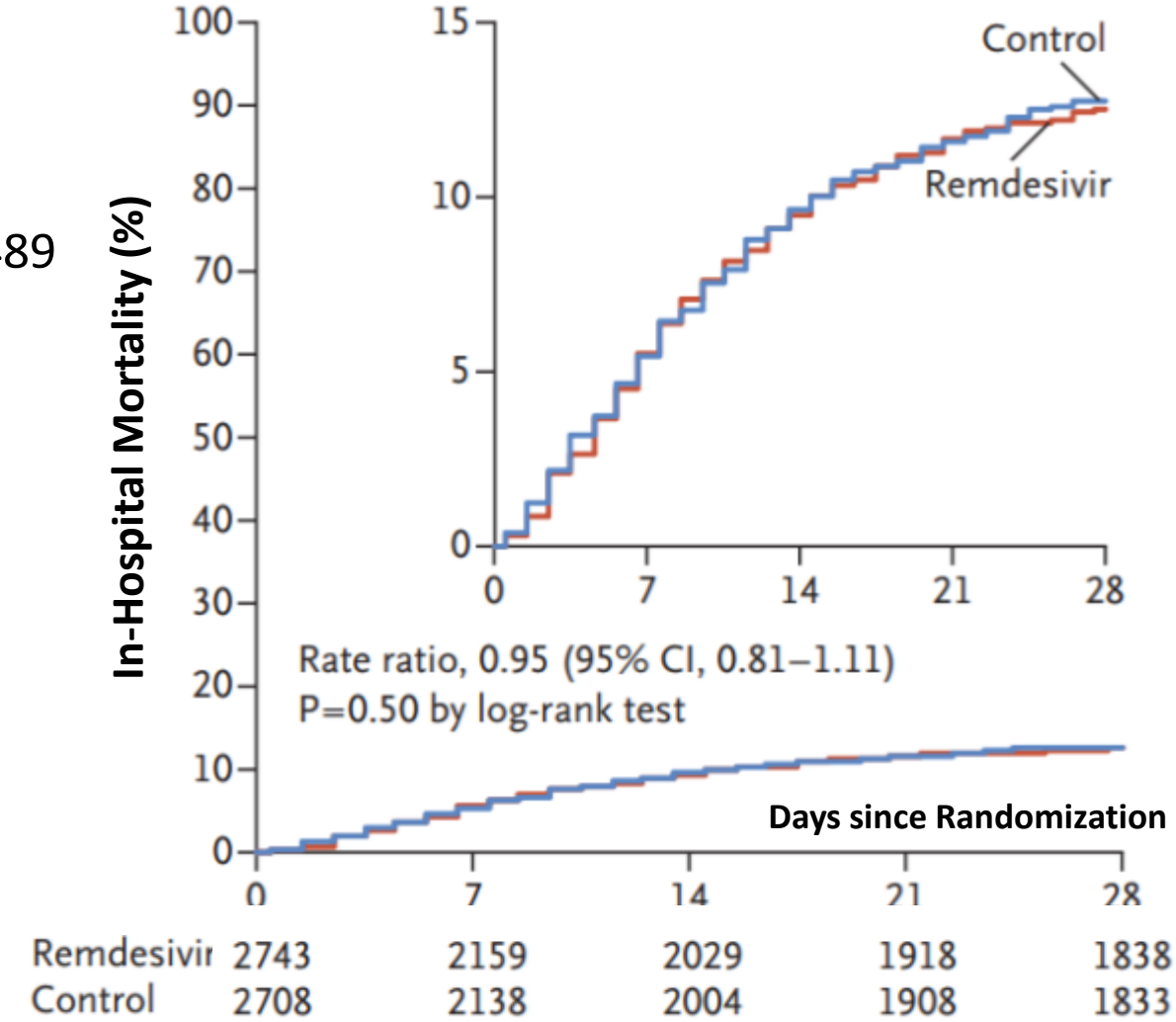
Characteristics		All (N= 11 266)	RDV (N= 2 743)	Control (N=2 708)
Age	< 50 yr – no (%)	3995 (35)	961	952
	50-69 yr – no (%)	5125 (45)	1282	1282
	≥ 70 yr – no (%)	2146 (19)	500	469
Sex	Male sex – no (%)	6985 (62)	1706	1725
Co existing conditions	Diabetes – no(%)	2768 (25)	707	666
	Heart disease – no (%)	2337 (21)	571	567
	Chronic lung disease – no (%)	635 (6)	151	145
Respiratory support	No supplemental O_2 at entry	3204 (28)	661	664
	Supplemental O_2 at entry	7146 (63)	1828	1811
	Already receiving ventilation	916 (8)	254	233

Anti viral effect

Remdesivir (RDV) - 3

- **All-cause mortality**: 301/2743 (12,5%) RDV group *vs.* 303/2708 (12,7%) placebo group; rate ratio: 0,95; $CI_{95\%}$[0,81-1,11]; p= 0,50
- **Initiation of mechanical ventilation**: RDV group: 295/2489 (11,9%) *vs*. control group 284/2475 (11,5%)
- **Time to discharge**: RDV did not reduced hospitalization duration





SOLIDARITY *NEJM* Dec 2020

Anti viral effect

Remdesivir (RDV) - 4

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Goldman	Open-label, randomized, placebo-controlled, multicenter, SIMPLE trial	RDV *5 days vs.* RDV *10 days* (**Hospitalized**)	**N = 402** SpO_2 < 94%* or requiring supplemental O_2, Symptoms§ before 1st RDV dose (IQR) : RDV *5 days* : 8 days (5–11) *vs.* RDV *10 days :* 9 days (6–12)	Status assessed on day 14 on a 7-point ordinal scale	No significant difference in efficacy between 5-day and 10-day courses of remdesivir
Spinner	Randomized, open-label, placebo-controlled, multicenter	RDV *5 days vs.* RDV *10 days vs.* SoC (**Hospitalized**)	**N = 596** SpO_2 > 94%* Symptoms§ before 1st RDV dose, (IQR): RDV *5 days*: 8 (5-11) *vs.* RDV *10 days*: 8 (5-11) *vs.* SoC: 9 (6-11)	Clinical status assessed on the 7-point ordinal scale on study day 11	5-day RDV group higher clinical status distribution compare to SoC; OR: 1,65 $_{95\%}$CI[1,09-2,48]; p= 0,02

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* Room air ** Mechanical ventilation
§ Median duration

Spinner CD *et al*. *JAMA* Aug 2020
Goldman JD *et al*. *NEJM* Nov 2020

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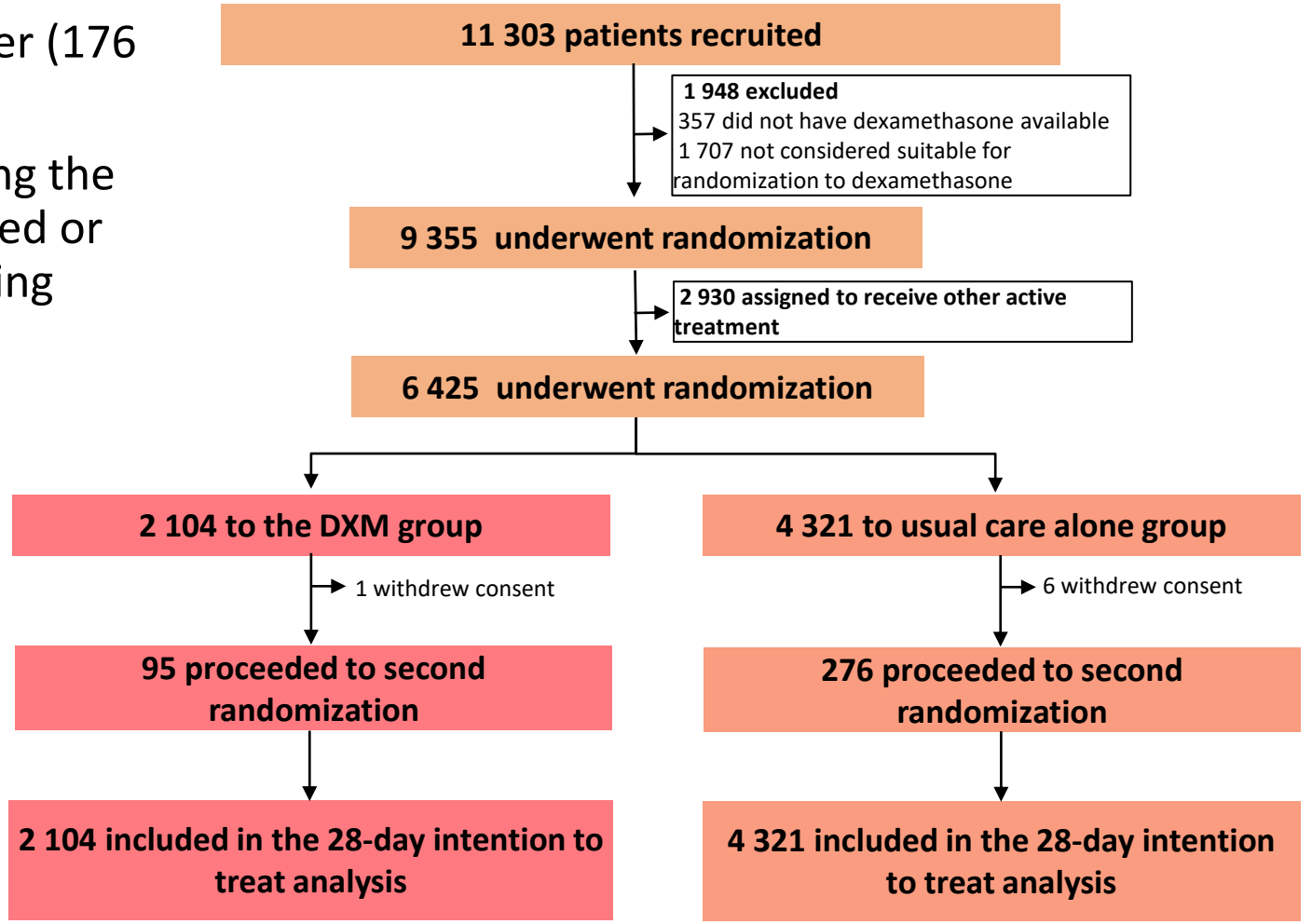
Immunomodulatory effect

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

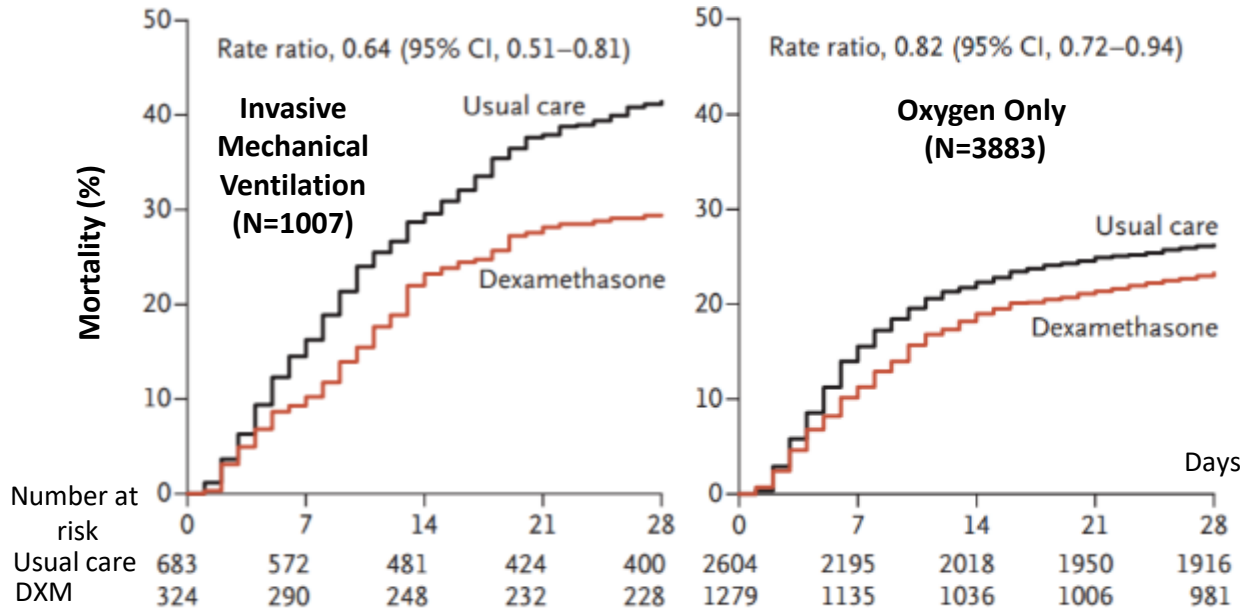
Corticosteroids (CT) - 1

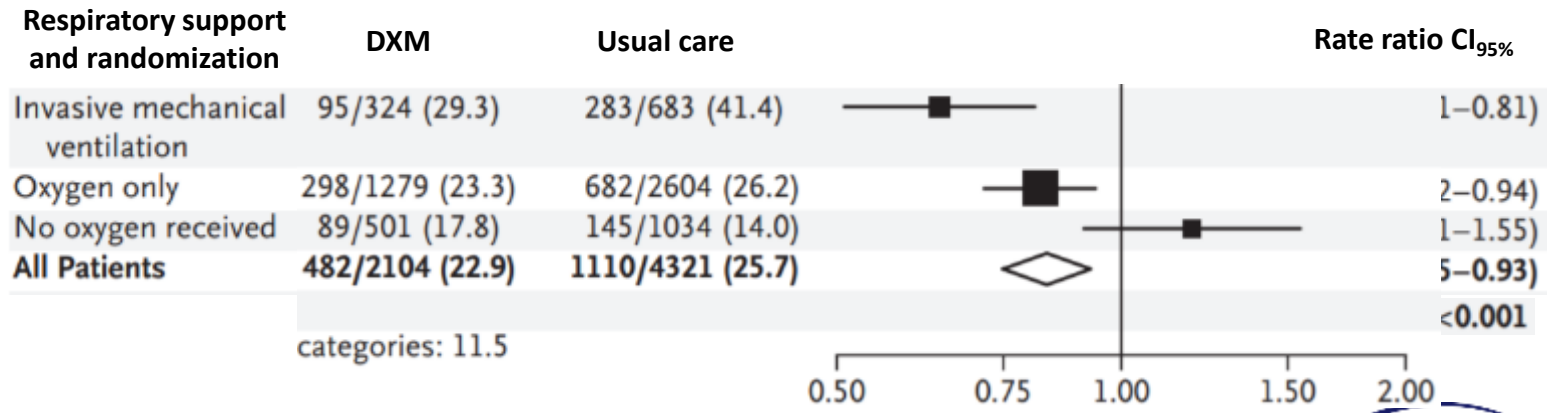
	Treatment assignment	
Characteristics	**DXM (N=2 104)**	**Usual care (N=4 321)**
Age ≥ 70 yr – no (%)	963 (45)	1817 (42)
Female sex – no (%)	766 (36)	1572 (36)
Coexisting conditions		
Diabetes – no (%)	521 (25)	1025 (24)
Heart disease – no (%)	586 (49,1)	1171 (27)
Chronic lung disease – no (%)	415 (20)	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





RECOVERY *collaborative group NEJM* Jul 2020

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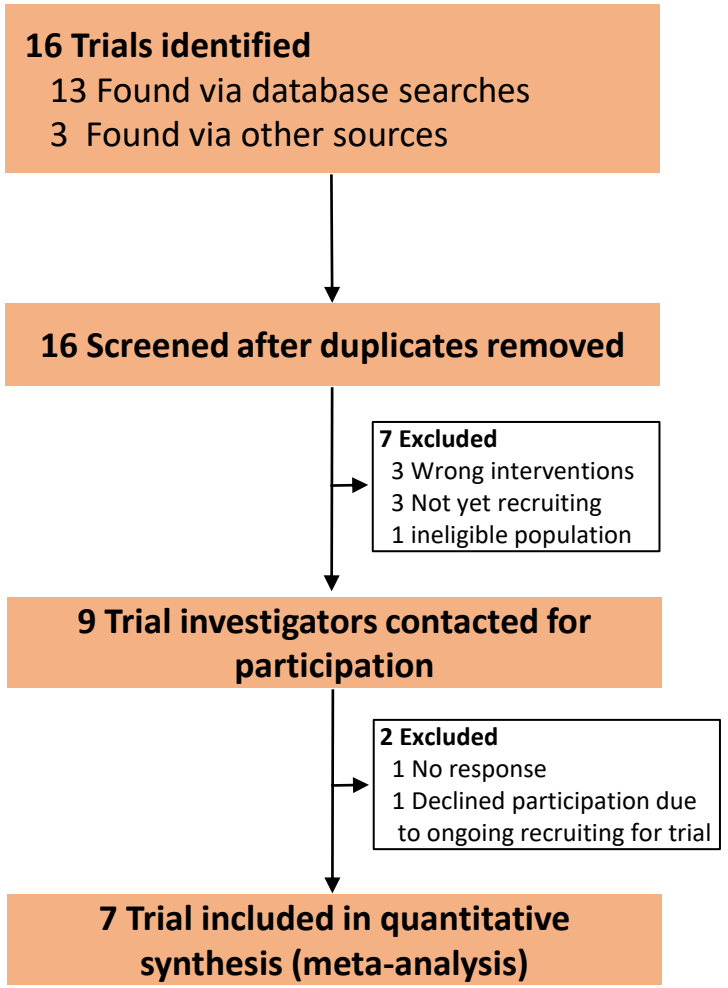
Immunomodulatory effect

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**

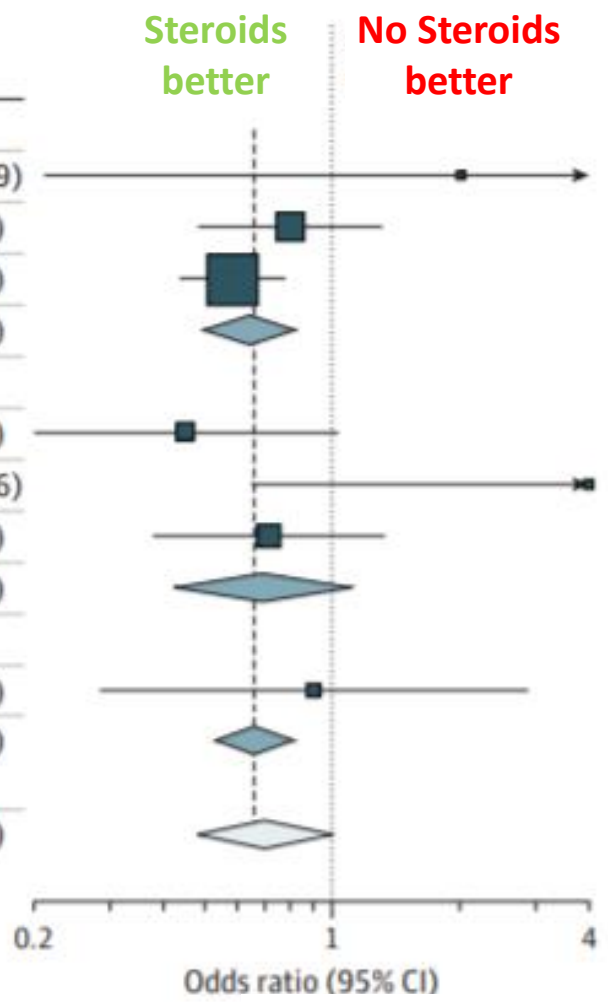


Immunomodulatory effect

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) - 3

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) - 4

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 - 1

Author	Design	Groups	Participants	Outcome	Main results
Hermine	Multicenter, open-label, RCT	TCZ + usual care *vs.* usual care (**Hospitalized**)	**N= 154** Pneumonia requiring O_2 support (≥ 3 L/min, no NIV nor MV) **Not admitted in ICU**	Survival without need of ventilation at D14	TCZ + UC 15/63 (24%) *vs.* UC 24/67 (36%) Δ: -12; $_{95\%}$CI [-28-4]
				D28 mortality	TCZ + UC 7/63 (11%) *vs.* UC 8/67 (12%) HR_a: 0,92; $_{95\%}$CI [0,33-2,53]
				CRP (mg/L) median (IQR)	TCZ + UC 119,5 (74,5-219,5) *vs.* UC 127 (84-171)
				Days from symptoms onset to randº	TCZ + UC 10 (7-13) *vs.* UC 10 (8-13) median (IQR)
Stone	Multicenter, double-blind, placebo, RCT	TCZ *vs.* placebo (**Hospitalized**)	**N= 243** Need for supplemental O_2 in order to maintain SpO_2 ≥ 92% **Not admitted in ICU**	D28 dead or intubated	TCZ 17/161 (10,6%) *vs.* placebo 10/82 (12,5%) HR: 0,83; $_{95\%}$CI [0,38-1,81], p=0,64
				CRP (mg/L) median (IQR)	TCZ 116,0 (67,1-190,6) *vs.* placebo 94,3 (58,4-142,0)
				Days from symptoms onset to randº	TCZ 9 (6-13) *vs.* placebo 10 (7-13) median (IQR)

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TCZ: tocilizumab - UC: usual care
ICU: intensive care unit - randº : randomization

Hermine O *et al. JAMA Int Med* Oct 2020
Stone JH *et al. NEJM* Dec 2020

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Immunomodulatory effect

IL-6 Receptor Antagonist - 2

Author	Design	Groups	Participants	Outcome	Main results
Salvarani	Prospective, open-label, randomized, multicenter	TCZ *vs*. standard of care (SoC) (**Hospitalized**)	**N= 126** Pneumonia with acute respiratory failure PaO_2/FiO_2 between 200-300 mmHg **Not admitted in ICU**	Clinical worsening within 14 days since randomization	TCZ 17/60 (28,3%) *vs.* SoC 17/63 (27%) RR: 1,05; $CI_{95\%}$[0,59-1,86], p=0,87
				D30 death	TCZ 2/60 (3,3%) *vs.* SoC 1/63 (1,6%) RR: 2,10; $CI_{95\%}$[0,20-22,6]
				CRP (mg/L) median (IQR)	TCZ 105 (50-146) *vs.* SoC 65 (32-118)
				Days from symptoms onset to randº median (IQR)	TCZ 7 (4-11) *vs.* SoC 8 (6-11)

TCZ: tocilizumab - SoC: standard of care
randº : randomization

Salvarani C *et al. JAMA Int Med* Oct 2020

Immunomodulatory effect

IL-6 Receptor Antagonist - 3

Author	Design	Groups	Participants	Outcome	Main results
Salama	Randomized, double-blind, placebo-controlled	TCZ *vs.* placebo (**Hospitalized**)	**N= 388** SpO_2 < 94% (room air) without continuous positive airway pressure or MV **Not admitted in ICU**	D28 MV or death	TCZ 30/249 (12%) $_{95\%}$CI [8,5-16,9] *vs.* placebo 25/128 (19,3%) $_{95\%}$CI [13,3-27,4] HR: 0,56; $_{95\%}$CI [0,33-0,97] p=0,04
				D28 mortality	TCZ 26/249 (10.4%) $_{95\%}$CI [7,2-14,9] *vs.* placebo 11/128 (8,6%) $_{95\%}$CI [4,9-14,9]
				CRP (mg/L) median (IQR)	TCZ 124,5 (2,5–2099) *vs.* SoC 143,4 (9–3776)
				Days from symptoms onset to randº	Not specified
Veiga	Randomized, multicenter, open label trial	TCZ + SoC *vs*. SoC (**Hospitalized**)	**N= 129** Receiving supplemental O_2 or MV **Not admitted in ICU**	D15 MV or death	TCZ + SoC 18/65 (28%) *vs.* SoC 13/64 (20%); effect size 1,54; $_{95\%}$CI [0,66-3,66], p= 0,32
				D28 mortality	TCZ + SoC 14/65 (21%) *vs.* SoC 6/64 (9%); OR 2,70; $_{95\%}$CI [0,97-8,35], p= 0,07
				CRP (mg/L) mean (SD)	TCZ + SoC 160 (104) *vs.* SoC 193 (283)
				Days from symptoms onset to randº mean (SD)	TCZ + SoC 10 (3,1) vs. SoC 9,5 (3,0)

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TCZ: tocilizumab
SoC: standard of care - MV: mechanical ventillation

Salama C *et al. NEJM* Jan 2021
Veiga VC *et al. BMJ Jan* 2021

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Immunomodulatory effect

IL-6 Receptor Antagonist - 4

Author	Design	Groups	Participants	Outcome	Main results
Rosas COVACTA trial	International, RCT, double blind	TCZ vs. placebo (**Hospitalized**)	**N= 452** $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mm Hg **Not admitted in ICU**	D28 clinical status on 7-category ordinal scale	TCZ 1 $_{95\%}$CI [1-1] *vs.* placebo 2 $_{95\%}$CI [1-4] HR: -1; $_{95\%}$CI [-2,5;0], p=0,31
				D28 mortality	TCZ 58/294 (19,7%) *vs.* placebo 28/144 (19,4%); HR: 0,3; $_{95\%}$CI [-7,6-8,2], p=0,94
				CRP (mg/L) median (IQR)	TCZ 150 (85-221) *vs.* SRL 136 (105-204) *vs.* control 130 (71-208)
				Days from symptoms onset to rand°	TCZ 12,1 (6,6) *vs.* placebo 11,4 (6,9) mean (SD)
Lescure	Multicenter, double-blind, placebo, RCT	SRL (200mg and 400mg) *vs.* no placebo (**Hospitalized**)	**N= 416** Severe or critical disease **Admitted and not admitted in ICU**	Time from baseline to clinical improvement of ≥ 2 points on ordinal scale	SRL_{200} 10 $_{95\%}$CI [9-12] *vs.* SRL_{400} 10 $_{95\%}$CI [9-13] *vs.* placebo 12 $_{95\%}$CI [9-15] median ($_{95\%}$CI)
				D29 patients alive	SRL_{200} 143/159 (90%) *vs.* placebo 77/84 (92%); Δ: -1,7 $_{95\%}$CI [−9,3-5,8] ; p=0,63 SRL_{400} 159/173 (92%) *vs.* placebo 77/84 (92%); Δ: 0,2 $_{95\%}$CI [−6,9-7,4] ; p=0,85
				CRP and Days from symptoms onset to rand°	Not specified

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TCZ: tocilizumab - SRL: sarilumab
SoC: standard of care - MV: mechanical ventillation

Rosas IO *et al*. *NEJM* Feb 2021
Lescure FX *et al. Lancet Respir Med* Mar 2021

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Immunomodulatory effect

IL-6 Receptor Antagonist - 5

Author	Design	Groups	Participants	Outcome	Main results
REMAP-CAP	International, adaptive platform trial	TCZ vs. SRL vs. control (**Hospitalized**)	**N= 797** Respiratory or cardiovascular organ support **Admitted in ICU**	Days of respiratory and cardiovascular organ support–free up to day 21	TCZ 10 IQR [-1;16] *vs.* SRL 11 days IQR [0;16] *vs.* control 0 days IQR [-1;15]; TCZ median ORa: 1,64; $_{95\%}$CI [1,25-2,14] SRL median ORa: 1,76; $_{95\%}$CI [1,17-2,91] compared with control
				In-hospital mortality	TCZ 98/350 (28 %) *vs.* SRL 15/45 (22 %) *vs.* control 142/397 (36%); TCZ median ORa: 1,64; $_{95\%}$CI [1,14-2,35] SRL median ORa: 2,01; $_{95\%}$CI [1,18-4,71] compared with control
				CRP (mg/L) median (IQR)	TCZ 150 (85–221) *vs.* SRL 136 (105–204) *vs.* control 130 (71–208)
				Days from symptoms onset to rand°	Not specified
Gupta	Multicenter, double-blind, placebo, RCT	TCZ *vs.* no TCZ (**Hospitalized**)	**N= 3924** **Admitted in ICU**	In-hospital death	TCZ 125/433 (28,9%) *vs.* no TCZ 1419/3491 (40,6%) aHR: 0,71; $_{95\%}$CI [0,56-0,92]
				CRP and Days from symptoms onset to rand°	Not specified

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

TCZ: tocilizumab - SRL: sarilumab
SoC: standard of care - MV: mechanical ventillation

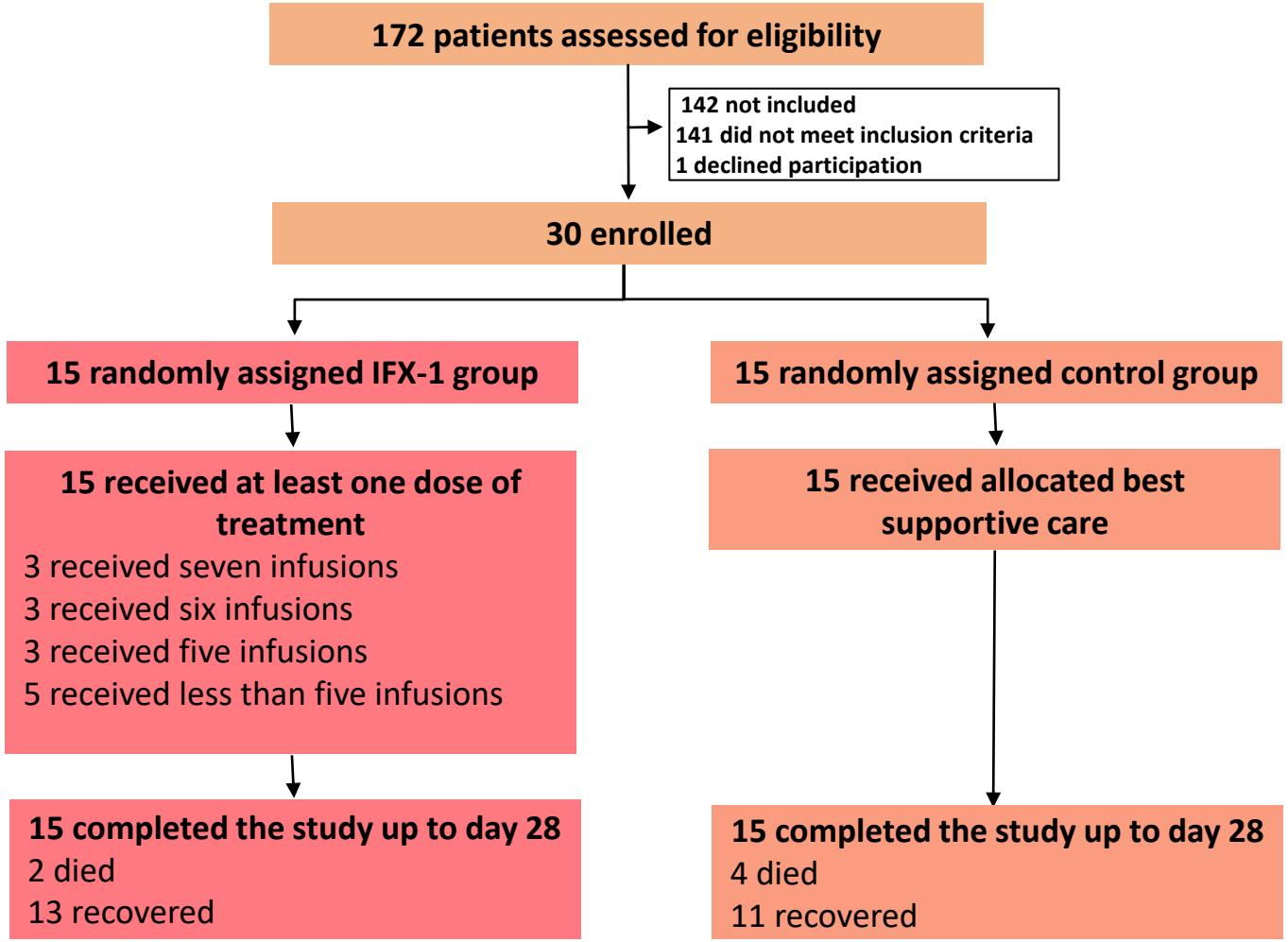
REMAP-CAP *NEJM* Feb 2021
Gupta S *et al. JAMA Int Med* Oct 2020

anrs MALADIES INFECTIEUSES ÉMERGENTES

Monoclonal antibody

Vilobelimab (IFX-1) - 1

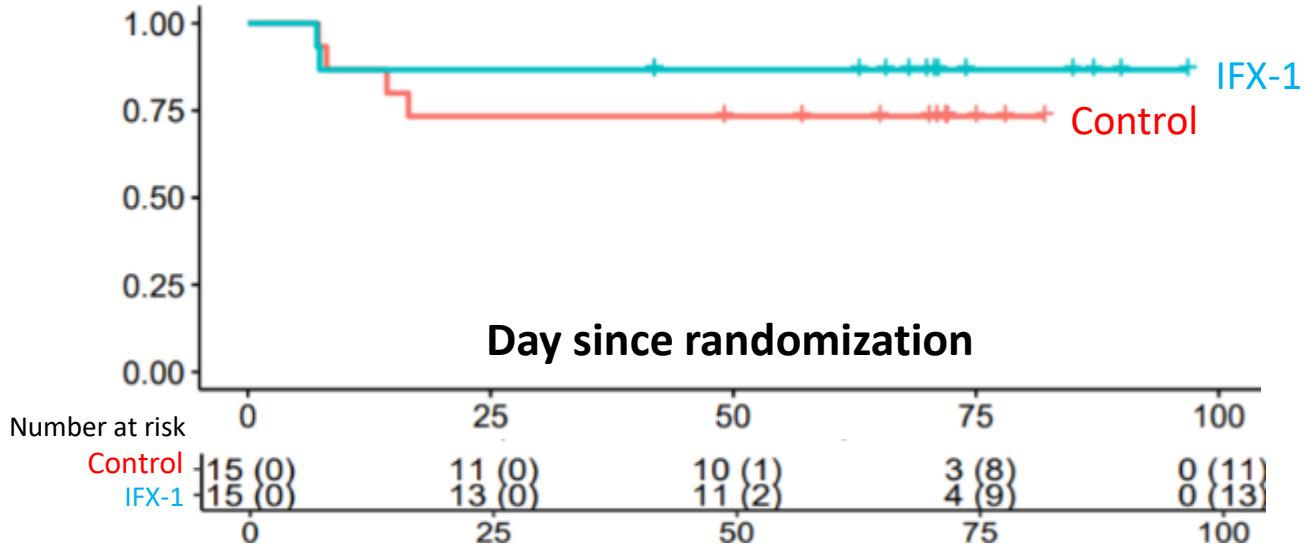
- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria** : age ≥ 18yo, severe pneumonia (PaO_2/FiO_2 between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive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



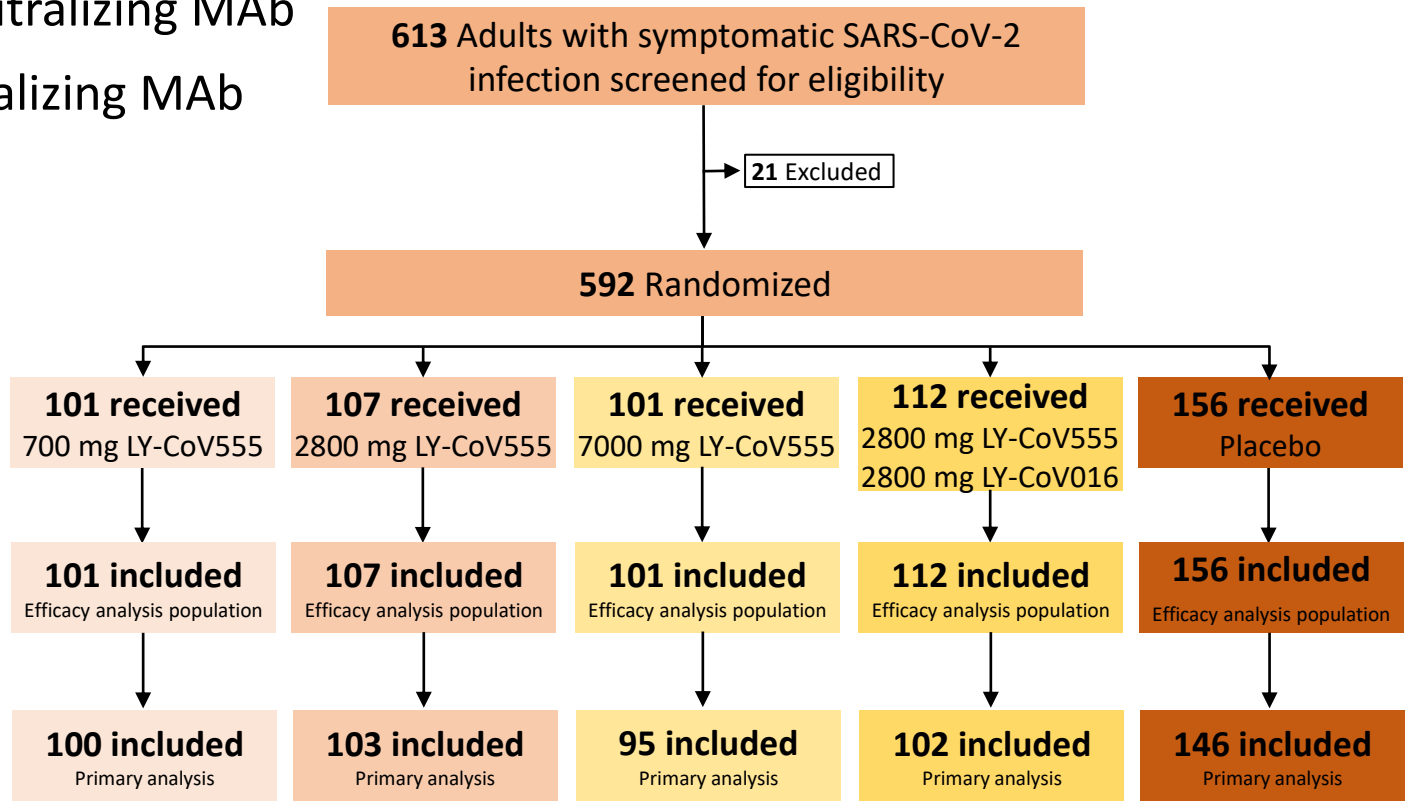
- **Limits**: patient heterogeneity, open label study

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

- **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

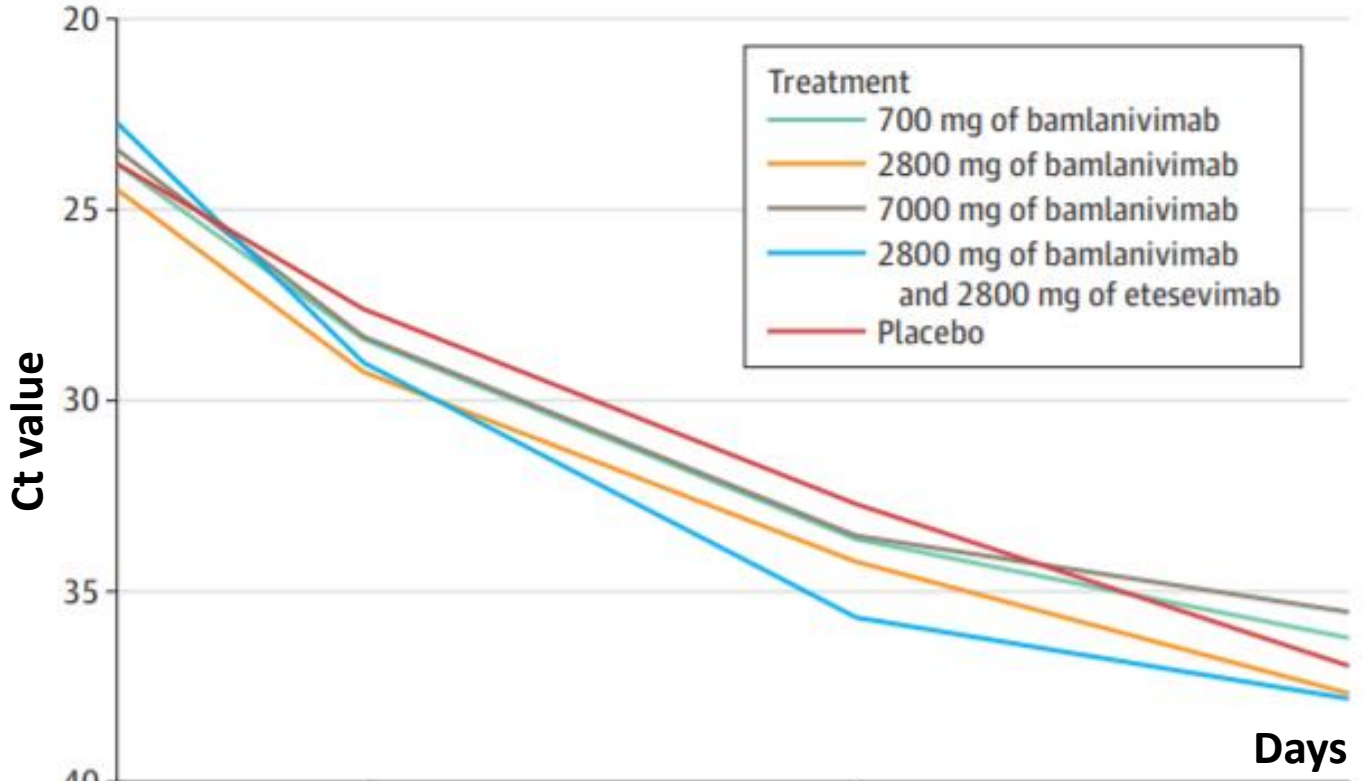
LY-CoV555 and LY-CoV016

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

- **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



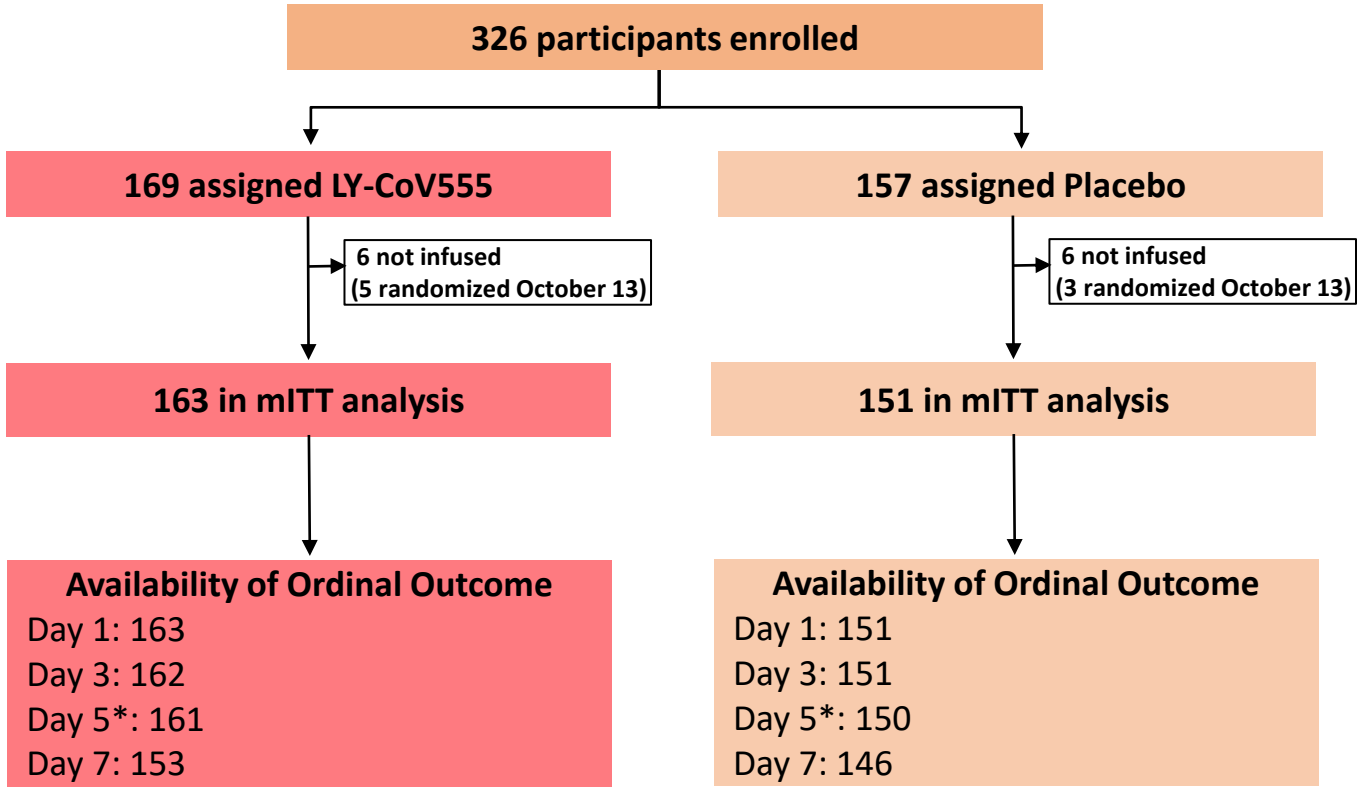
Treatment, No.				
700 mg of bamlanivimab	101	96	98	100
2800 mg of bamlanivimab	107	98	101	103
7000 mg of bamlanivimab	101	93	95	95
2800 mg of bamlanivimab and 2800 mg of etesevimab	109	96	95	102
Placebo	152	141	142	146

Gottlieb RL *et al. JAMA* Jan 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

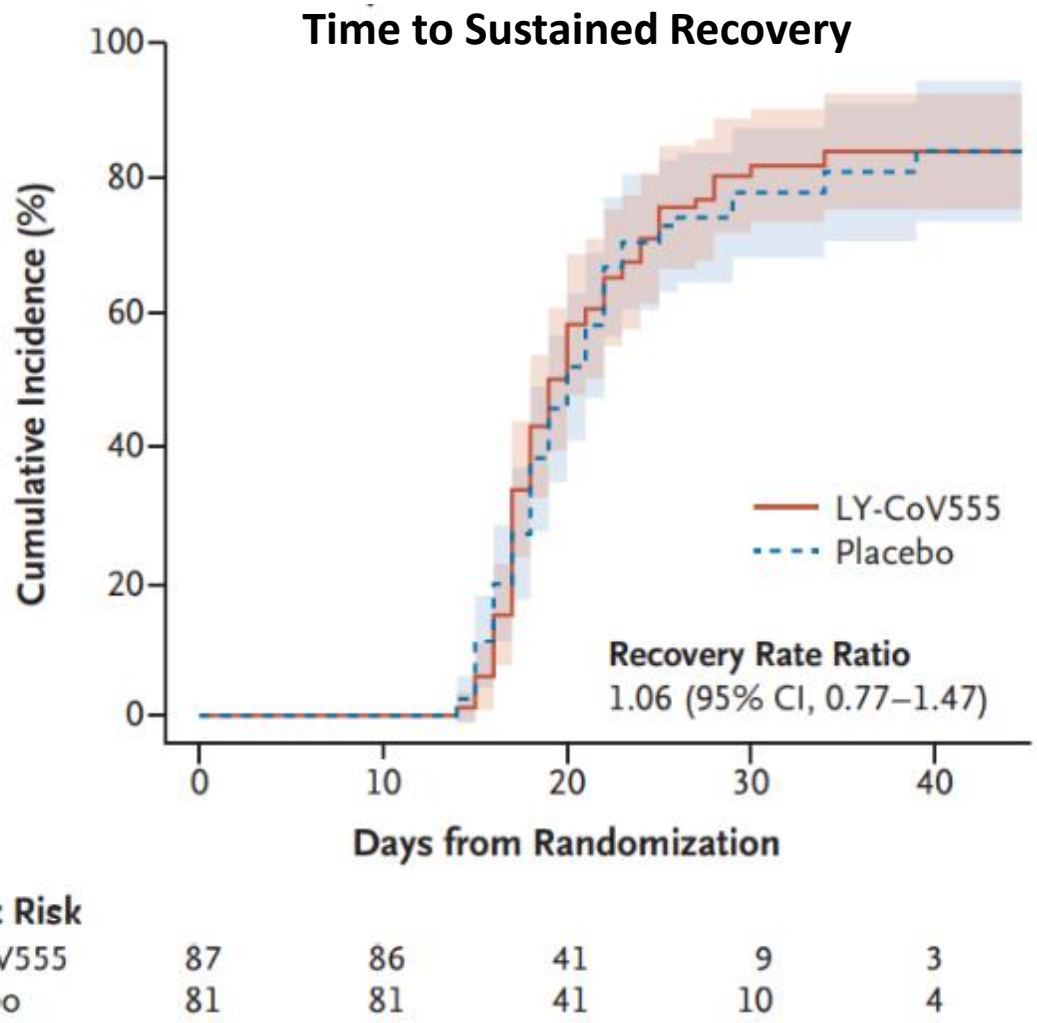
LY-CoV555

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

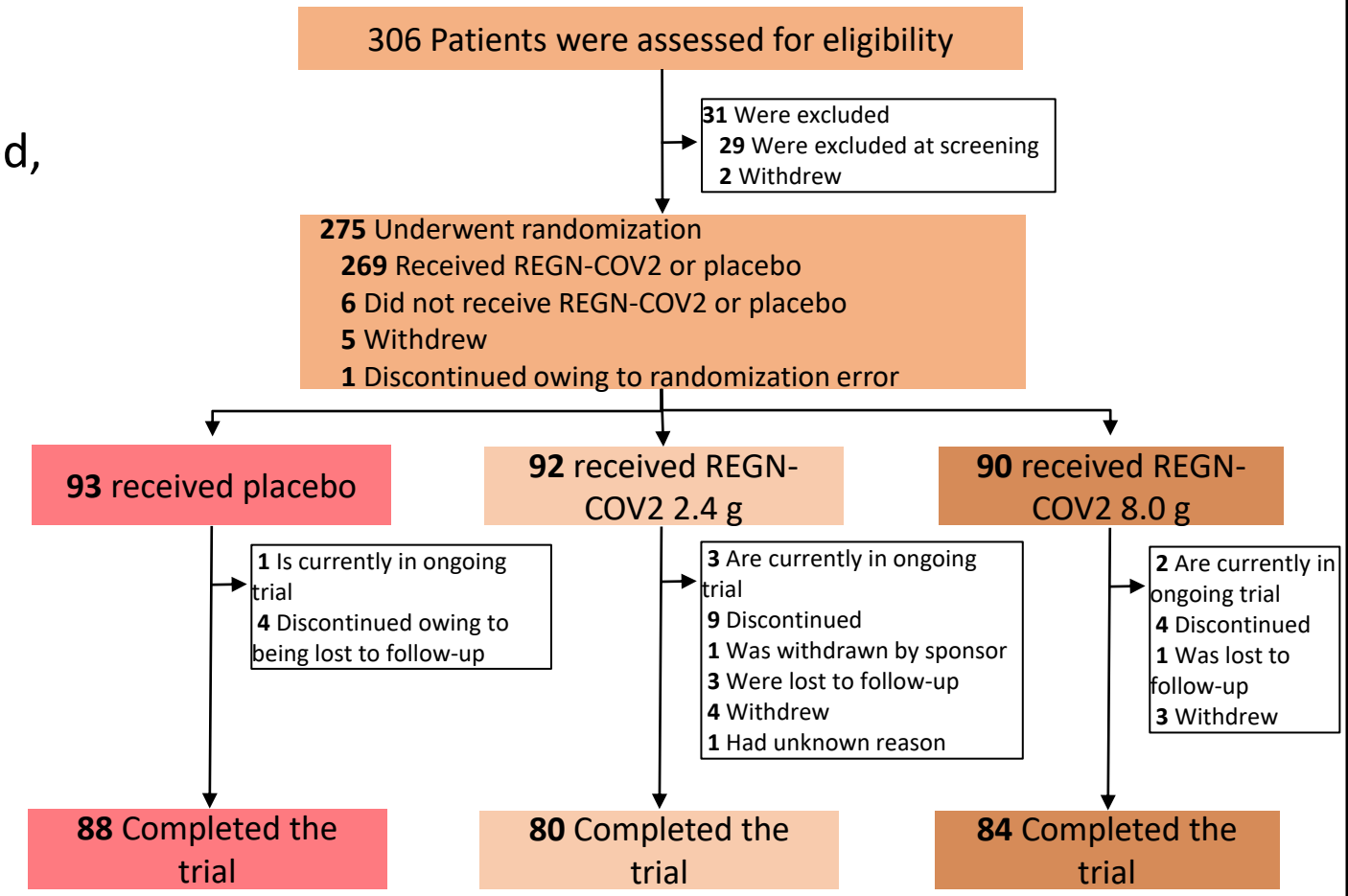
- **Time to sustained recovery**: 71/87 (82%) Ly-CoV555 group *vs.* 64/81 (79%) placebo group, rate ratio 1,06 $CI_{95\%}$[0,77-1,47]
- **Time to hospital discharge**: 143/163 (88%) Ly-CoV555 group *vs.* 136/151 (79%) placebo group, rate ratio 0,97 $CI_{95\%}$[0,78-1,20]
- **Death**: 9/163 (6%) Ly-CoV555 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

REGN-COV2

- **REGN-COV2**: antibody cocktail containing two SARS-CoV-2 neutralizing antibodies
- 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)



Monoclonal antibody

REGN-COV2

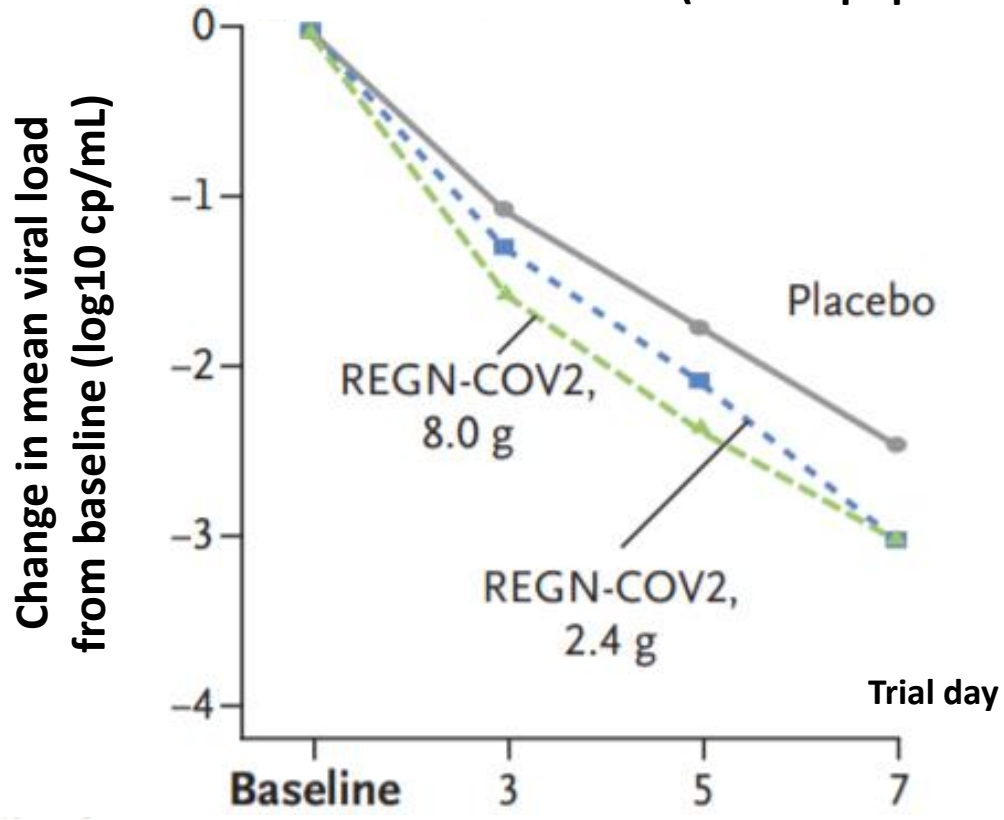
Characteristics	REGN-COV2 (N=182)	Placebo (N=93)
Age (y) - median (IQR)	43,0 (35,0–52,0)	45,0 (34,0–54,0)
Female sex - no (%)	98 (54)	43 (46)
BMI (kg/m²) - mean (SD)	30,51 (6,87)	29,73 (7,15)
Days from symptom onset to randomization - median (range)	3,0 (0–8)	3,0 (0–8)
Positive baseline qualitative RT-PCR - 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

Viral load over time (overall population)



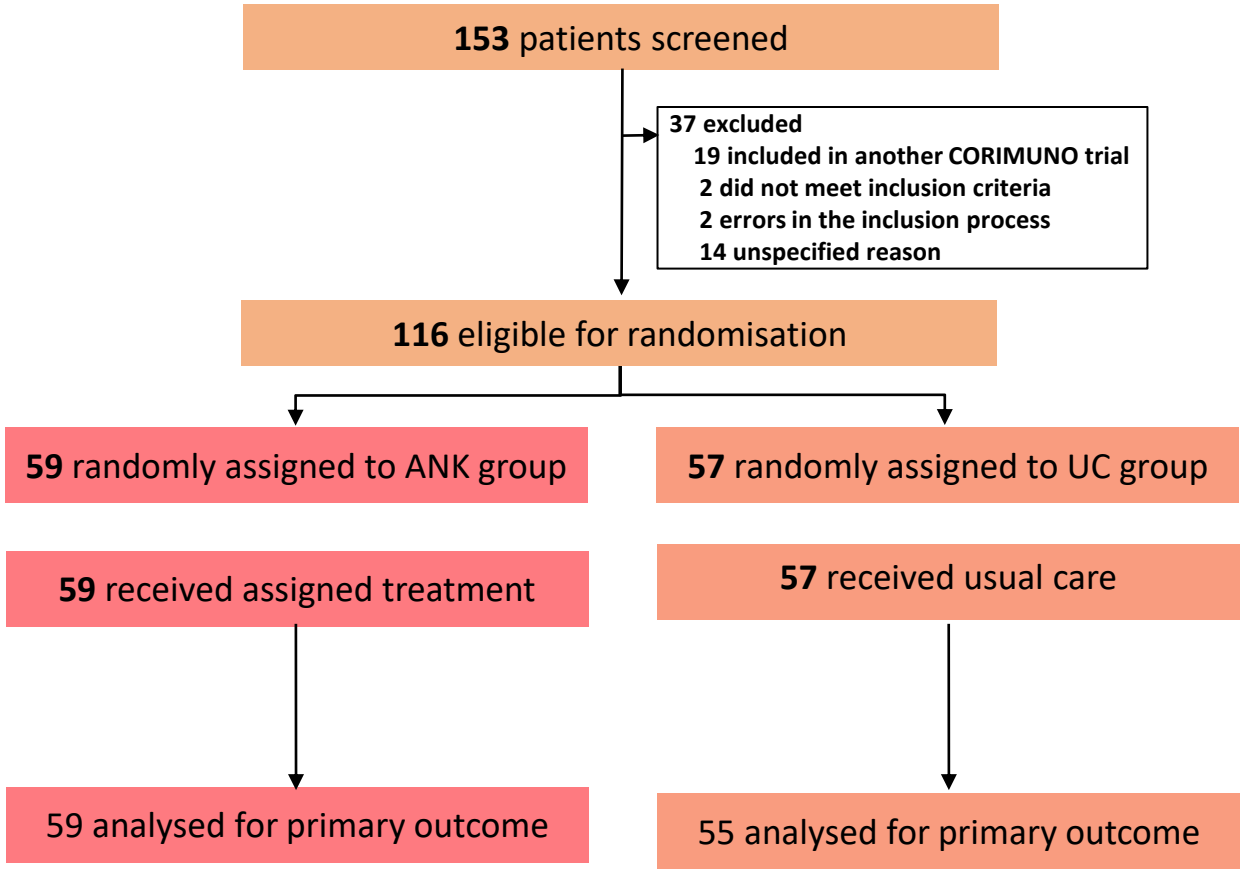
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

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

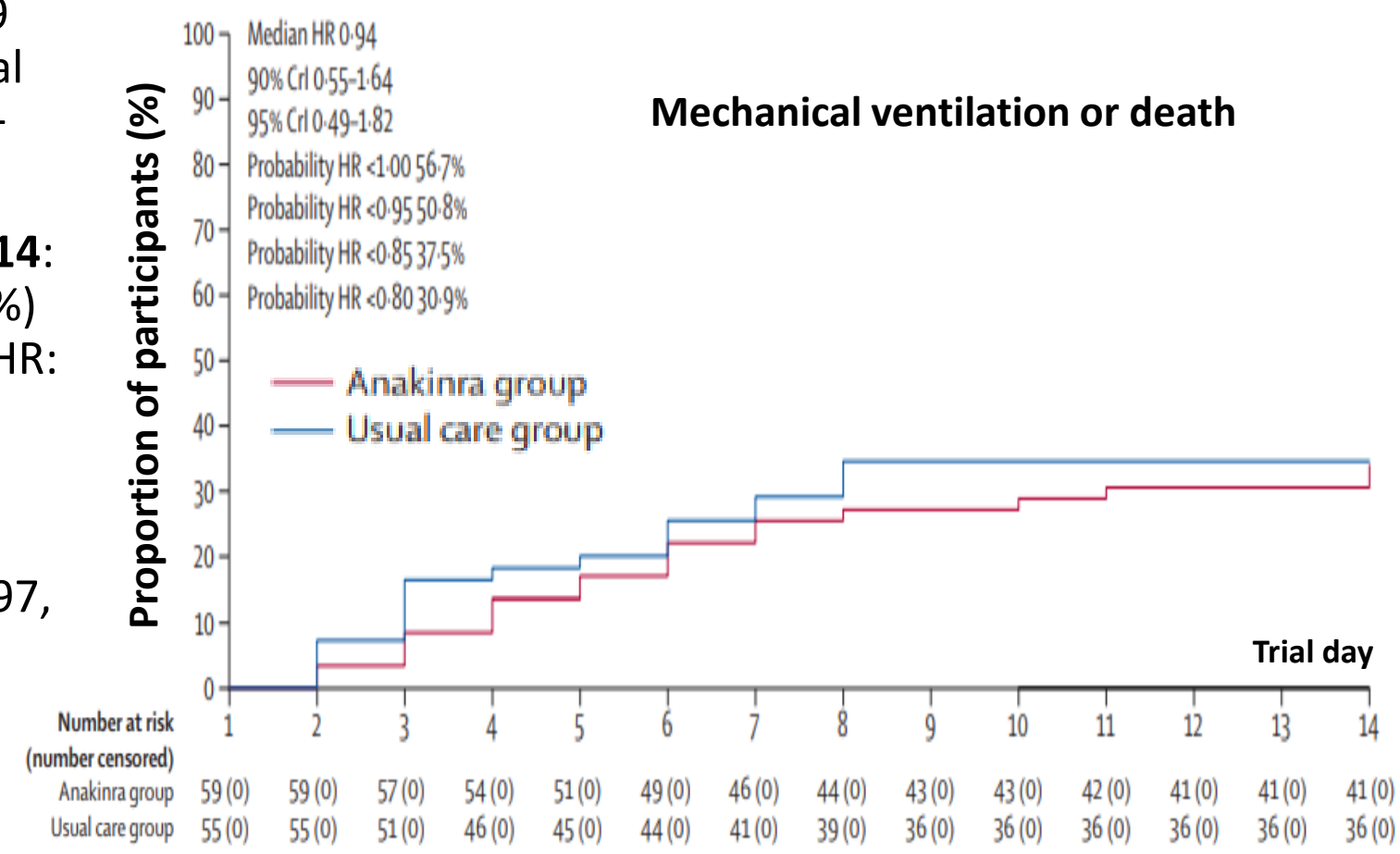
Anakinra (ANK)

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>**

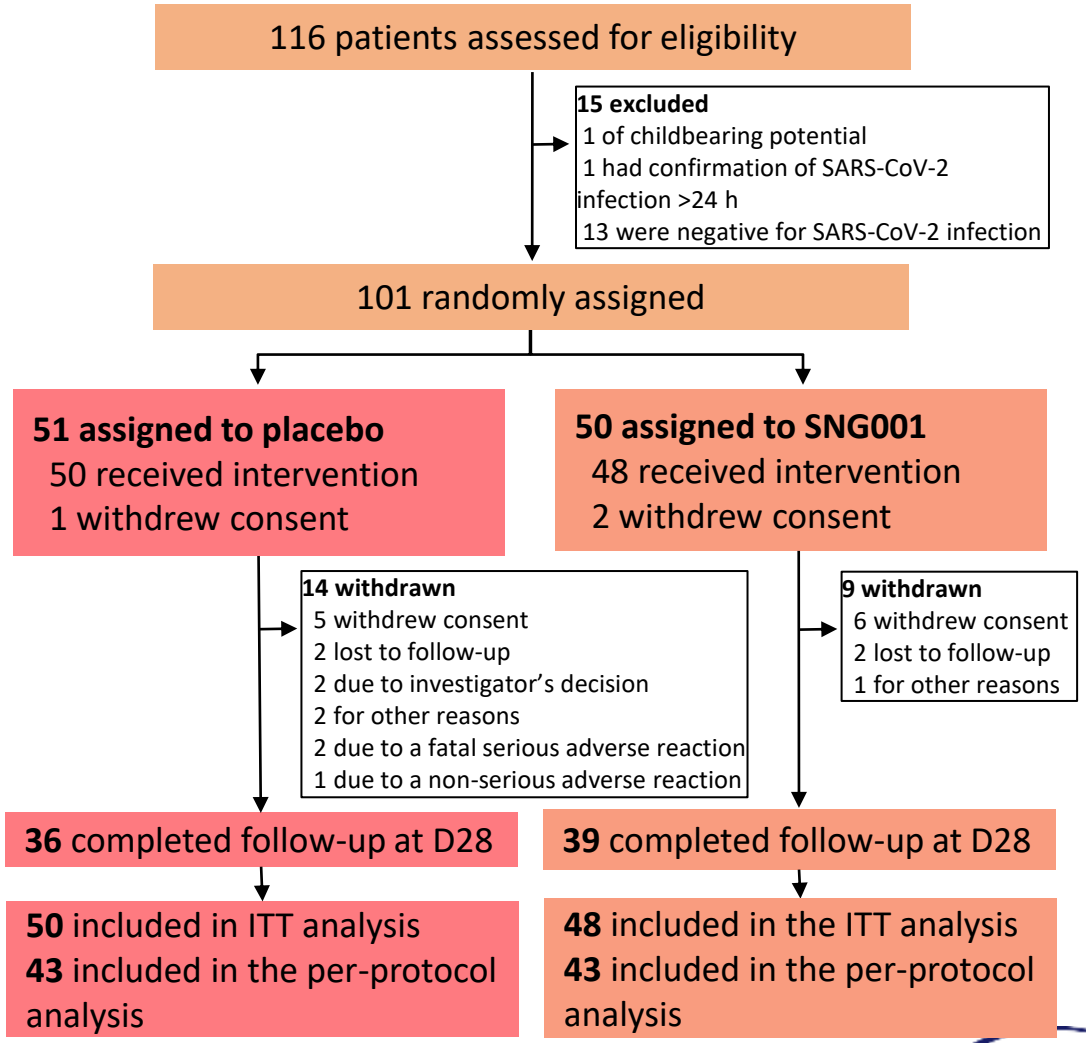


The CORIMUNO-19 Collaborative group. *Lancet Resp Med* Jan 2021

Immunomodulatory effect

Interferon beta 1a (INFβ-1a)

- **SNG001**: inhaled nebulized 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

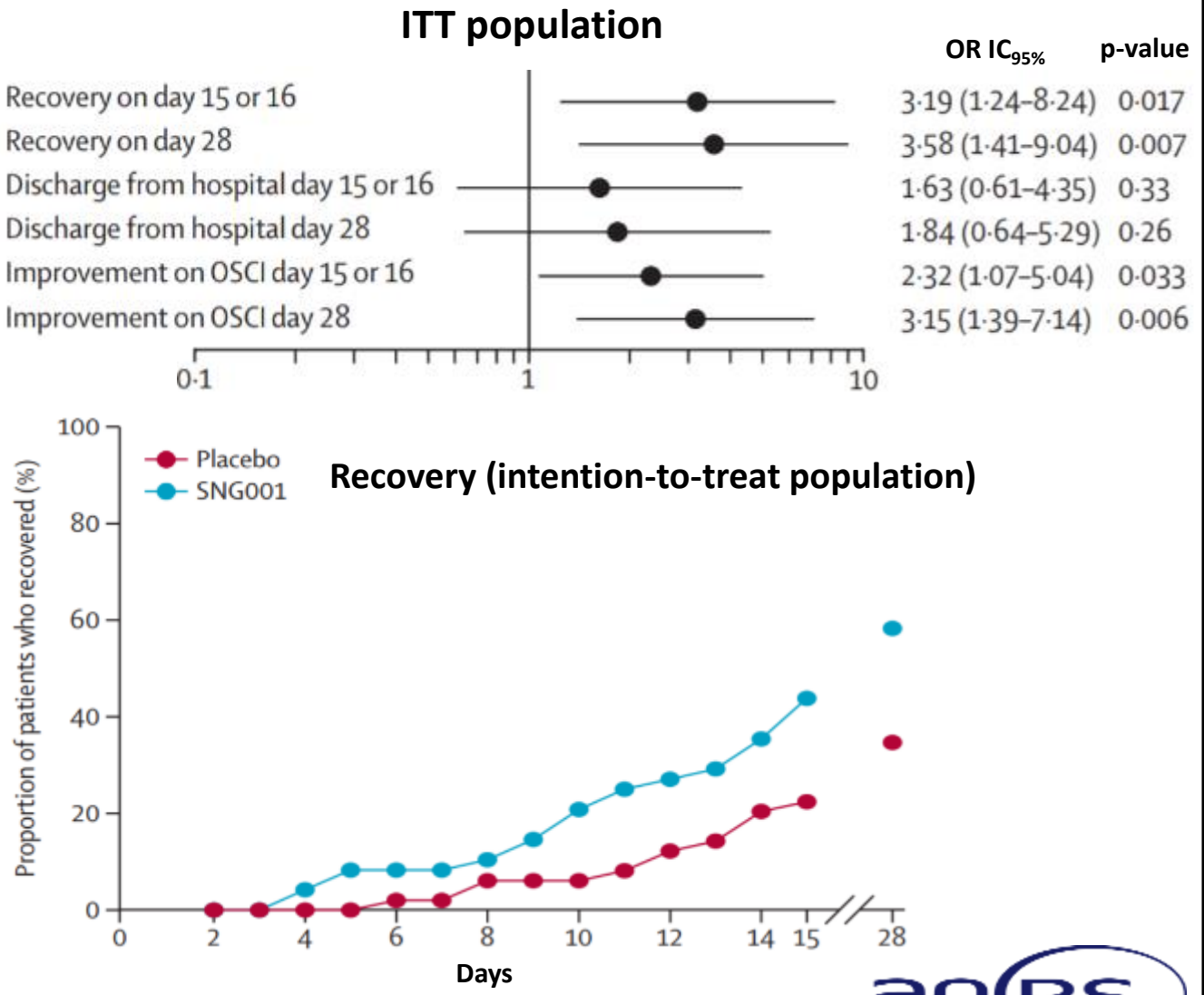
Interferon beta 1a (INFβ-1a)

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 (INFβ-1a)

- **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

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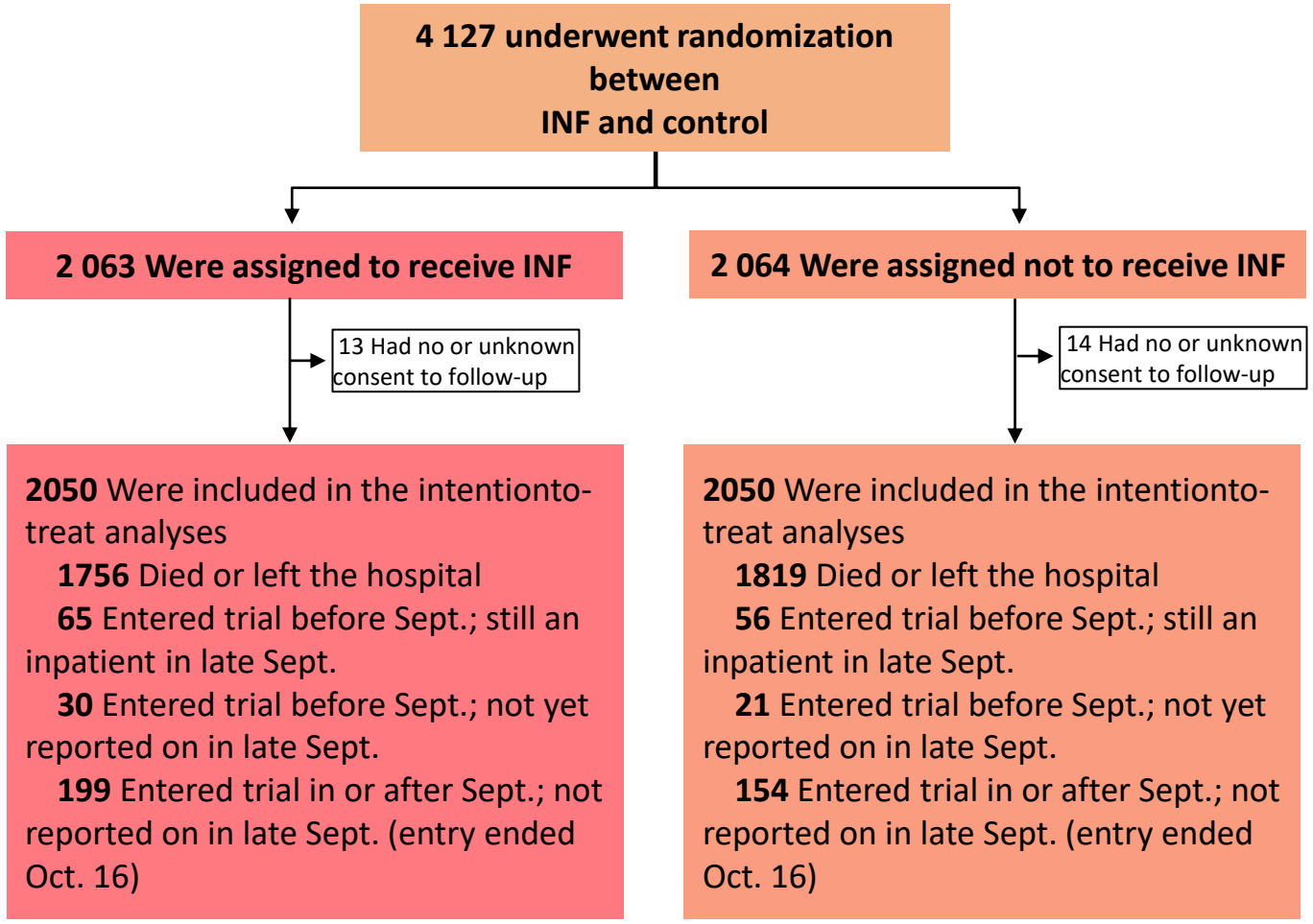
Immunomodulatory effect

Interferon beta 1a (INFβ-1a)

- 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 (INFβ-1a)

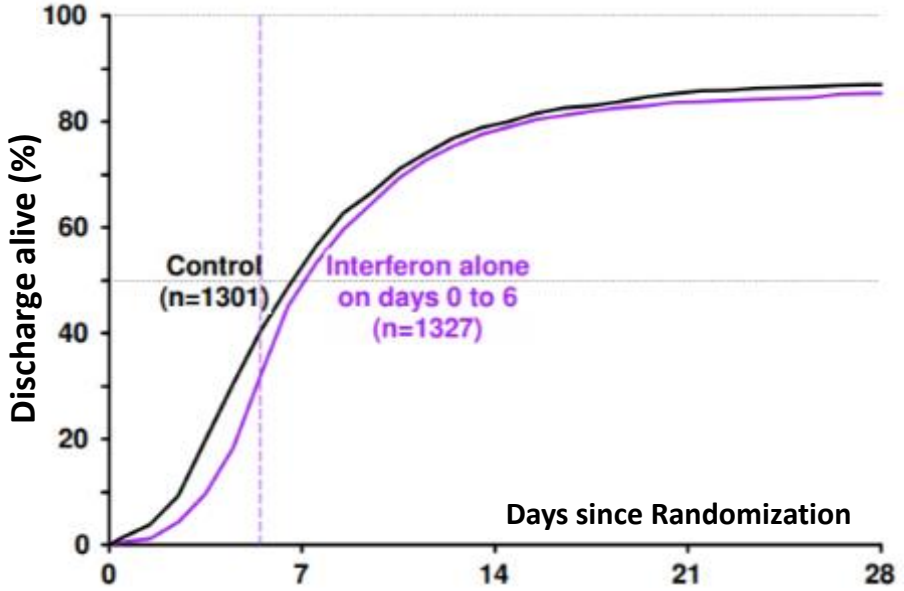
Characteristics		All (N= 11 266)	INF (N= 2 050)	Control (N=2 050)
Age	< 50 yr – no (%)	3995 (35)	720	697
	50-69 yr – no (%)	5125 (45)	934	973
	≥ 70 yr – no (%)	2146 (19)	396	380
Sex	Male sex – no (%)	6985 (62)	1303	1278
Co existing conditions	Diabetes – no(%)	2768 (25)	489	537
	Heart disease – no (%)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

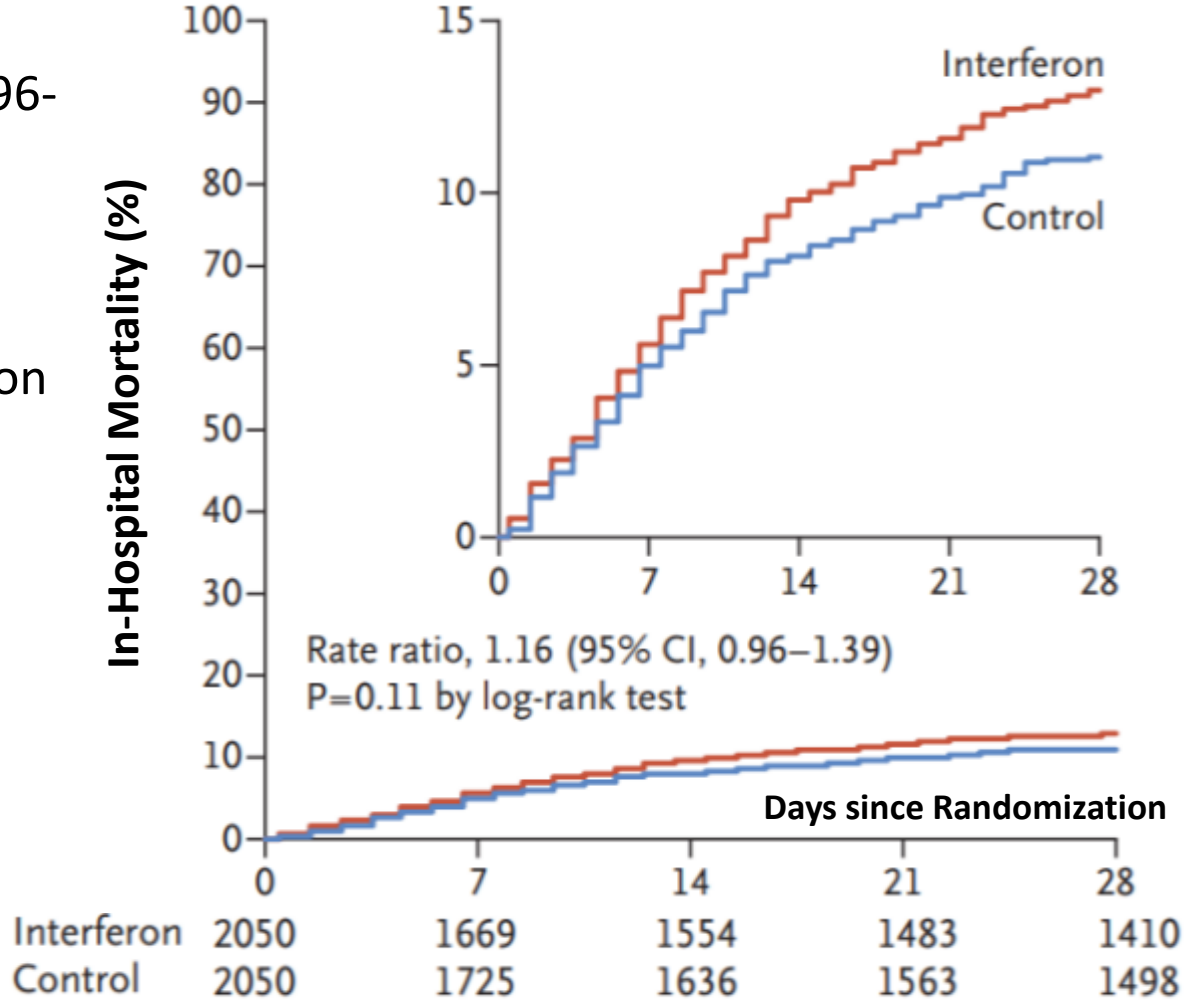
Immunomodulatory effect

Interferon beta 1a (INFβ-1a)

- **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



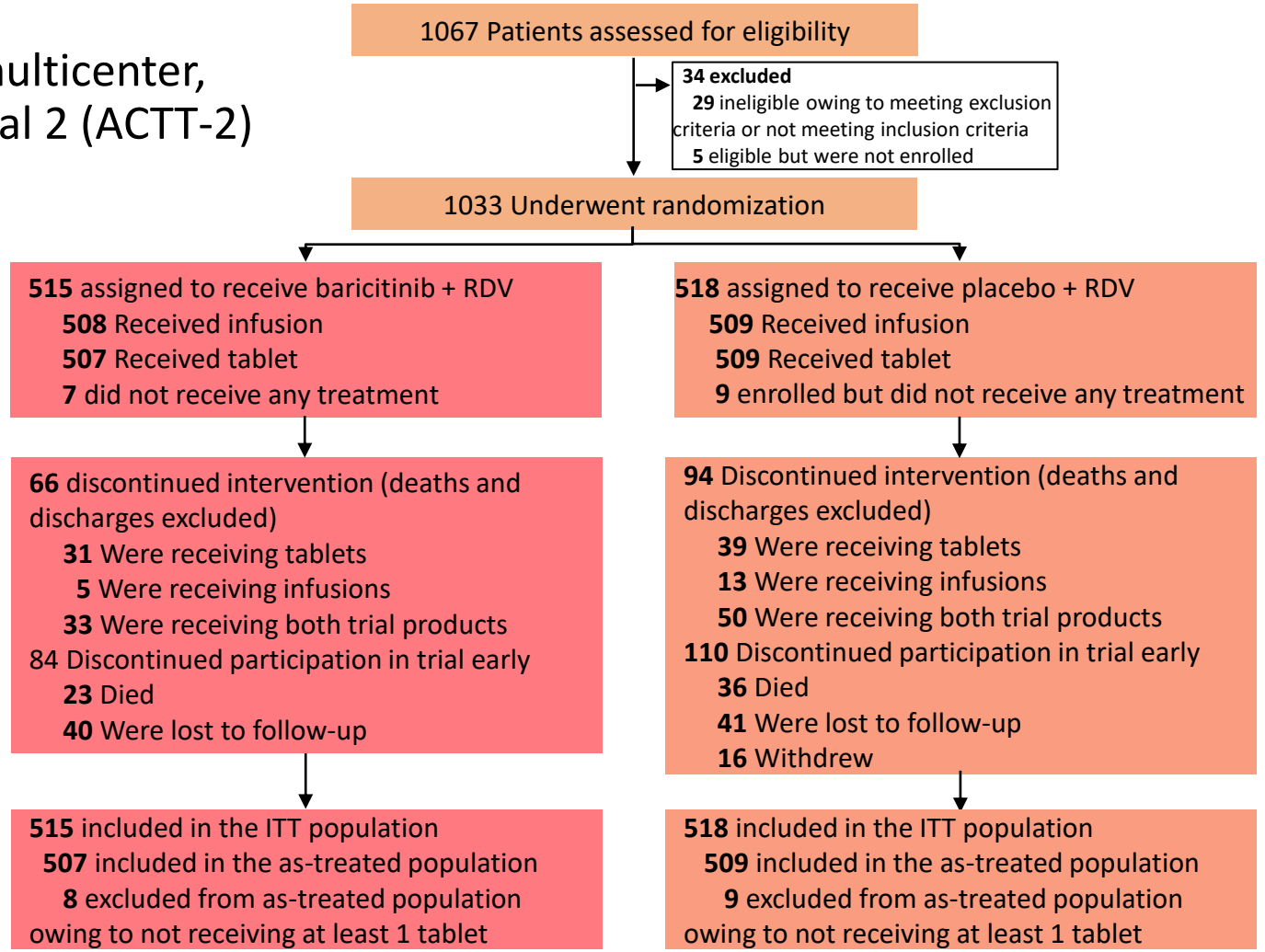


SOLIDARITY *NEJM* Dec 2020

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)

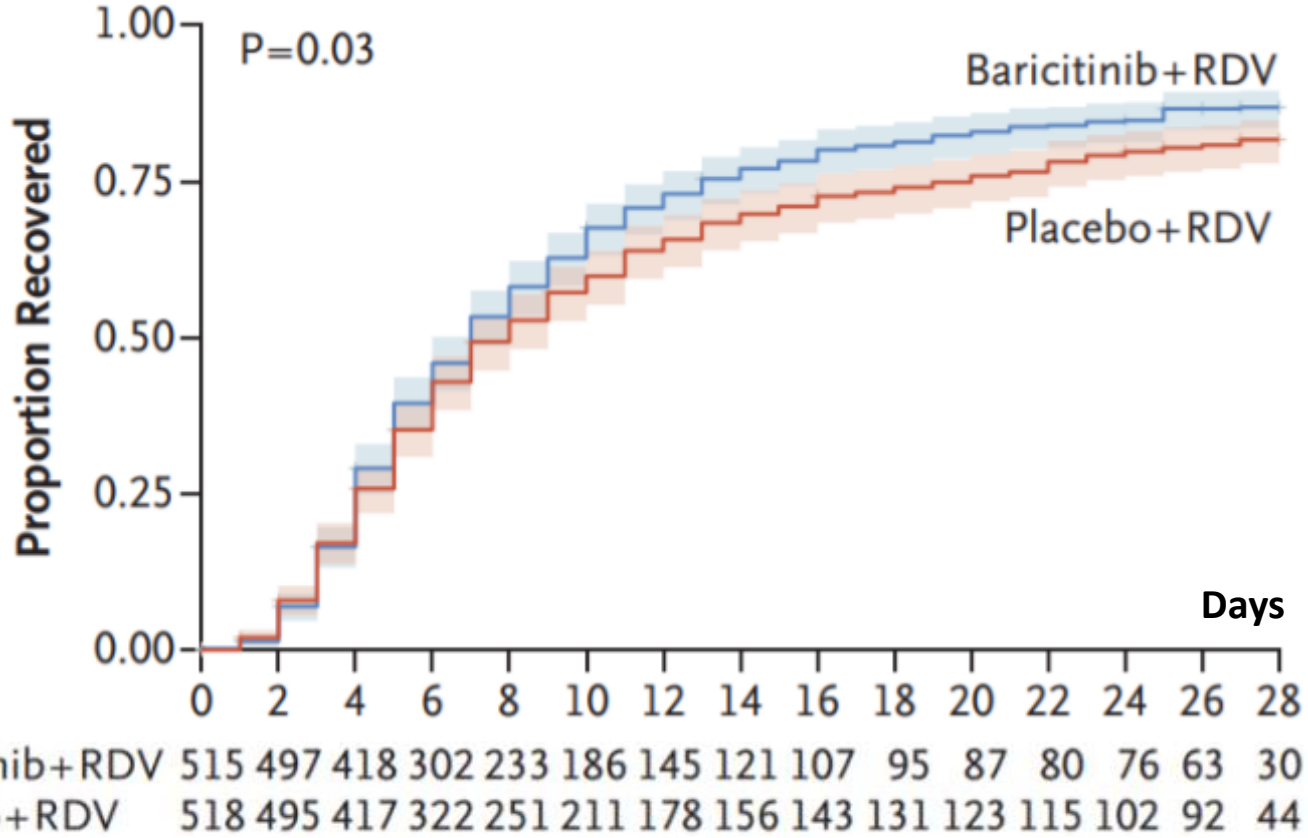
NIV: Non invasive ventilation
MV: mechanical ventilation

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 $_{95\%}$IC[1,01-1,32]; p = 0,03
- **Clinical status at day 15**: baricitinib + RDV group 30% higher odds of improvement; OR: 1,3 $_{95\%}$IC[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; $_{95\%}$IC[0,39-1,09]
- **Serious adverse events:** baricitinib + RDV group:81/515 (16%) *vs.* RDV group: 107/518 (21%) between-group difference: −5.0; $_{95\%}$IC[-9,8:-0,3]; p=0.03

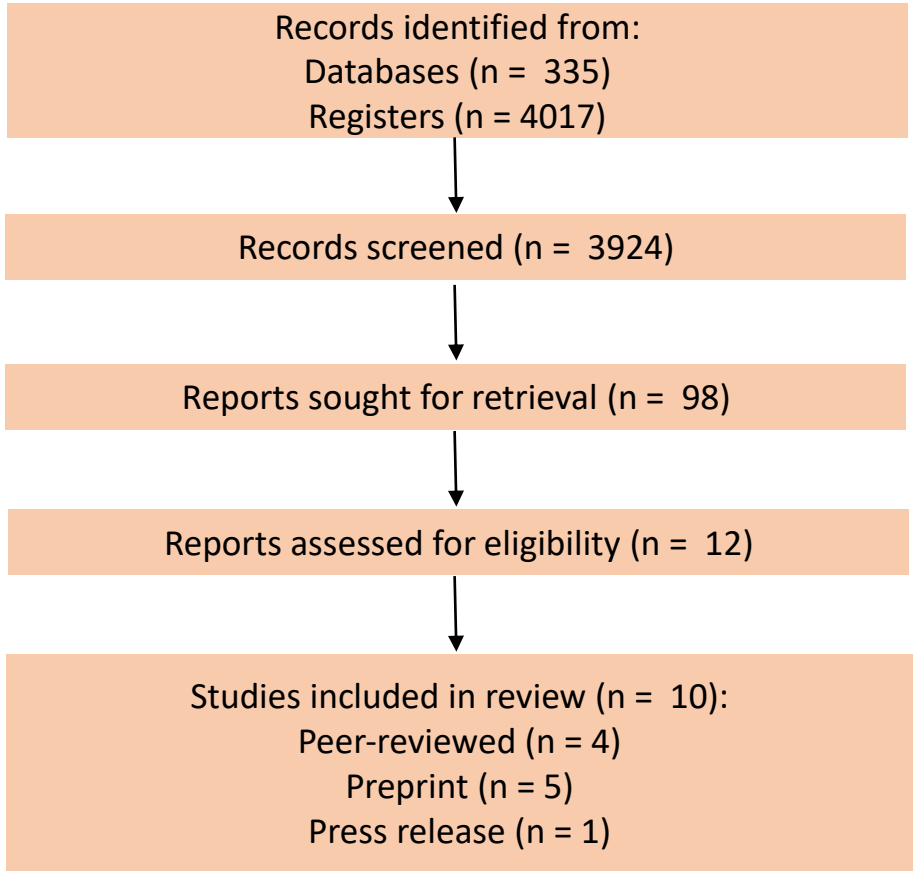


Kalil AC *et al. NEJM* Dec 2020

Passive immunity

Convalescent plasma (CP) - 1

- Systematic review and meta analysis of randomized controlled trials, academic study, Switzerland
- **Inclusion criteria:** RCTs selected compared any type of convalescent plasma *vs.* placebo or standard of care for patients with confirmed or suspected COVID-19 in any treatment setting
- **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
- **Main outcome**: All-cause mortality, length of hospital stay, clinical improvement, clinical deterioration, mechanical ventilation use, and serious adverse events



Passive immunity

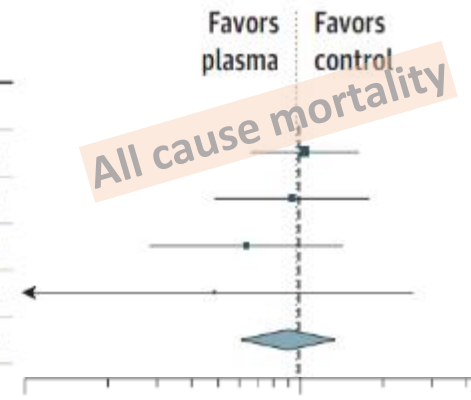
Convalescent plasma (CP) - 2

- **All cause mortality:** convalescent plasma 69/595 (11.6%) *vs.* control 59/465 (12,7%) RR: 0,93, $_{95\%}$CI [0,63:1,38], p=0,60; 1060 participants; 4 trials

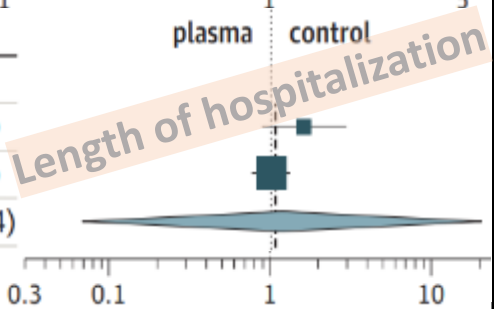
- No significant associations between treatment with CP and **length of hospital stay** reduction RR: 1,17 $_{95\%}$CI [0,07:20,34] p=0,35; 436 participants; 3 trials

- **Mechanical ventilation use**; no significant reduction associated with CP, RR: 0,76 $_{95\%}$CI [0,20:2,87] p=0,35 ; 957 participants; 3 trials

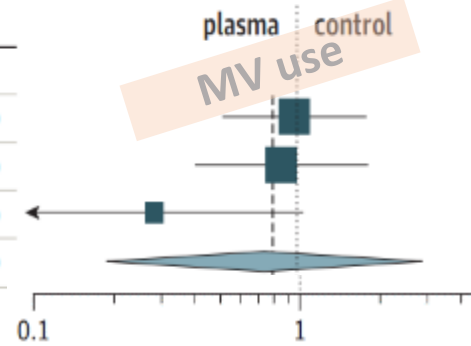
Trial	Plasma	Control	RR (95% CI)
Studies published in peer-reviewed journals			
PLACID[17]	34/235	31/229	1.07 (0.68-1.68)
PlasmAr[18]	25/228	12/105	0.96 (0.50-1.83)
ChiCTR2000029757[19]	8/52	12/51	0.65 (0.29-1.47)
NCT04479163[16]	2/80	4/80	0.50 (0.09-2.65)
Summary for peer-reviewed studies			0.93 (0.63-1.38)
Heterogeneity: I^2 = 0%, τ^2 = 0, P = .65			



Trial	Plasma	Control	HR (95% CI)
Studies published in peer-reviewed journals			
ChiCTR2000029757[19]	NA/52	NA/51	1.61 (0.88-2.95)
PlasmAr[18]	NA/228	NA/105	1.00 (0.76-1.32)
Summary for peer-reviewed studies			1.17 (0.07-20.34)
Heterogeneity: I^2 = 49%, τ^2 = 0.0559, P = .16			



Trial	Plasma	Control	RR (95% CI)
Studies published in peer-reviewed journals			
PLACID[17]	19/235	19/229	0.97 (0.53-1.79)
PlasmAr[18]	19/228	10/105	0.87 (0.42-1.82)
NCT04479163[16]	3/80	10/80	0.30 (0.09-1.05)
Summary for peer-reviewed studies			0.76 (0.20-2.87)
Heterogeneity: I^2 = 29%, τ^2 = 0.1194, P = .25			



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MV: mechanical ventilation

Janiaud P *et al*. *JAMA Feb* 2021

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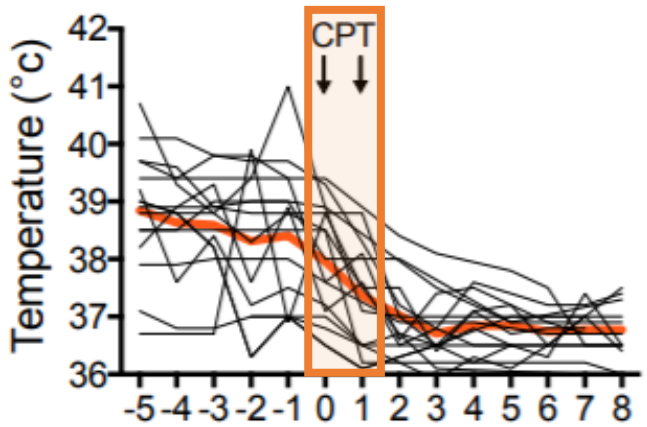
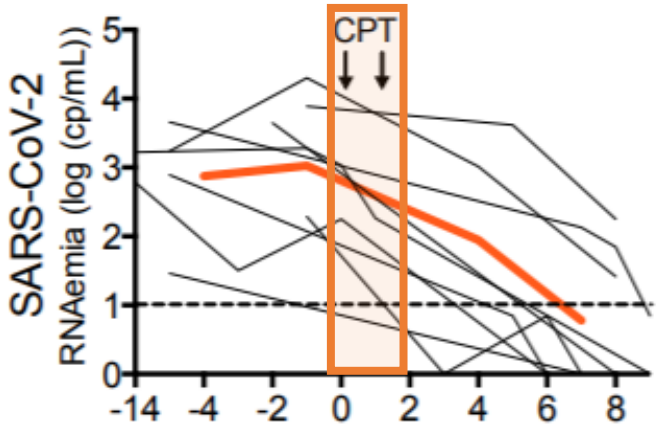
Passive immunity

Convalescent plasma (CP) - 3

- 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

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Hueso T *et al. Blood* Sep 2020

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THERAPEUTIC (April 19th 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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