COREB
mission nationale
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THERAPEUTIC

REACTing
research & action
targeting emerging infectious diseases

https://reacting.inserm.fr/

Scientific update on COVID-19

Updated on December 21th 2020

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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

- Remdesivir
- (Hydroxy)chloroquine
- Lopinavir/ritonavir

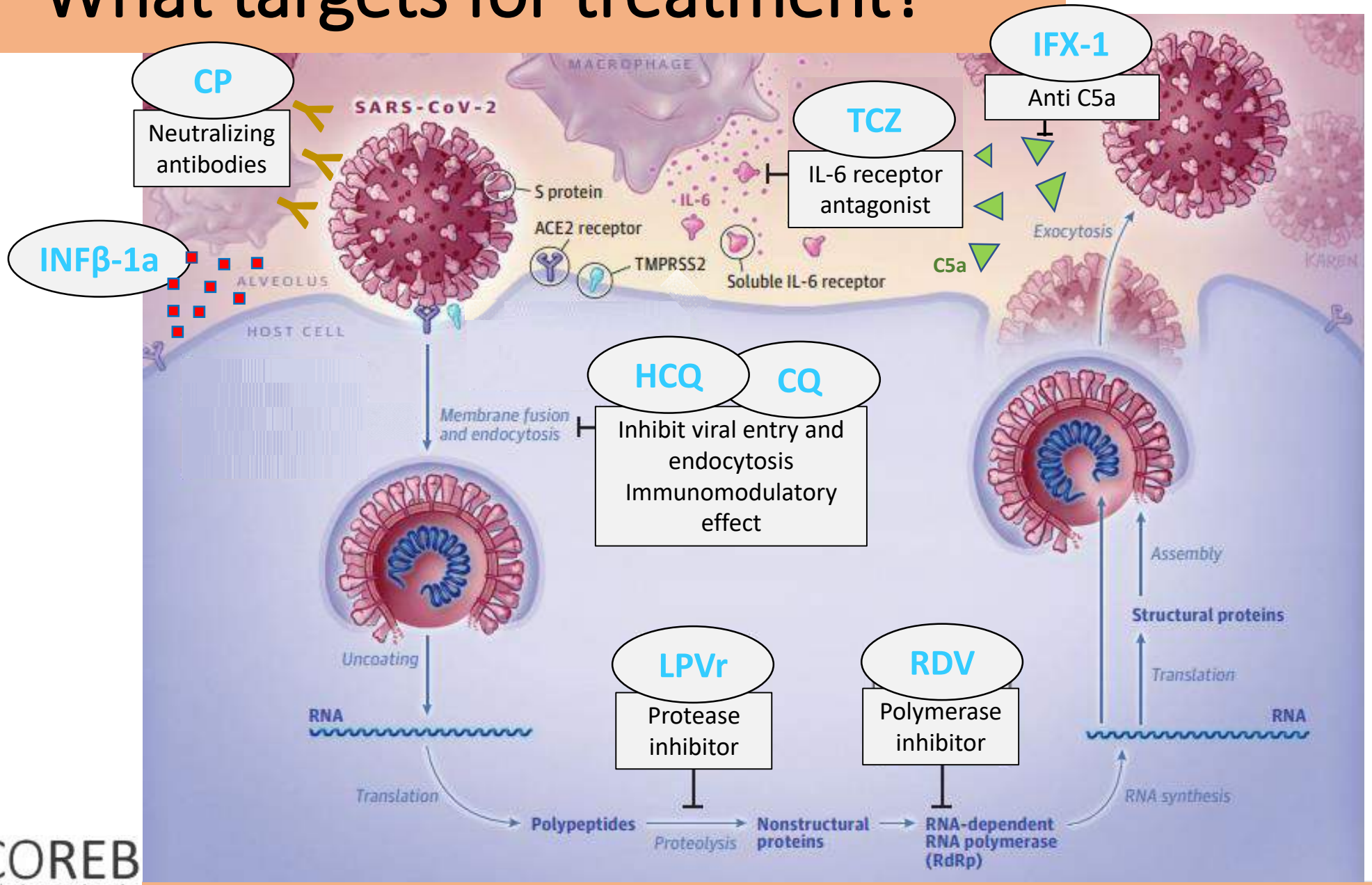
Immunomodulatory effect

- Corticosteroids
- INFβ-1a
- Baricitinib
- Monoclonal antibody

Passive immunity

- Convalescent plasma

What targets for treatment?



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

Sanders JM *et al. JAMA* May 2020

Anti viral effect

Hydroxychloroquine (HCQ)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Abella	Randomized, double-blind, placebo-controlled	HCQ *vs.* placebo (**Pre-exposure prophylaxis**)	**N= 130** Hospital HCW (ED and COVID-19 units)	Incidence of SARS-CoV-2 infection	Early termination of the study HCQ group: 4/64 (6,3%) *vs.* placebo group: 4/61 (6,6%); p > 0,99
Rajasingham	Randomized, double-blind, placebo-controlled	HCQ once/week *vs.* placebo HCQ twice/week *vs.* placebo (**Pre-exposure prophylaxis**)	**N= 1483** Hospital HCW (ED, ICU, COVID-19 units, first responders)	Confirmed or probable COVID-19 compatible illness	HCQ once/week group: 29/494 (5,9%) *vs.* placebo group: 39/494 (7,9%); HR: 0,72 $CI_{95\%}$[0,44-1,16] HCQ twice/week group: 29/495 (5,9%) *vs.* placebo group: 39/494 (7,9%); HR: 0,74 $CI_{95\%}$[0,46-1,19]

No virological data on some studies

ED: emergency department – ICU: intensive care unit
HCW: health care worker

Abella BS *et al. JAMA Int Med.* Sep 2020
Rajasingham R *et al. CID* Oct 2020

Anti viral effect

Hydroxychloroquine (HCQ)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Boulware	Randomized, double-blind, placebo-controlled	HCQ *vs.* placebo (**Post exposure prophylaxis**)	**N= 821** Exposed to a known COVID-19 individual	Incidence of either laboratory confirmed COVID-19 or illness compatible with COVID-19 within 14 days	HCQ group: 49/414 (11,8%) *vs.* placebo group: 58/407 (14,3%); p=0,35
Mitjà	Open-label, cluster-randomized trial	HCQ *vs.* usual care (**Post exposure prophylaxis**)	**N= 2314** Healthy contacts of 672 index case patients with COVID-19	D14 PCR-confirmed, symptomatic COVID-19	HCQ group: 64/1116 (5,7%) *vs.* usual care group: 74/1198 (6,2%); RR=0.86 $IC_{95\%}$[0,52-1,42)

No virological data on some studies

Anti viral effect

Hydroxychloroquine (HCQ)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Mitjà	Multicenter, open label, randomized controlled trial	HCQ *vs.* placebo (**Non-hospitalized**)	**N= 353** Mild symptoms < 5 days before enrollment	D3 and D7 reduction of viral RNA load from nasopharyngeal swab	D3 VL[$]: HCQ group: -1,41 *vs.* placebo group: -1,41 Log_{10} copies/mL; difference: 0,01 $CI_{95\%}$ [-0,28- 0,29] D7 VL[§]: HCQ group: -3,44 *vs.* placebo group: -3,37 Log_{10} copies/mL; difference: 0,07 $CI_{95\%}$ [-0,44- 0,29]
Skipper	Randomized, double-blind, placebo-controlled	HCQ *vs.* placebo (**Non-hospitalized**)	**N= 491**	D14 ordinal outcome of not hospitalized, hospitalized, or intensive care unit stay or death	Mean reduction from baseline: HCQ group: 2,60 points *vs.* placebo group: 2,33 points; absolute difference: 0,27 $CI_{95\%}$ [0,61-0,07]; p=0,117)

No virological data on some studies

VL: viral load
[$] Mean difference

Mitja *et al. CID* Jul *2020*
Skipper *et al. Ann Intern Med* Oct *2020*

Anti viral effect

Hydroxychloroquine (HCQ)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Cavalcanti	Multicenter, randomized, open-label, controlled	HCQ + AZ *vs.* SoC, HCQ *vs.* SoC, HCQ + AZ *vs.* HCQ (**Hospitalized**)	**N= 667** No supplemental O_2 or a max of 4 L/min supplemental, ≤14 days since symptom onset	D15 clinical status (seven-level ordinal scale)	HCQ + AZ *vs.* control: OR: 0,99 $IC_{95\%}$ [0,57-1,73]; HCQ *vs.* control: OR: 1,21 $IC_{95\%}$ [0,69-2,11]; HCQ + AZ *vs.* HCQ: OR: 0,82 $IC_{95\%}$ [0,47-1,43]
RECOVERY	Randomized, controlled, open-label	HCQ *vs.* usual care (**Hospitalized**)	**N= 4717** Median of days since symptom onset: 9 days	D28 mortality	HCQ group: 421/1561 (27.0%) vs. usual care group: 790/3155 (25.0%) RR: 1.09; $IC_{95\%}$ [0,97-1,23]; p=0,15

No virological data on some studies

AZ: azithromycin
SoC: standard of care

Cavalcanti *et al*. *NEJM* Jul 2020
RECOVERY *NEJM* Oct 2020

Anti viral effect

Hydroxychloroquine (HCQ)

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Self	Multicenter, randomized, blinded, placebo-controlled	HCQ *vs.* placebo (**Hospitalized**)	**N= 479** supplemental oxygen to maintain SpO_2 ≥92% Onset of symptoms to randomization: 5 days§	D14 clinical status (seven-level ordinal scale)	HCQ group: 6 (4-7) vs. placebo group: 6 (4-7); OR: 1,02 $IC_{95\%}$[0,73-1,42]
Tang	Randomized, controlled, multicenter, open label	HCQ + SoC *vs.* SoC (**Hospitalized**)	**N= 150** Mild to moderate or severe disease, onset of symptoms to randomization: 16,6 days+	D28 negative conversion of SARS-CoV-2	HCQ + SoC: 85,4%, $IC_{95\%}$[73,8% - 93,8%] *vs.* SoC: 81,3%, $IC_{95\%}$[71,2%-89,6%]
Ulrich	Multicenter, double-blind randomized	HCQ *vs.* placebo (**Hospitalized**)	**N= 128** Excluded patient admitted in ICU	D14 severe disease progression composite end point	HCQ group: 11/67 (16,4%) vs. placebo group: 6/61 (9,8%); p=0,35

No virological data on some studies

§ Median duration
+ Mean duration

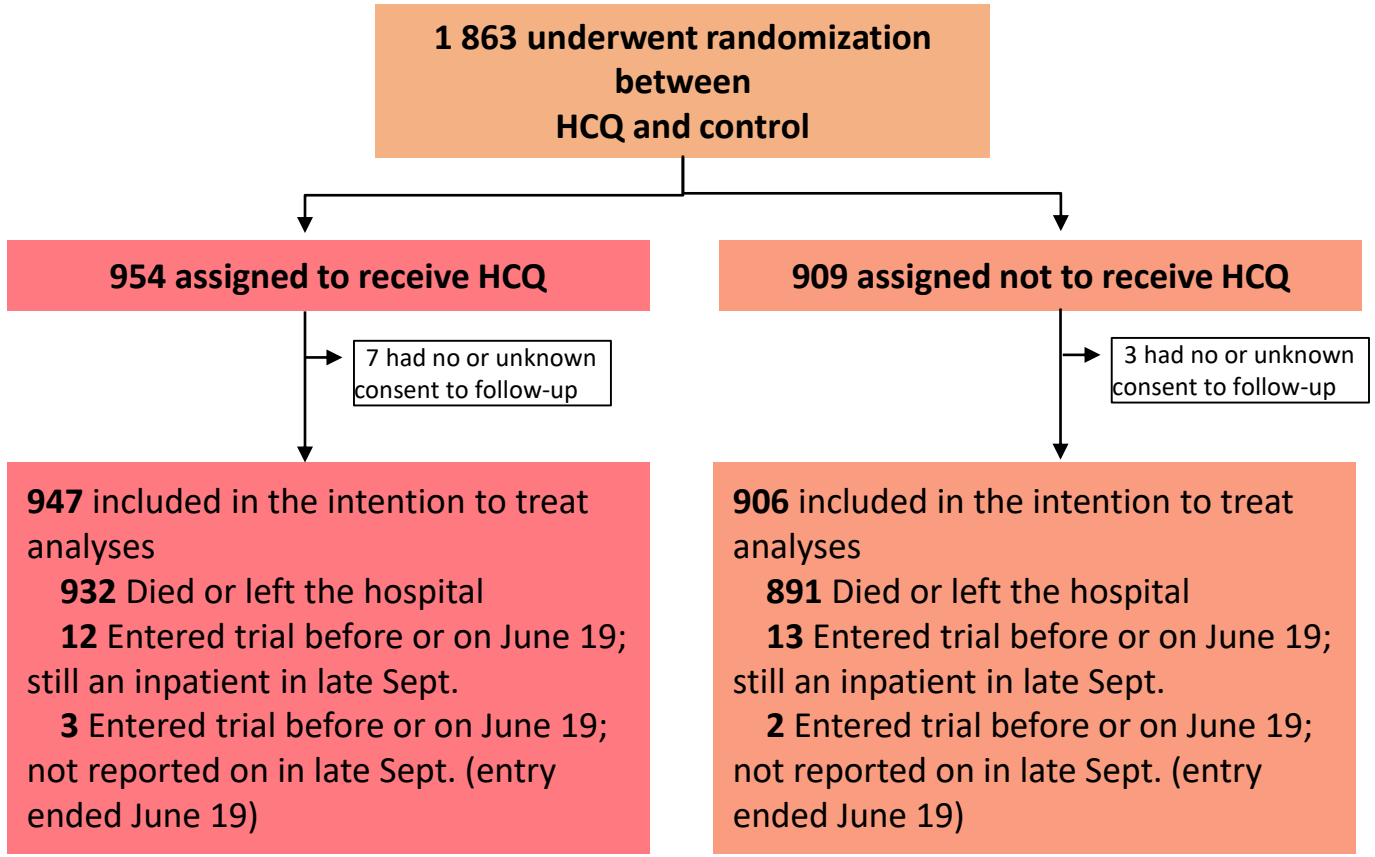
Ulrich *et al*. *Open Forum Infect Dis* Sep 2020

Self *et al*. *JAMA* Nov 2020
Tang W *et al*. *BMJ* May 2020

Anti viral effect

Hydroxychloroquine (HCQ)

- 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
- 1863 patients underwent randomization; 954 **HCQ** group, 909 **control** group (1:1)



Anti viral effect

Hydroxychloroquine (HCQ)

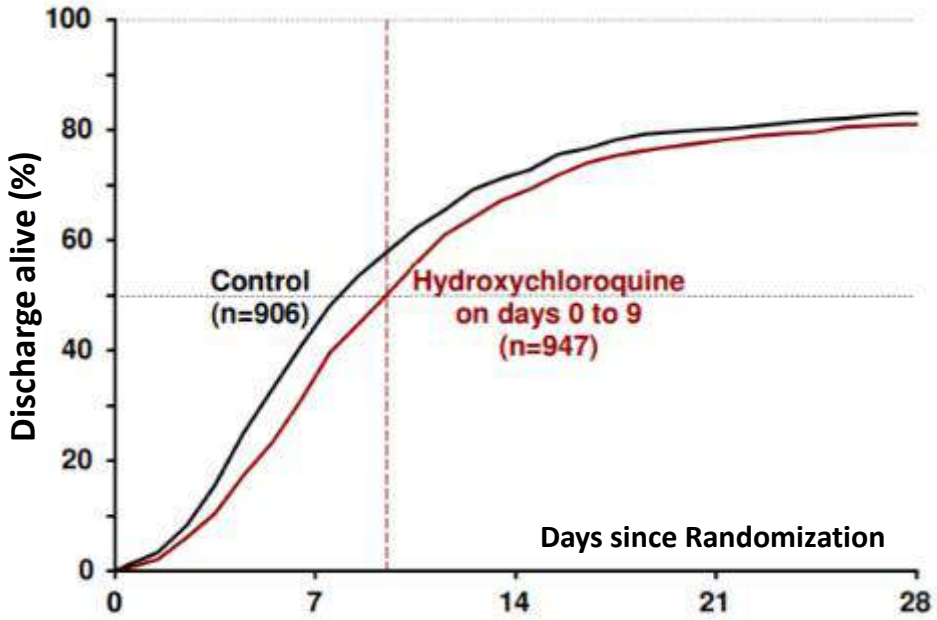
Characteristics		All (N= 11 266)	HCQ (N= 947)	Control (N=906)
Age	< 50 yr – no (%)	3995 (35)	335	317
	50-69 yr – no (%)	5125 (45)	410	396
	≥ 70 yr – no (%)	2146 (19)	202	193
Sex	Male sex – no (%)	6985 (62)	574	535
Co existing conditions	Diabetes – no(%)	2768 (25)	199	205
	Heart disease – no (%)	2337 (21)	193	194
	Chronic lung disease – no (%)	635 (6)	62	66
Respiratory support	No supplemental O_2 at entry	3204 (28)	345	341
	Supplemental O_2 at entry	7146 (63)	517	483
	Already receiving ventilation	916 (8)	85	82

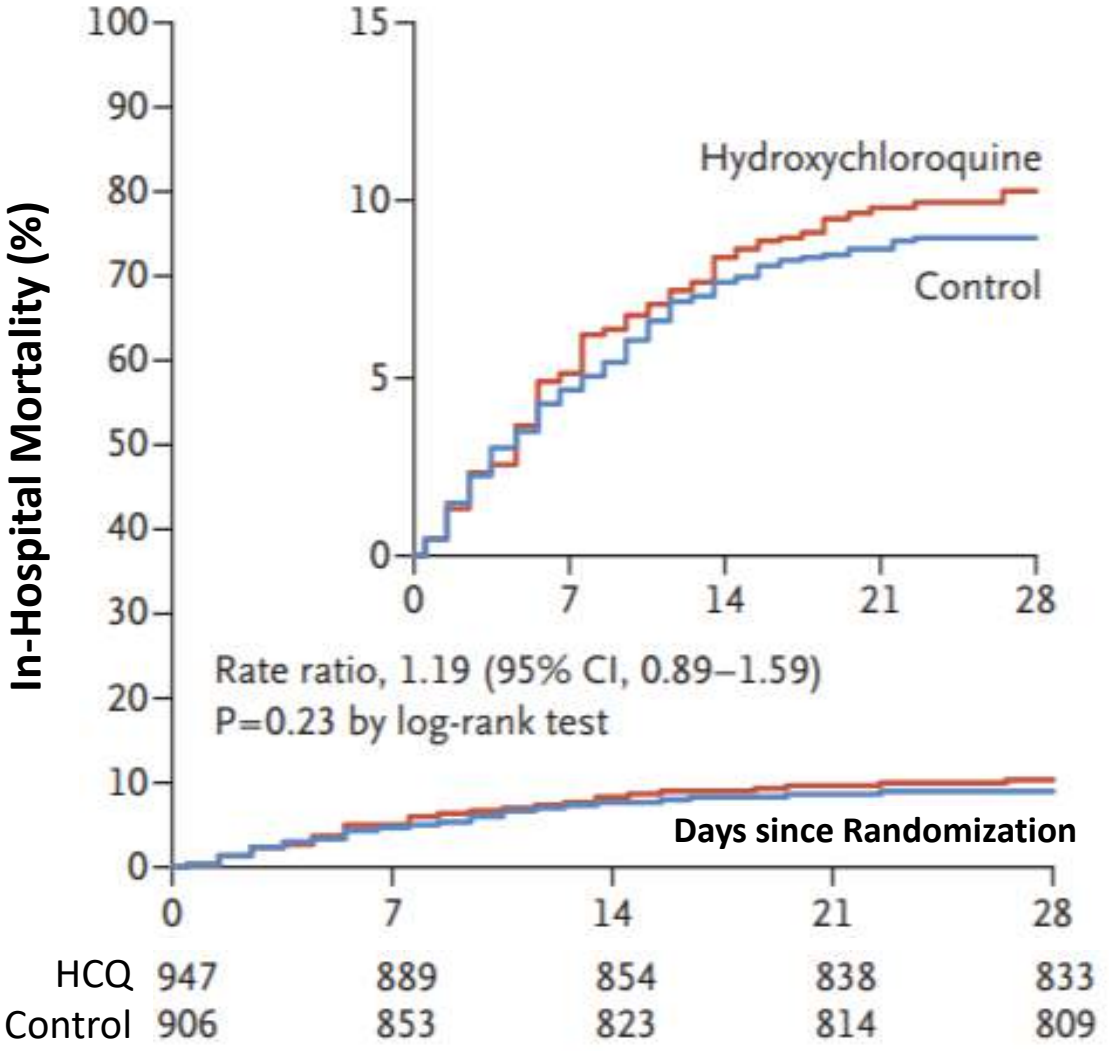
Anti viral effect

Hydroxychloroquine (HCQ)

- **All-cause mortality**: 104/947 (10,2%) HCQ group *vs.* 84/906 (8,9%) placebo group; rate ratio: 1,19; $CI_{95\%}$[0,89-1.59]; p= 0,23
- **Initiation of mechanical ventilation**: HCQ group: 75/862 (8,7%) *vs*. control group 66/824 (8%)
- **Time to discharge**: HCQ did not reduced hospitalization duration

Study stopped for futility on 19th June





SOLIDARITY *NEJM* Dec 2020

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 $CI_{95\%}$[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 $CI_{95\%}$[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)

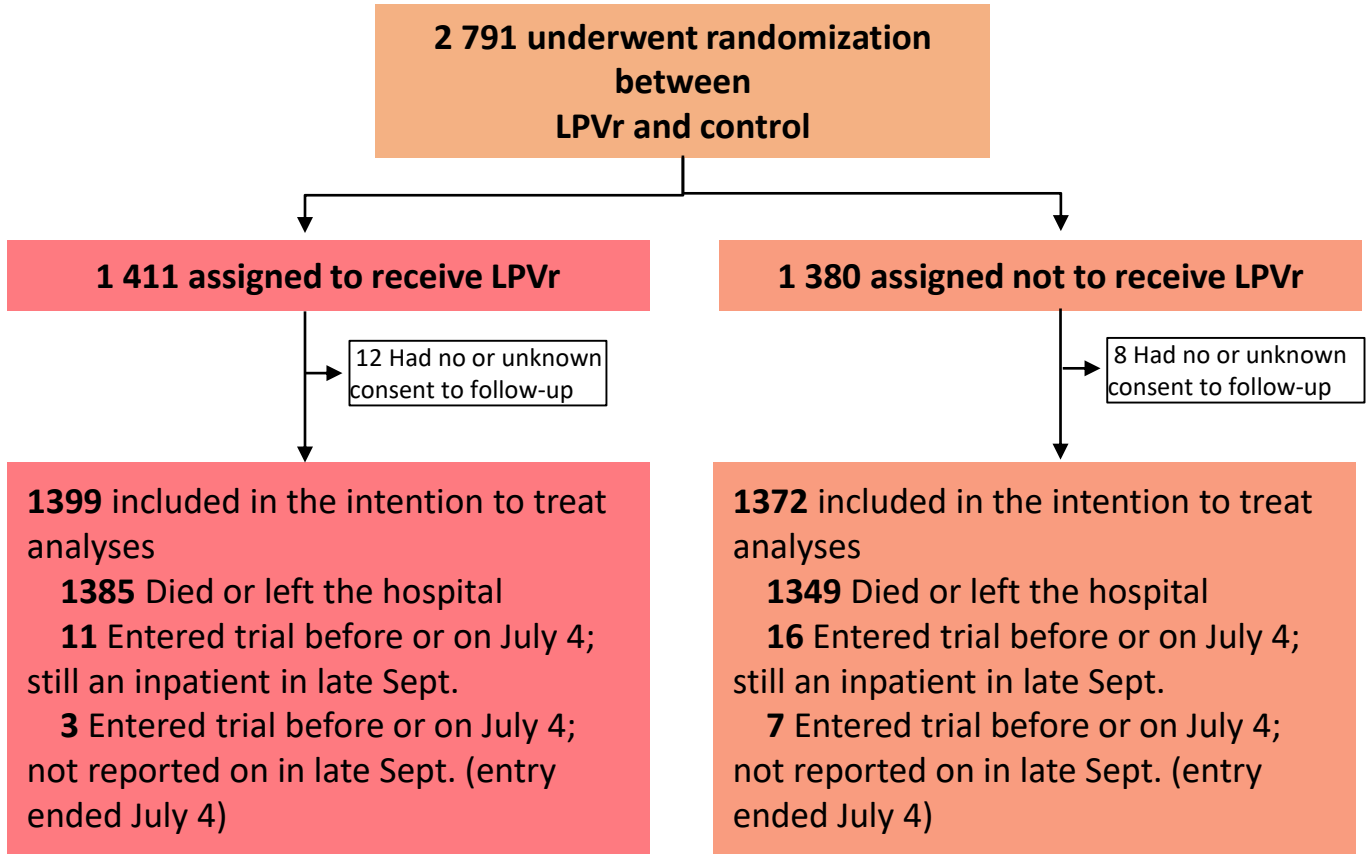
1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Zhang	Systematic review and meta-analysis	LPVr *vs.* control specified (**Hospitalized**)	**N= 4 023** Not specified	ARDS and Mortality rate	ARDS rate: LPVr group 15,6% *vs.* control group 24,2%; p= 0,49 Mortality rate: LPVr group 6,2% *vs.* control group 5,5%; p= 0,93

No virological data on some studies

Anti viral effect

Lopinavir/ritonavir (LPVr)

- 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
- 2 791 patients underwent randomization; 1441 **LPVr** group, 1380 **control** group (1:1)



Anti viral effect

Lopinavir/ritonavir (LPVr)

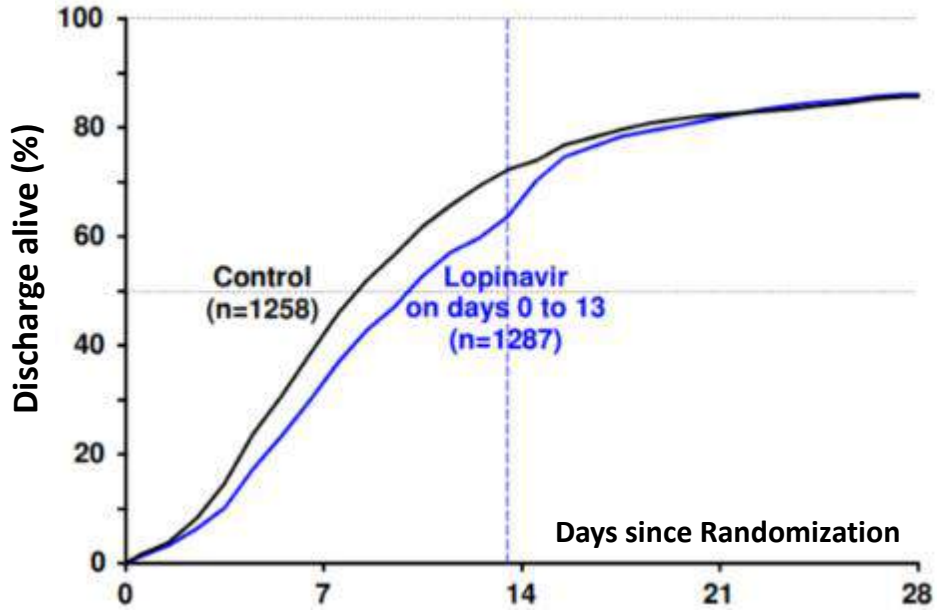
Characteristics		All (N= 11 266)	LPVr (N= 1 399)	Control (N=1 372)
Age	< 50 yr – no (%)	3995 (35)	511	501
	50-69 yr – no (%)	5125 (45)	597	596
	≥ 70 yr – no (%)	2146 (19)	291	275
Sex	Male sex – no (%)	6985 (62)	851	802
Co existing conditions	Diabetes – no(%)	2768 (25)	341	324
	Heart disease – no (%)	2337 (21)	289	290
	Chronic lung disease – no (%)	635 (6)	95	87
Respiratory support	No supplemental O_2 at entry	3204 (28)	528	539
	Supplemental O_2 at entry	7146 (63)	759	719
	Already receiving ventilation	916 (8)	112	114

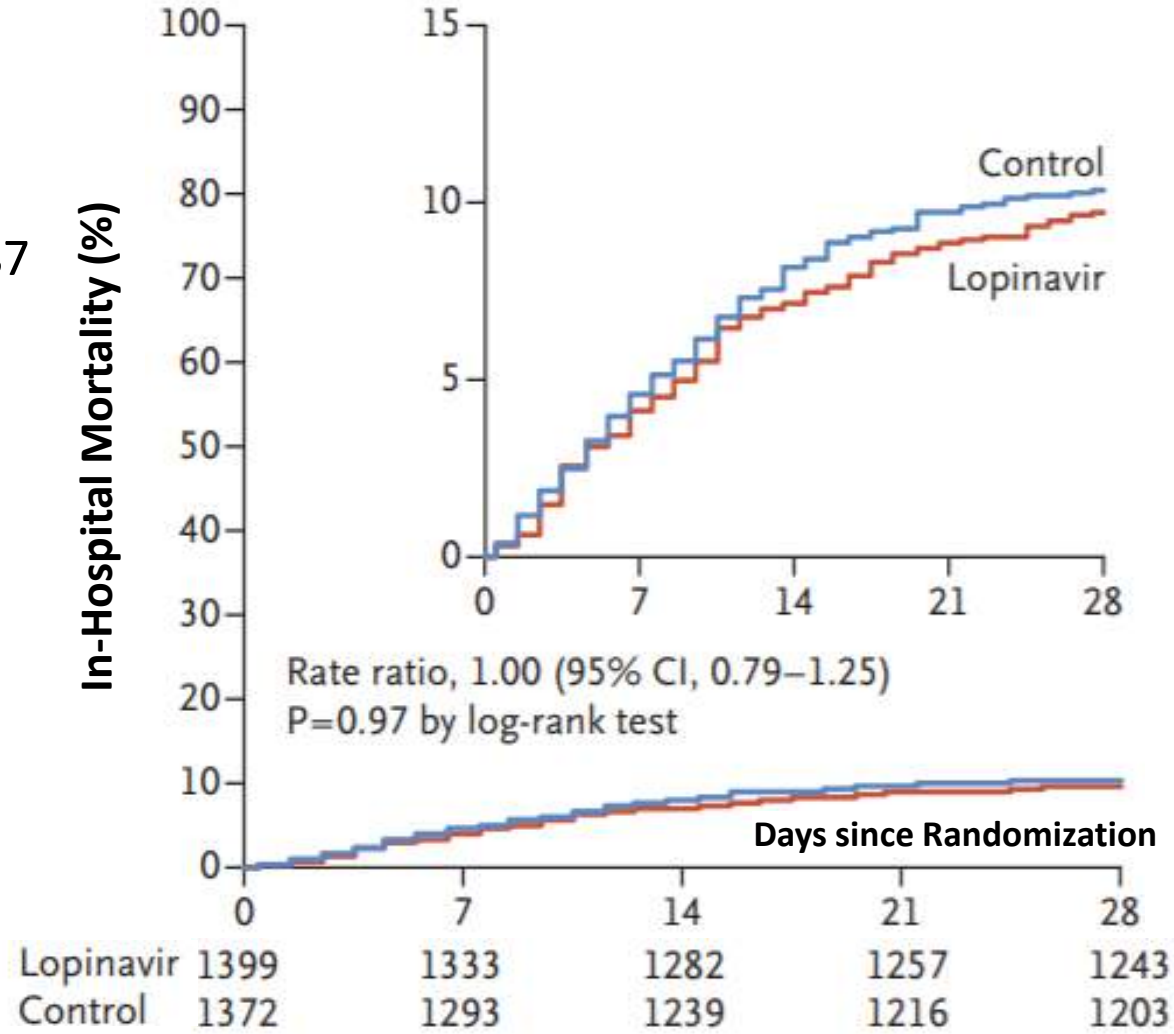
Anti viral effect

Lopinavir/ritonavir (LPVr)

- **All-cause mortality**: 148/1399 (9,7%) LPVr group *vs.* 146/1372 (10,3%) placebo group; rate ratio: 1,00; $CI_{95\%}$[0,79-1,25]; p= 0,97
- **Initiation of mechanical ventilation**: LPVr group: 126/1287 (9,8%) *vs*. control group 121/1258 (9,6%)
- **Time to discharge**: LPVr did not reduced hospitalization duration

Study stopped for futility on 4th July

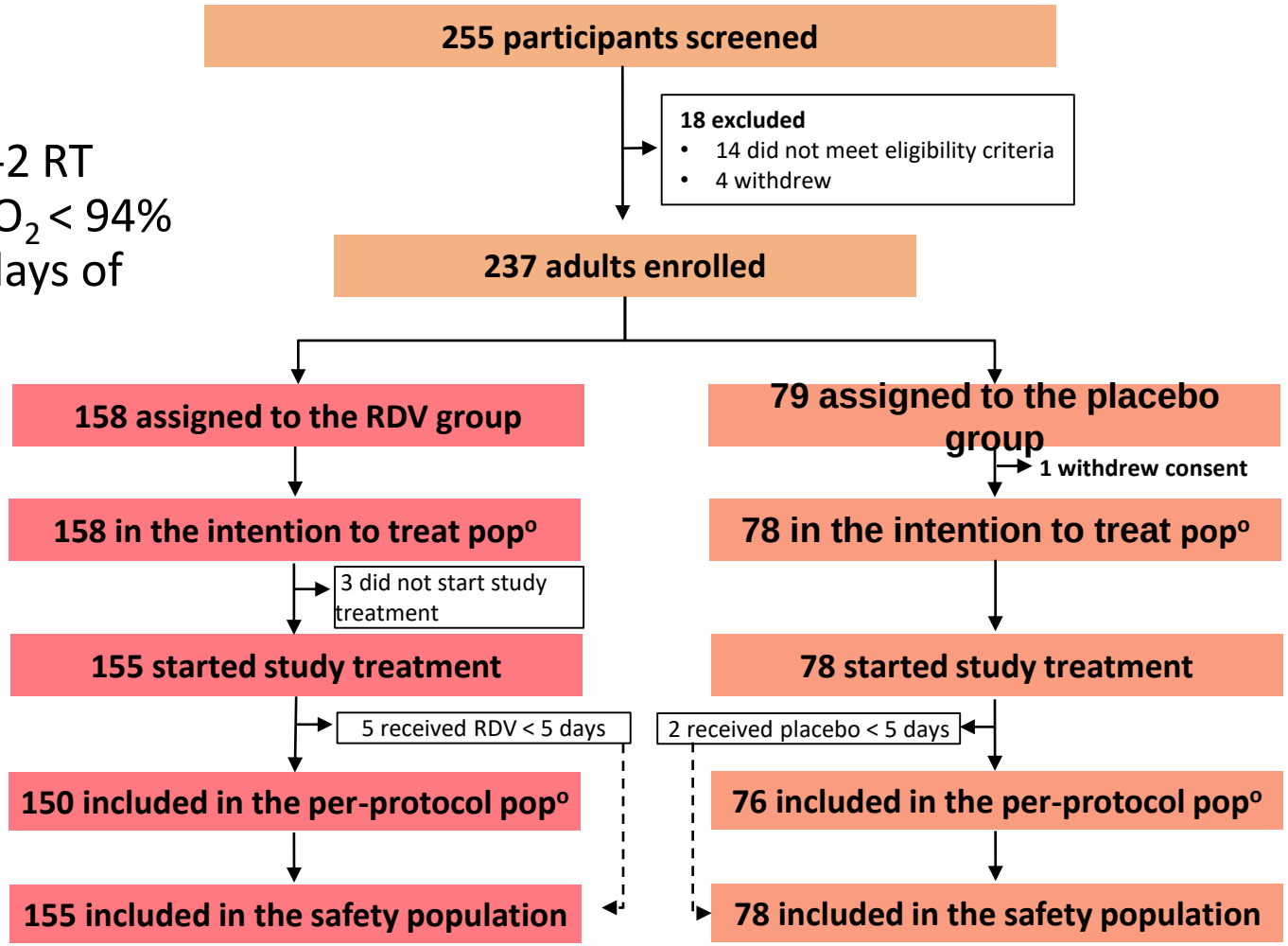




Anti viral effect

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 ≤ 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%)

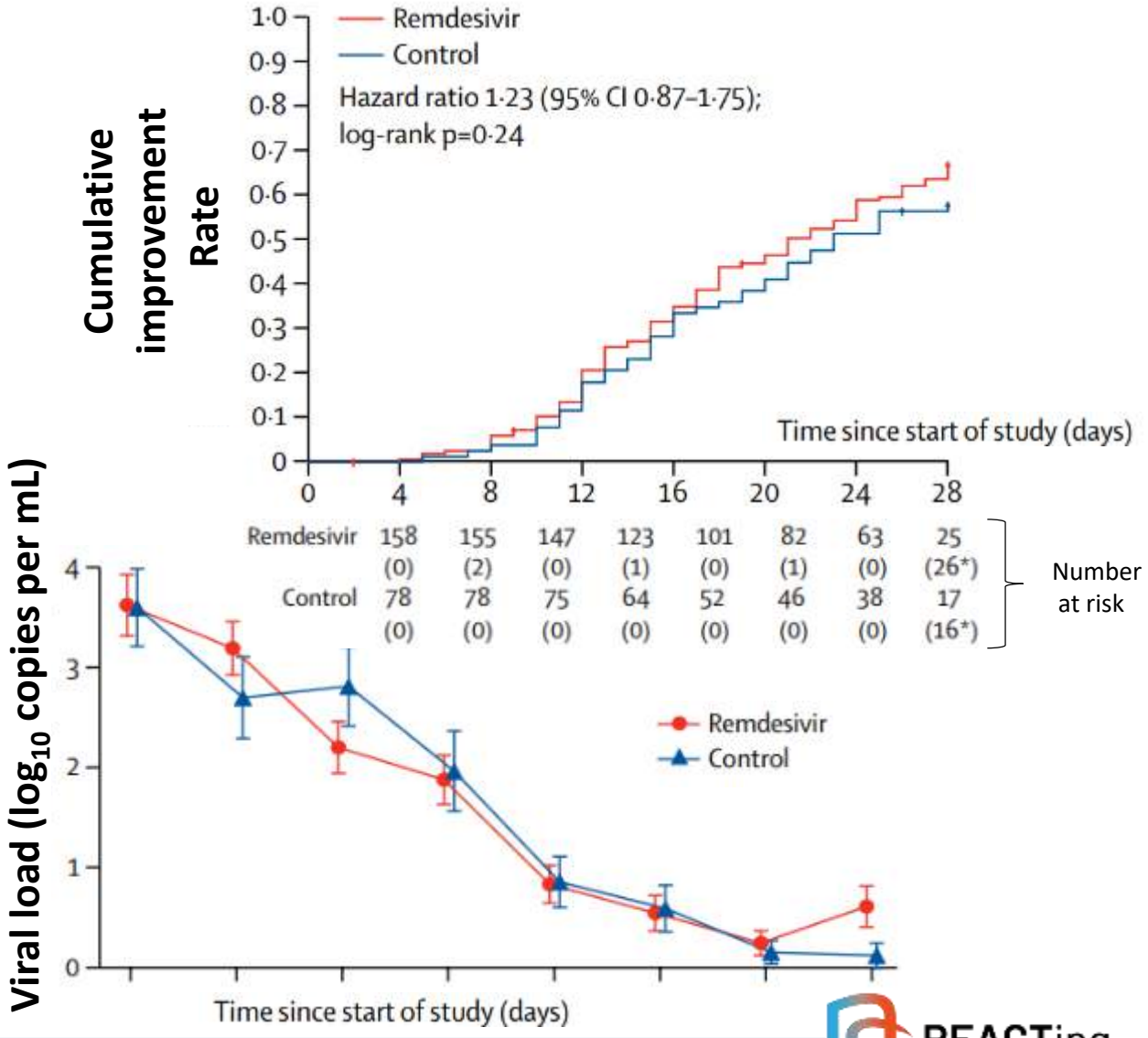
NP: nasopharyngeal
OP: oropharyngeal

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

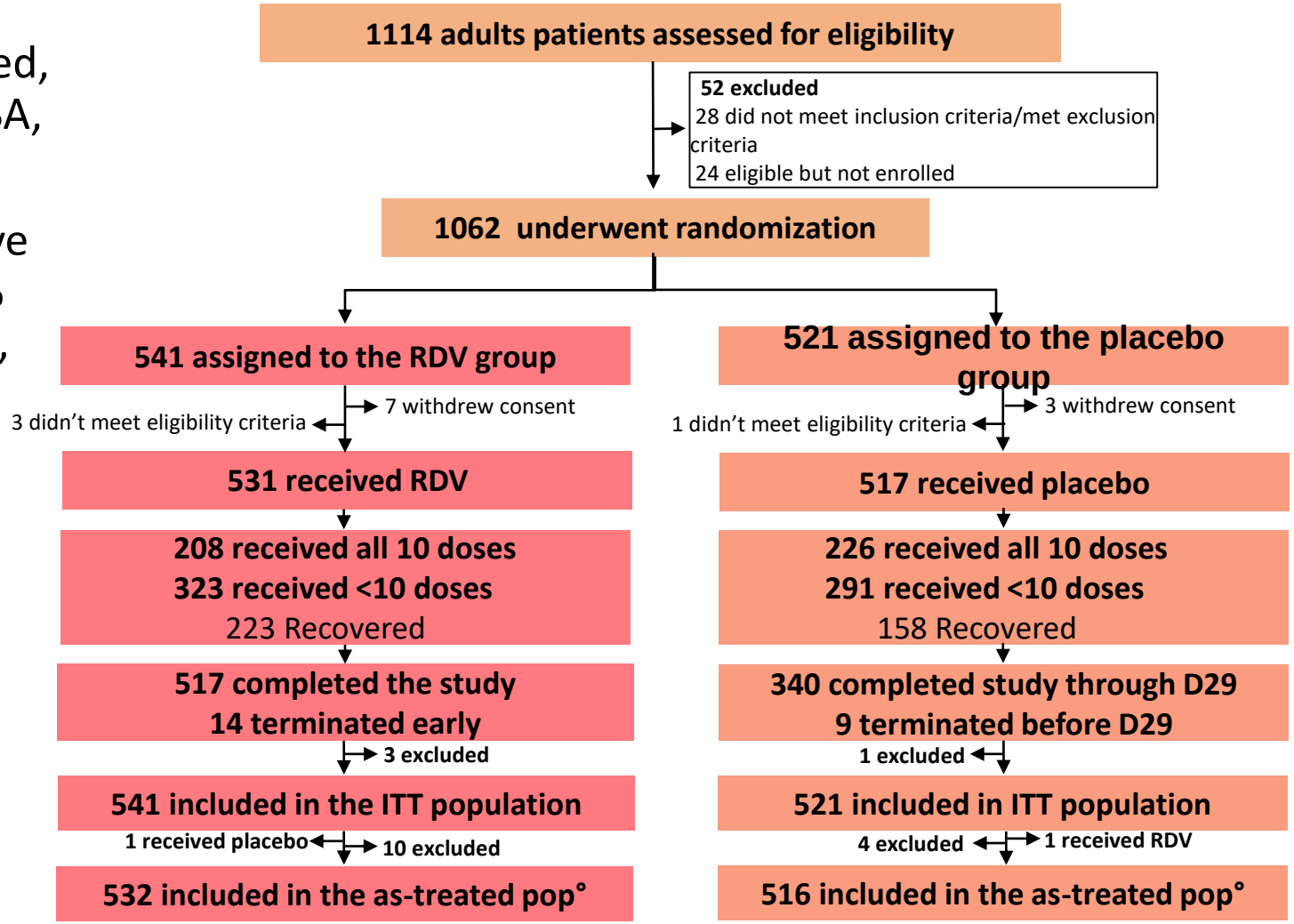


Wang Y *et al*. *Lancet* Apr 2020

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)



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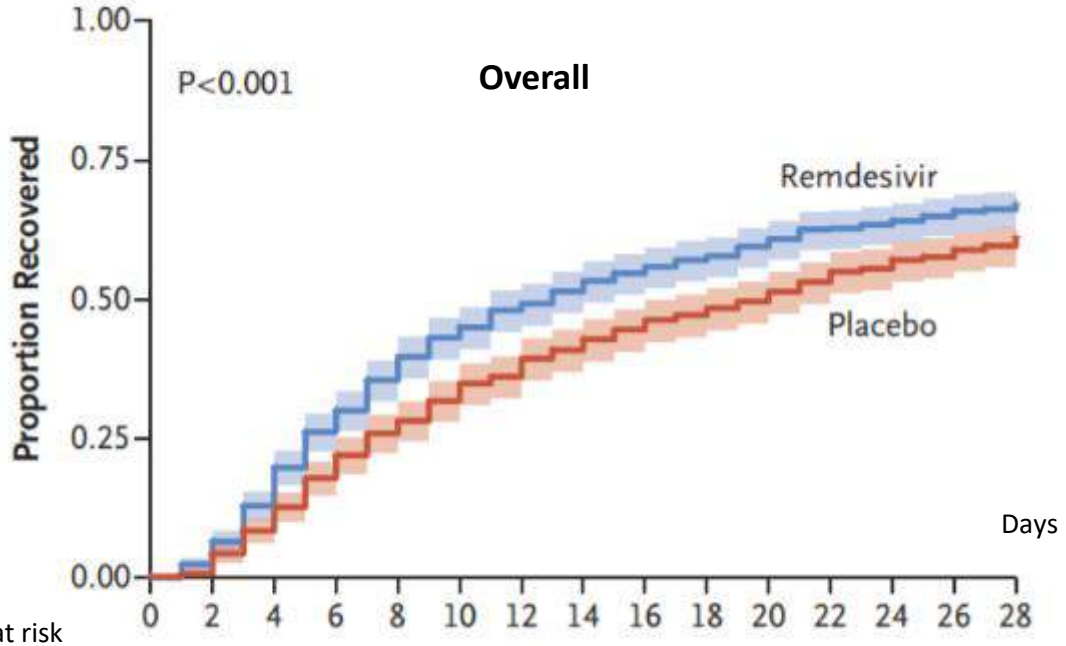
Beigel JH *et al*. *NEJM* Nov 2020

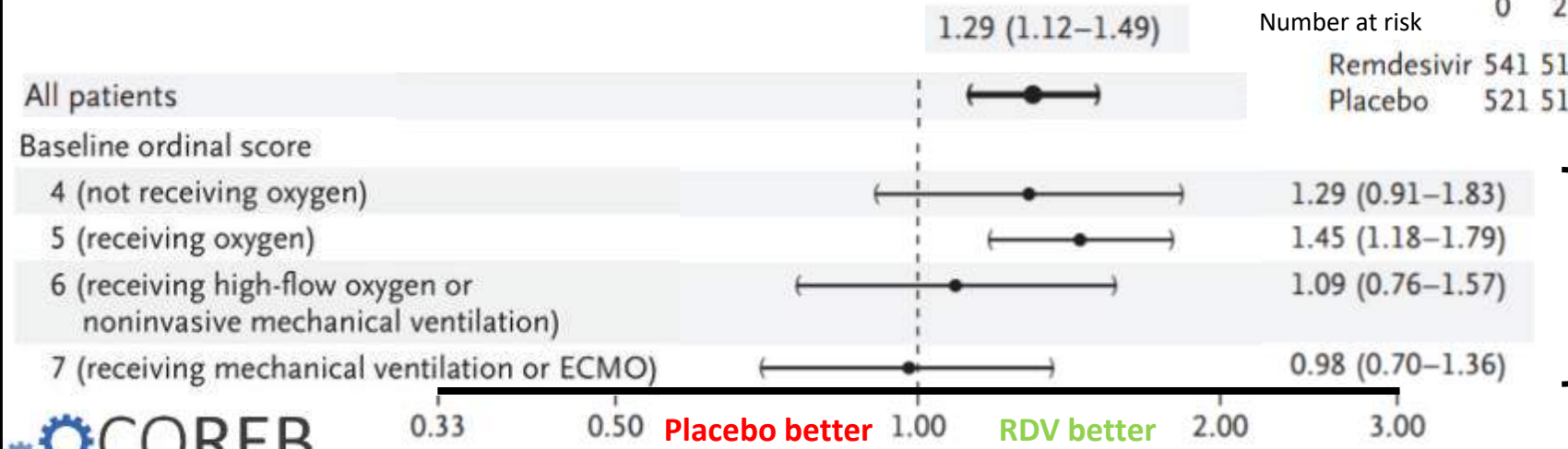
REACTing research & action targeting emerging infectious diseases

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





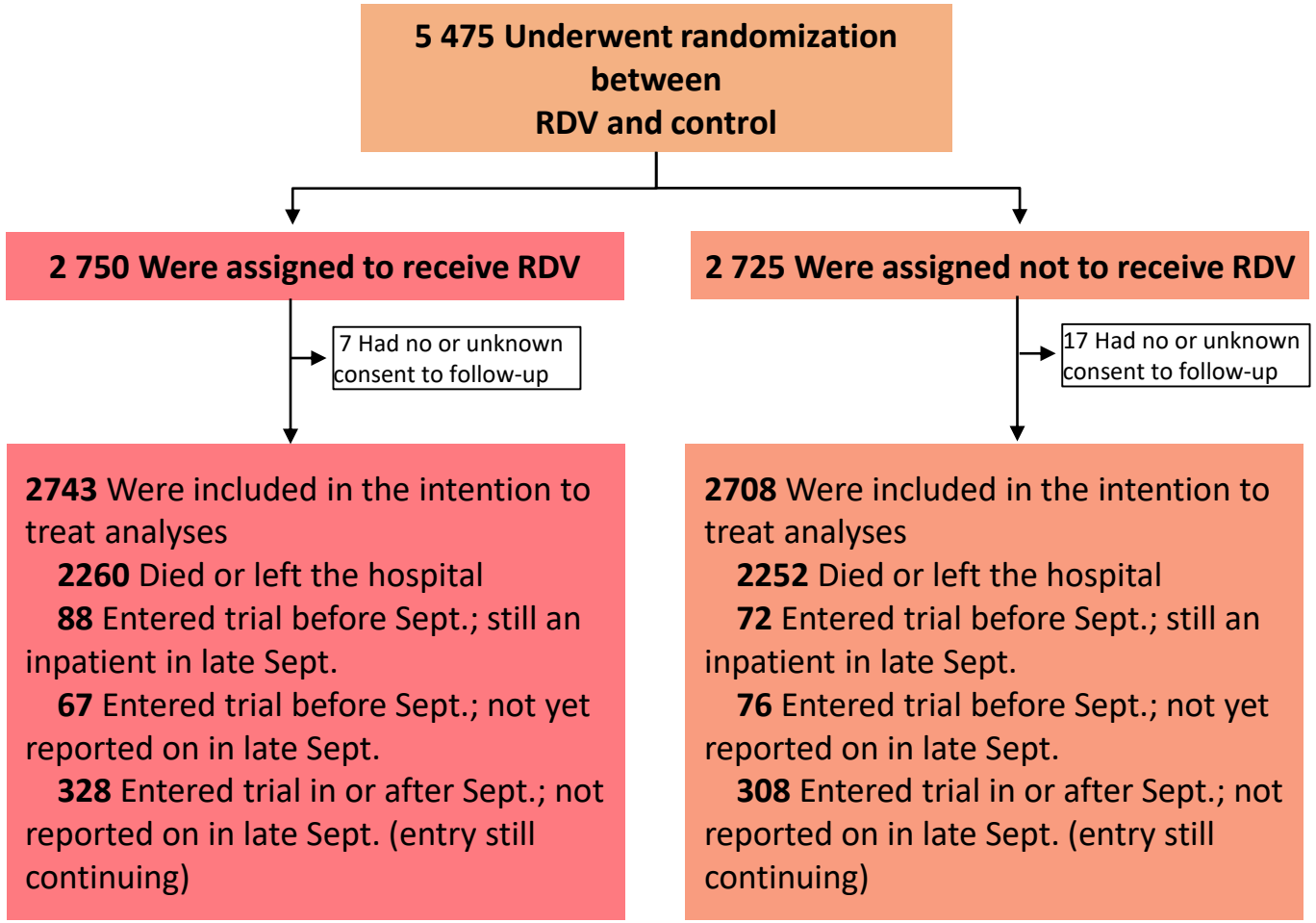
Recovery rate ratio $CI_{95\%}$

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

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

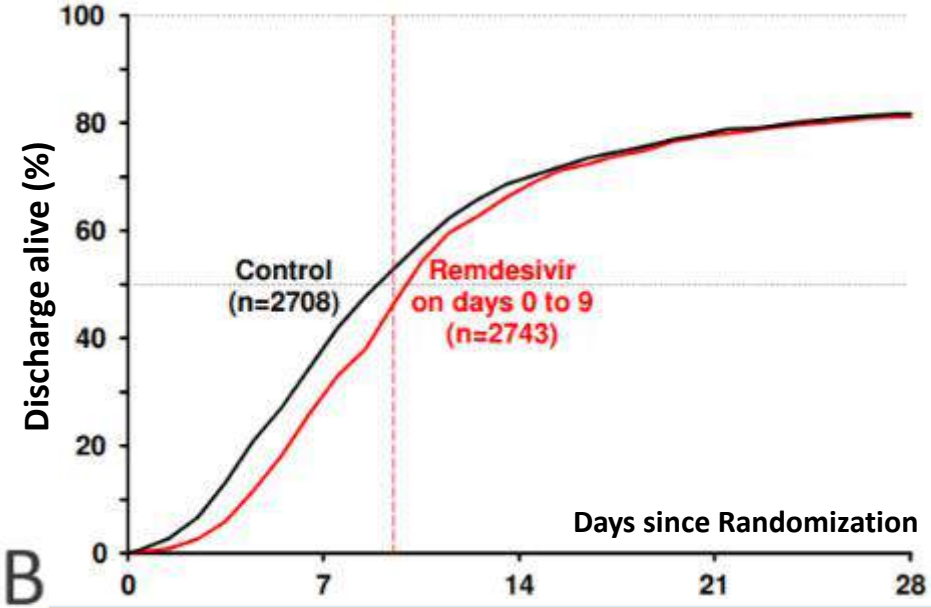
Remdesivir (RDV) - 3

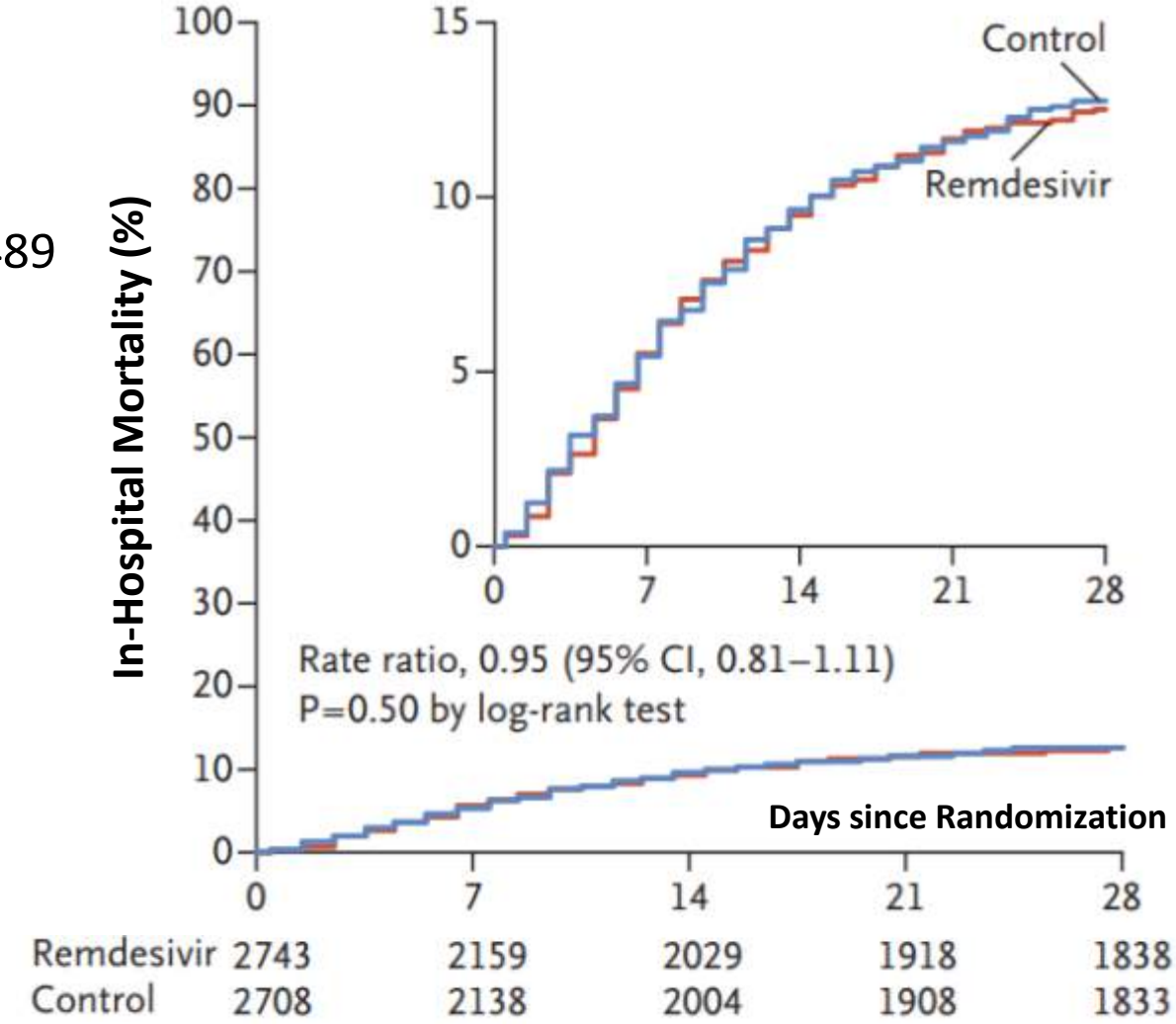
Characteristics		All (N= 11 266)	RDV (N= 2 743)	Control (N=2 708)
Age	< 50 yr – no (%)	3995 (35)	961	952
	50-69 yr – no (%)	5125 (45)	1282	1282
	≥ 70 yr – no (%)	2146 (19)	500	469
Sex	Male sex – no (%)	6985 (62)	1706	1725
Co existing conditions	Diabetes – no(%)	2768 (25)	707	666
	Heart disease – no (%)	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 IC $_{95\%}$[1,09-2,48]; p= 0,02

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

* Room air ** Mechanical ventilation
§ Median duration

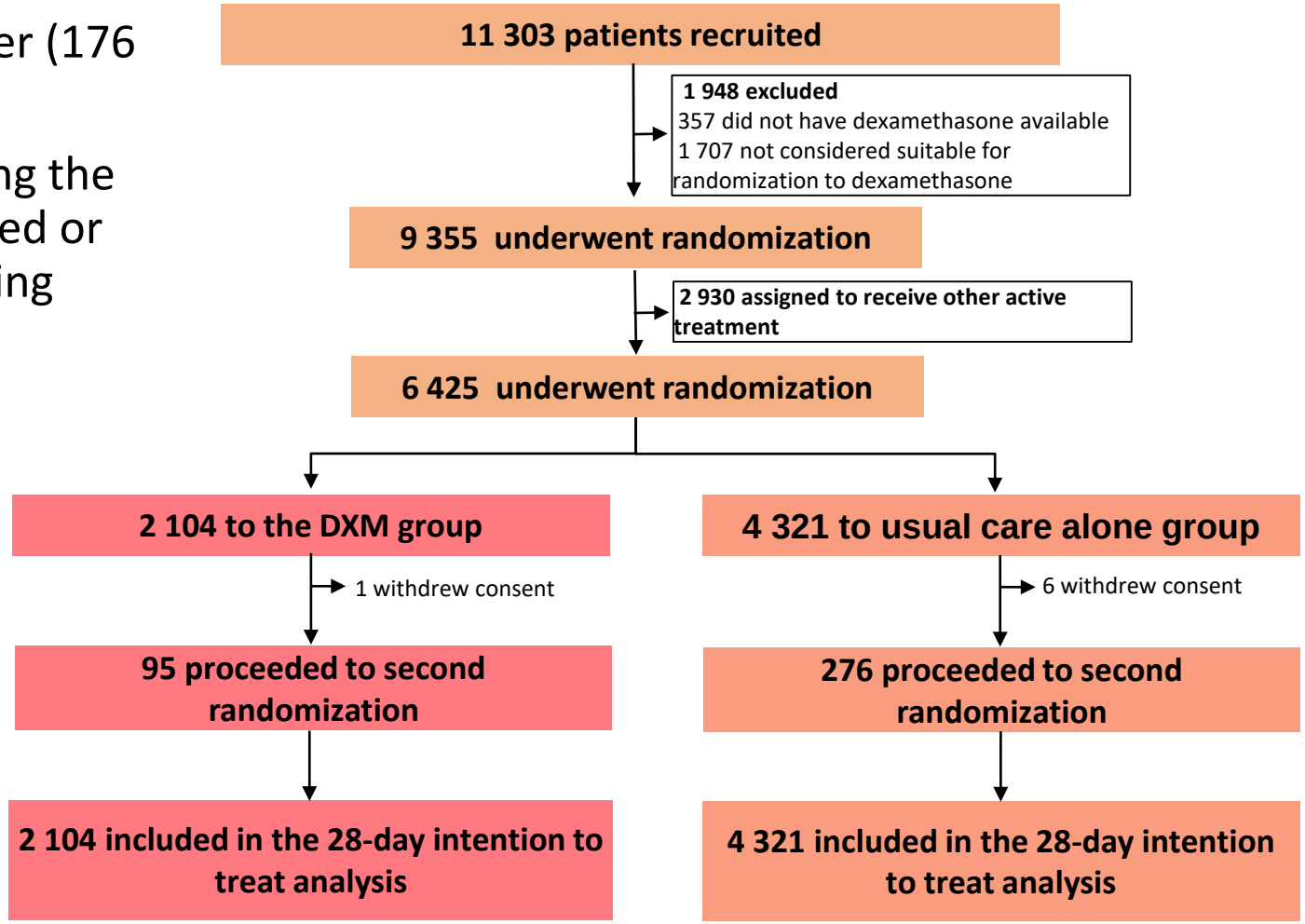
Spinner CD *et al*. *JAMA* Aug 2020
Goldman JD *et al*. *NEJM* Nov 2020

REACTing research & action targeting emerging infectious diseases

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)



Immunomodulatory effect

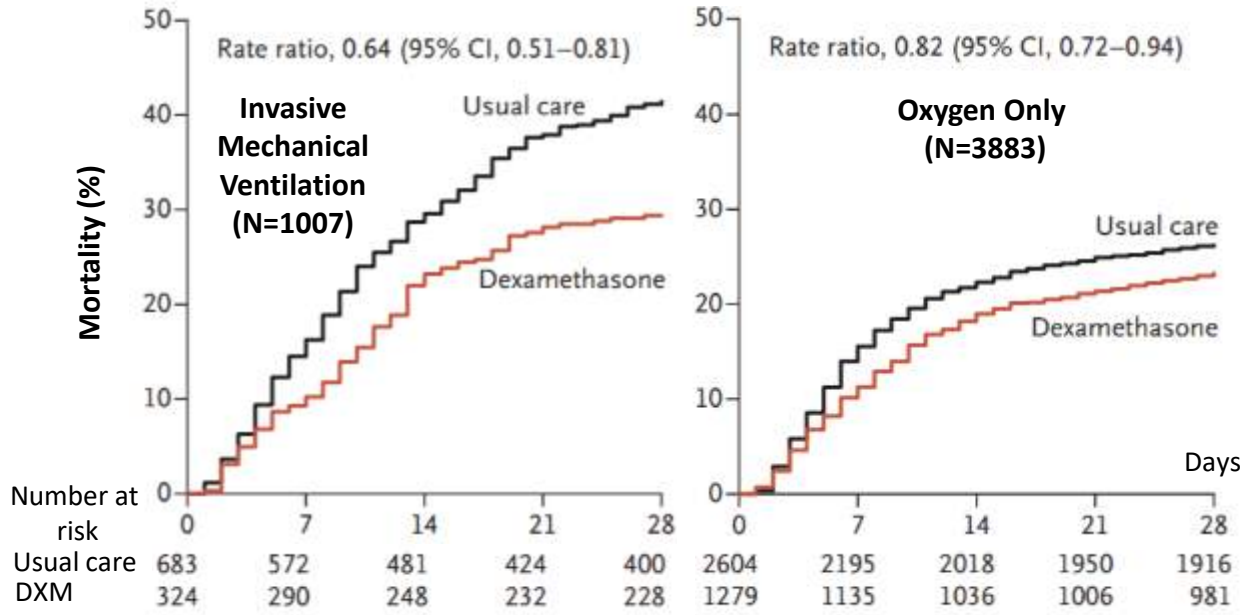
Corticosteroids (CT) - 1

	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)

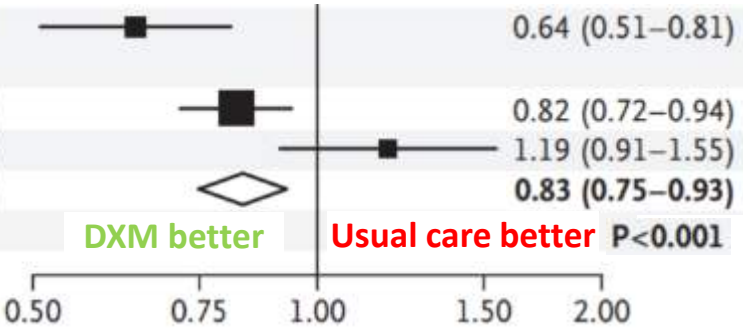
Immunomodulatory effect

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)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**

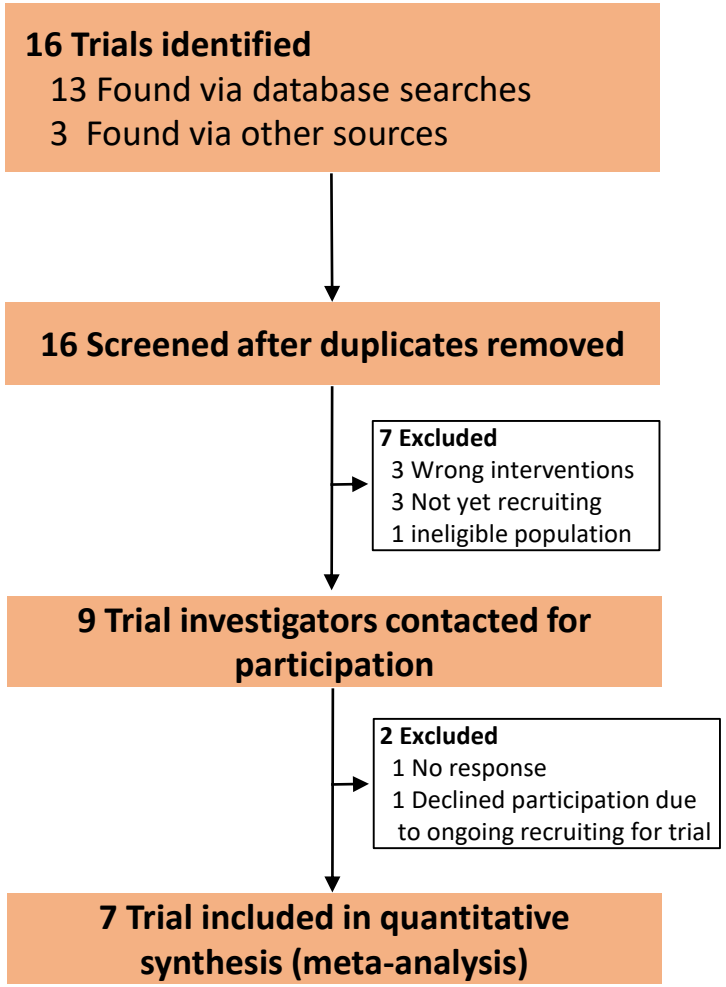


RECOVERY *collaborative group NEJM* Jul 2020

Immunomodulatory effect

Corticosteroids (CT) - 2

- Prospective Meta-analysis, academic study, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
- **Objective:** estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality
- **Primary outcome**: all-cause mortality at 28 days after randomization
- **Secondary outcome**: investigator-defined serious adverse events
- 1703 included participants; **678** (%) **corticosteroid group** (systemic dexamethasone, hydrocortisone, or methylprednisolone); **1025** (62%) **usual care or placebo group**



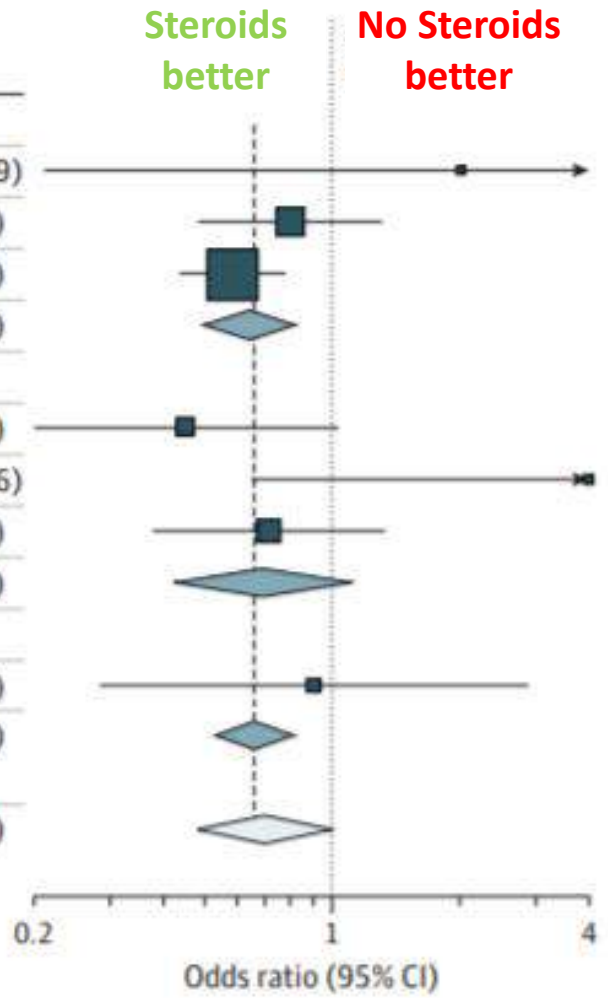
Sterne *et al. JAMA* Sep 2020

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 $CI_{95\%}$[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 $CI_{95\%}$[0,25-0,92], p= 0,025
					Death	SoC group 21 (26,3%) *vs.* CT group 18 (13,6%) OR: 0,45 $CI_{95\%}$[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 $CI_{95\%}$[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 $IC_{95\%}$ [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

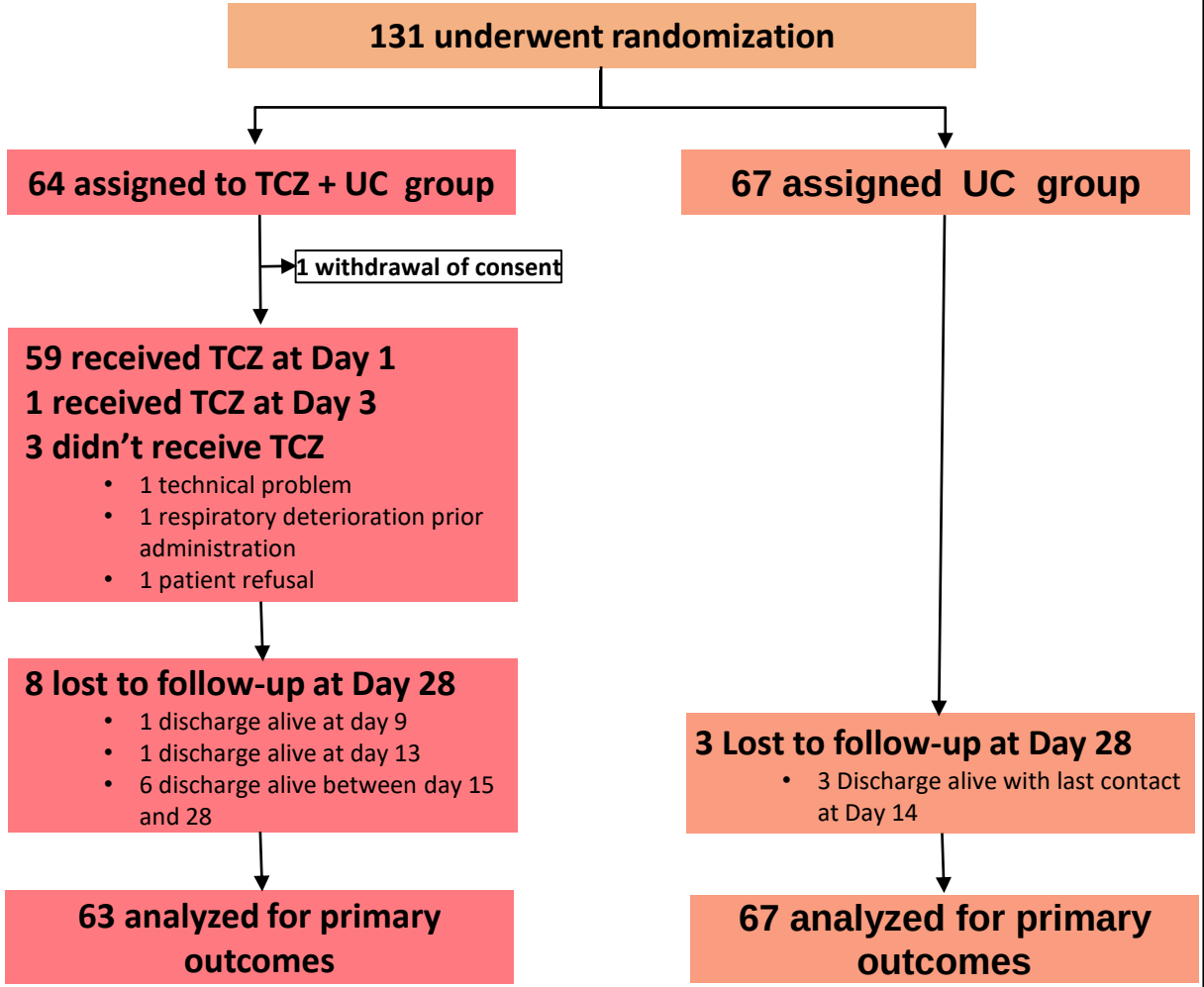
HC: hydrocortisone

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

Immunomodulatory effect

Tocilizumab (TCZ) - 1

- Multicenter, open-label, randomized, controlled clinical trial, academic study, France (CORIMUNO-TOCI 1 trial)
- **Inclusion criteria** : confirmed SARS-CoV-2 infection (positive RT-PCR and/or typical chest CT), moderate or severe pneumonia (at least 3 L/min of O_2, without ventilation) and patients with critical pneumonia (high-flow oxygen, non invasive ventilation (NIV) or MV)
- **Primary outcome**: scores >5 on the WHO 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival without need of ventilation at day 14
- **Secondary outcome**: overall survival, adverse events
- 154 participants; **76 usual care group, 78 TCZ + usual care group** (1:1)



UC: usual care
MV: mechanical ventilation

Hermine O *et al. JAMA Int Med* Oct 2020

Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 1

Characteristics	TCZ (N=63)	Usual care (N=67)
Age (y) – median (IQR)	64 (57,1-74,3)	63,3 (57,1-72,3)
Female sex – no (%)	19 (30)	23 (34)
BMI (kg/m²) – median (IQR)	27,9 (23,3-30,8)	27,4 (24,5-31,3)
Coexisting conditions		
Diabetes – no (%)	20/61 (33)	23/67 (34)
Chronic cardiac disease – no (%)	20/61 (33)	20/67 (30)
Chronic kidney disease – no (%)	5/61 (8)	13/67 (19)
Other		
Time from symptoms onset to randomization – days – median (IQR)	10 (7-13)	10 (8 – 13)
Respiratory rate – median (IQR), bpm	24 (22-30)	26 (24-30)
Flow – median (IQR), L/min	5 (3-8)	5 (3-6)
Patients who received CT during the trial – no (%)	21 (33%)	41 (61%)

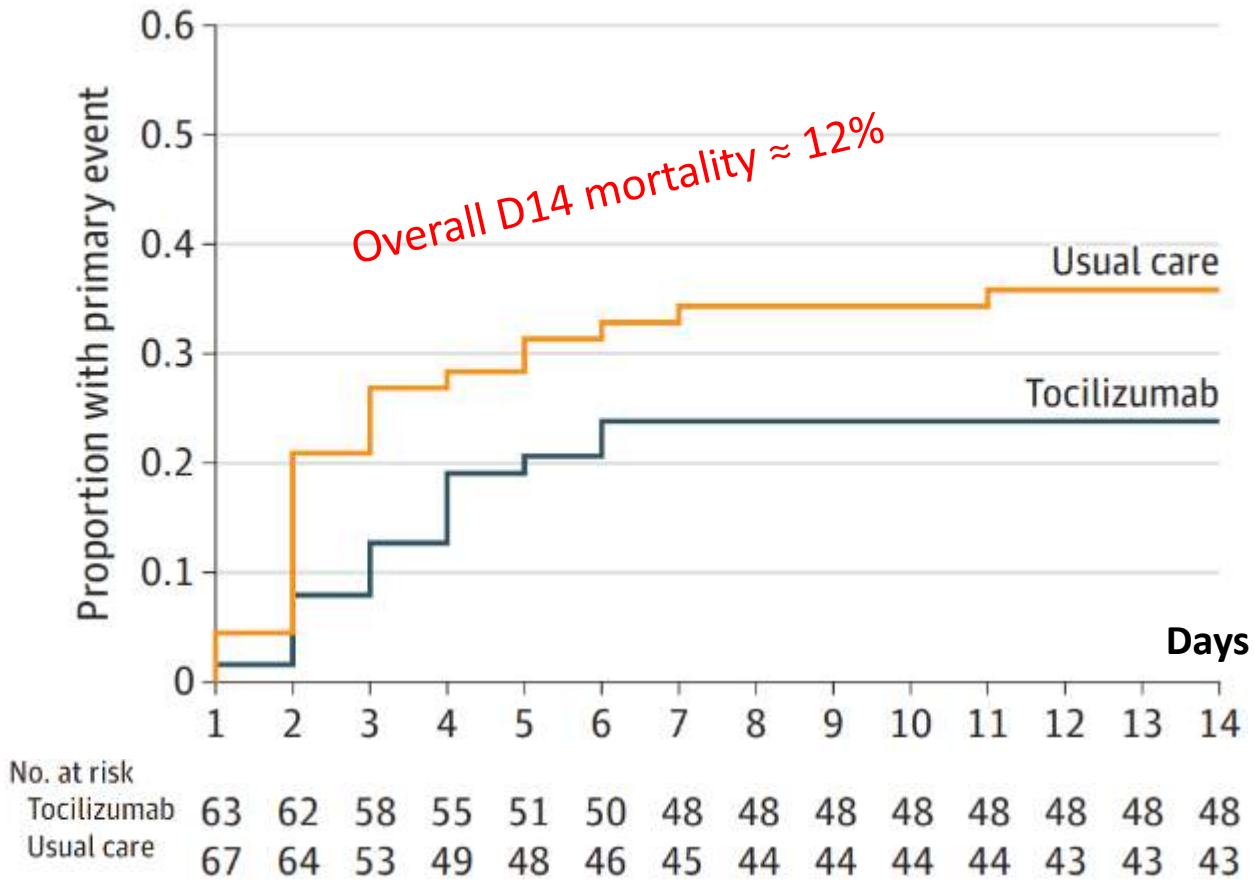
Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 1

- **Day 4 WHO-CPS scores >5** : 12/63 (19%) TCZ group *vs.* 19/67 (28%) UC group, median posterior absolute risk difference -9,0%; $CrI_{90\%}$[-21,0-3,1], **no difference**
- **Day 14 Primary outcome** : 15/63 (24%) TCZ group *vs.* 24/67 (36%) UC group. TCZ group: 12% fewer patients needed NIV or MV or died. Posterior probability of hazard ratio (HR) <1 of 95,0%, achieving the predefined efficacy threshold. MV or death HR: 0,58; $CrI_{90\%}$[0,33-1,00]
- **D28 survival** : 7/63 TCZ group *vs.* 9/67 UC group, adjusted HR: 0,92; $CI_{95\%}$[0,33-2,53], **no difference**
- **Serious adverse events** : 20/63 (32%) TCZ group *vs.* 29/67 (43%) UC group; p=0,21
- **Limits:** not a blind study, UC may have differed among centers and over time

Probability of primary outcome at day 14



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

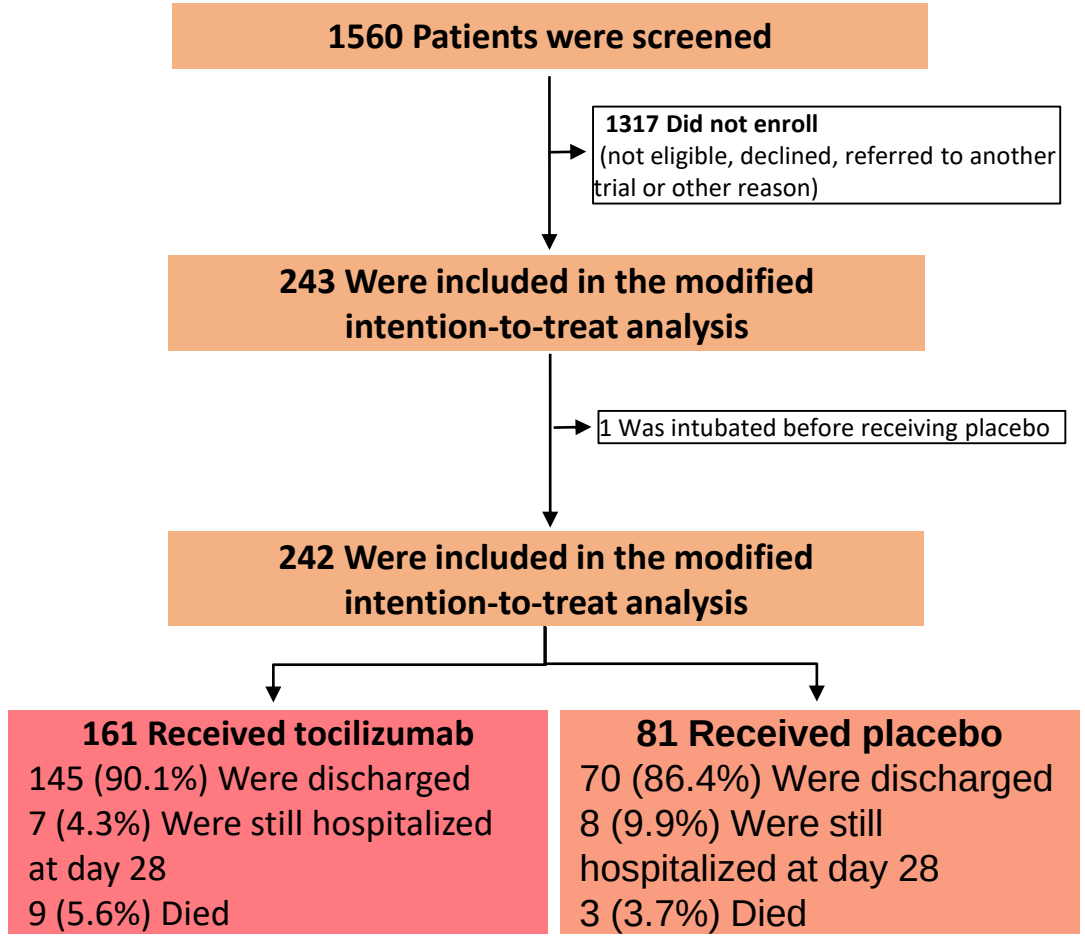
Hermine O *et al. JAMA Int Med* Oct 2020

Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 2

- Randomized, double-blind, placebo-controlled, multicenter, USA (BACC Bay Tocilizumab Trial)
- **Inclusion criteria** : age 18-85 yo, confirmed SARS-CoV-2 infection (nasopharyngeal swab RT-PCR or serum IgM antibody assay), fever or pulmonary infiltrates or a need for O_2 to maintain SpO_2 > 92%, CRP > 50mg/L or ferritin > 500 ng/mL or D-dimer > 1000 ng/mL or LDH > 250 U/L
- **Exclusion criteria** : supplemental O_2 > 10L/min, history of biologic agents treatment or immunosuppressive therapy or diverticulitis
- **Primary outcome**: intubation or death after TCZ or placebo administration
- **Secondary outcome**: clinical worsening on ordinal scale
- 242 participants; **161 TCZ + standard care group, 81 placebo group** (2:1)



Stone JH *et al. NEJM* Dec 2020

Immunomodulatory effect

Tocilizumab (TCZ) - 2

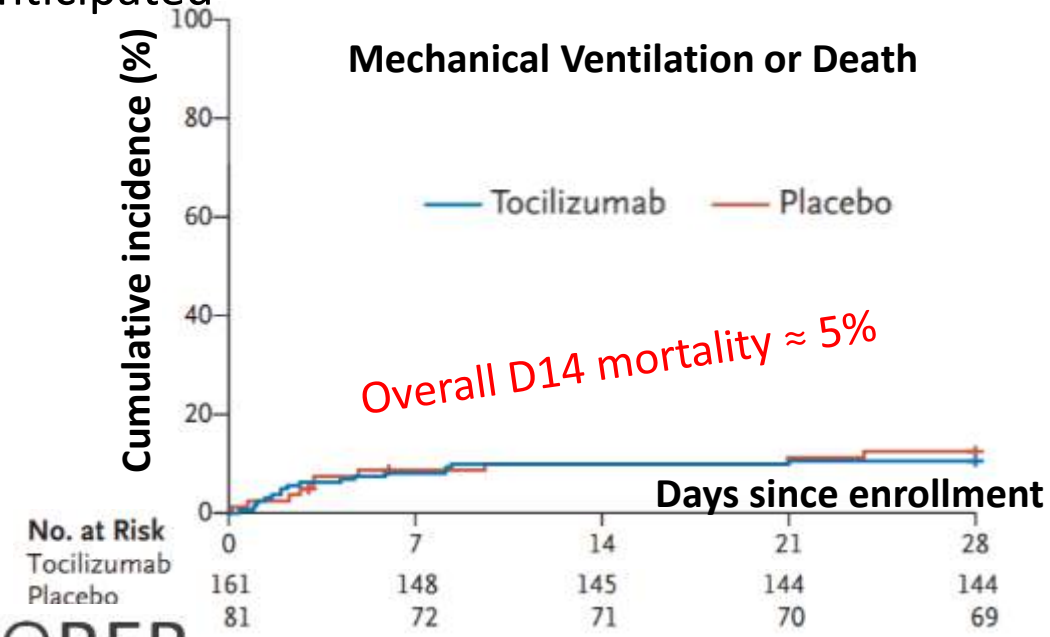
Characteristics	TCZ (N=161)	Placebo (N=82)	Overall (N=243)
Age (y) – median (IQR)	61,6 (46,4-69,7)	56,5 (44,7-67,8)	59,8 (45,3-69,4)
Male sex – no (%)	96 (60)	45 (55)	141 (58)
BMI (kg/m²) – median (IQR)	29,9 (26,0–34,2)	30,2 (25,7–33,8)	30,1 (25,9–34,2)
Median time from symptom onset to randomization (IQR) — days	9,0 (6,0–13,0)	10,0 (7,0–13,0)	9,0 (6,0–13,0)
Patients who received CT during the trial – no (%)	18 (11%)	5 (6%)	23 (9,5)
Coexisting conditions			
Diabetes – no (%)	45 (28)	30 (37)	75 (31)
Hypertension – no (%)	80 (50)	38 (46)	118 (49)
Chronic kidney disease – no (%)	29 (18)	13 (16)	42 (17)
Ordinal scale score — no. (%)			
2	23 (14)	15 (18)	38 (16)
3	133 (83)	61 (74)	194 (80)
4	5 (3)	5 (6)	10 (4)

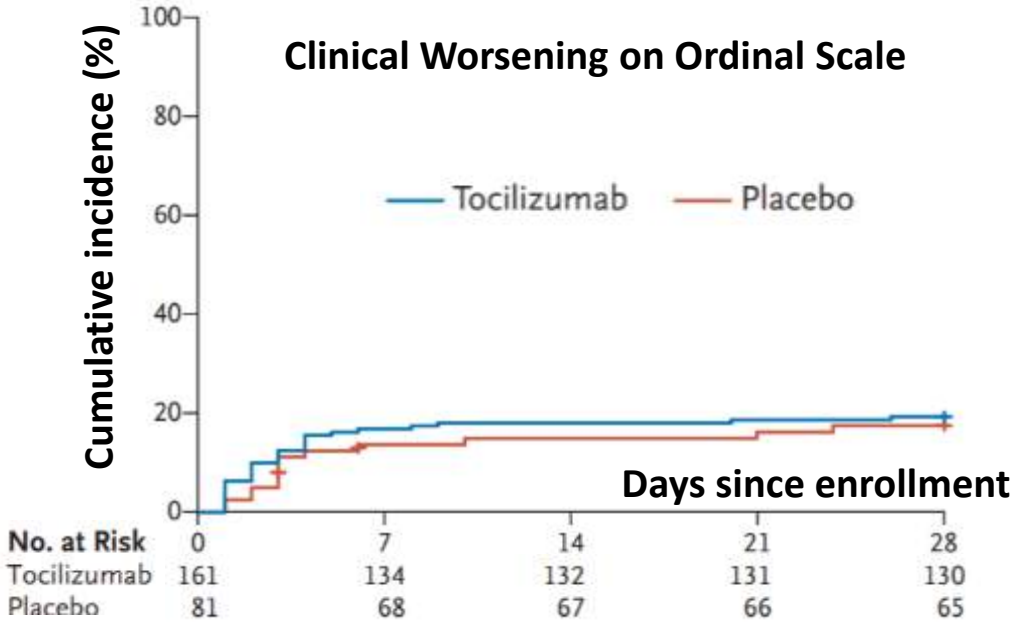
Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 2

- **Mechanical ventilation or death**: 10,6% $CI_{95\%}$[6,7–16,6] TCZ group *vs.* 12,5% $CI_{95\%}$[6,9–22,0] placebo group, Hazard ratio: 0,83 $CI_{95\%}$[0,38–1.81], p=0,64
- **Clinical worsening on ordinal scale**: 19,3% $CI_{95\%}$[14,0–26,2] TCZ group *vs.* 17.4% $CI_{95\%}$[10,7–27,7] placebo group, Hazard ratio: 1,11 $CI_{95\%}$[0,59–2,10], p=0,73
- **Limits:** Remdesivir became available early in the trial, primary event rate we observed was lower than anticipated





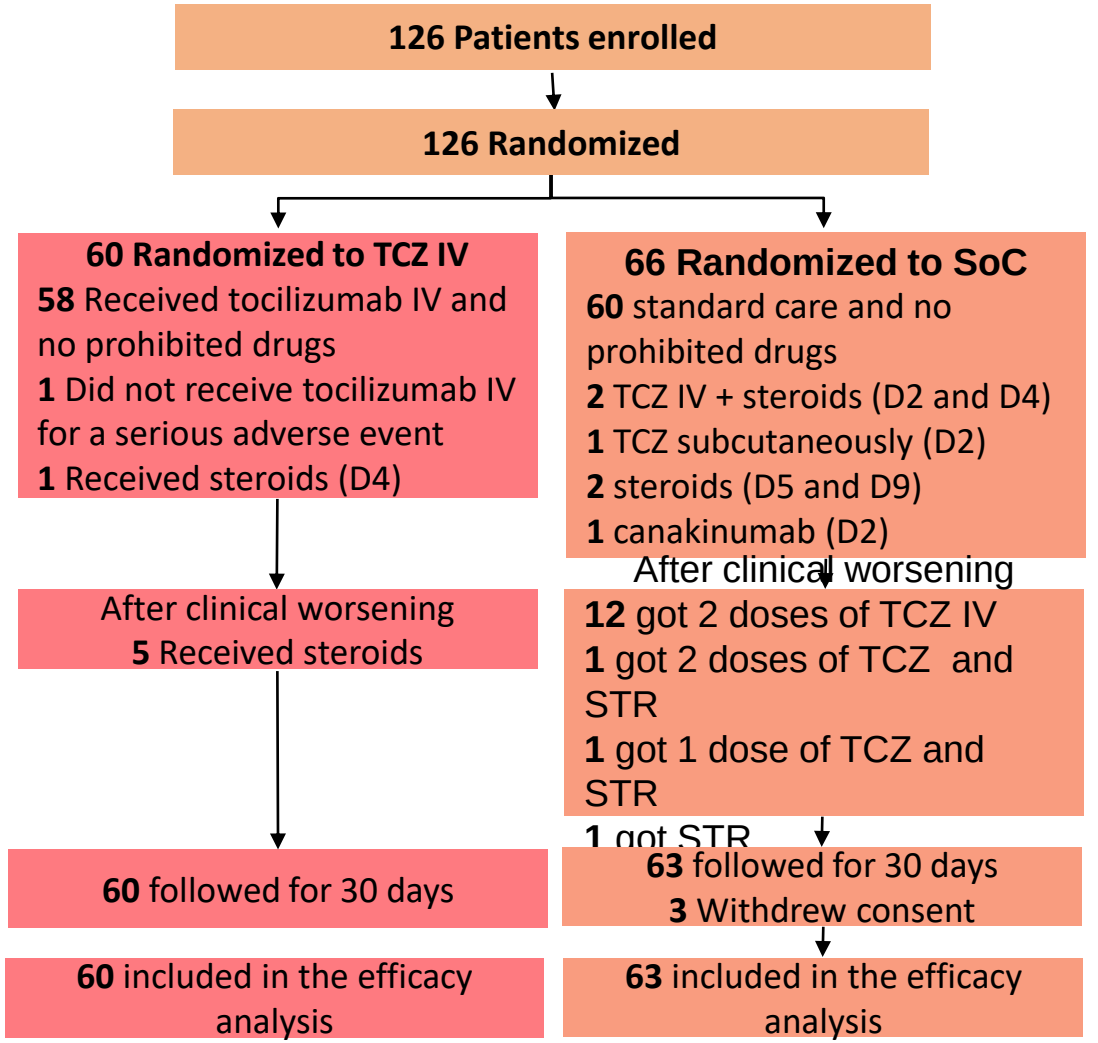
Stone JH *et al. NEJM* Dec 2020

Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 3

- Prospective, open-label, randomized, multicenter, academic study, Italy (RCT-TCZ-COVID-19 trial)
- **Inclusion criteria**: hospitalized patients, age ≥ 18 yo, confirmed COVID-19 pneumonia (positive SRAS-CoV-2 PCR), acute respiratory failure (PaO_2/FiO_2 [200-300mmHg]), fever > 38°C for at least 48h and/or CRP ≥ 100mg/L
- **Exclusion criteria** : patient receiving at enrollment mechanical ventilation, TCZ hypersensitivity
- **Primary outcome**: clinical worsening within 14 days since randomization (occurrence of one of these events: entry into ICU with IMV or death from any causes or clinical aggravation (PaO_2/FiO_2 < 150 mmHg))
- **Secondary outcome** (one of them): hospital discharge rates
- 126 participants; **60 TCZ group, 63 standard of care group** (1:1)



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

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

Immunomodulatory effect

Tocilizumab (TCZ) - 3

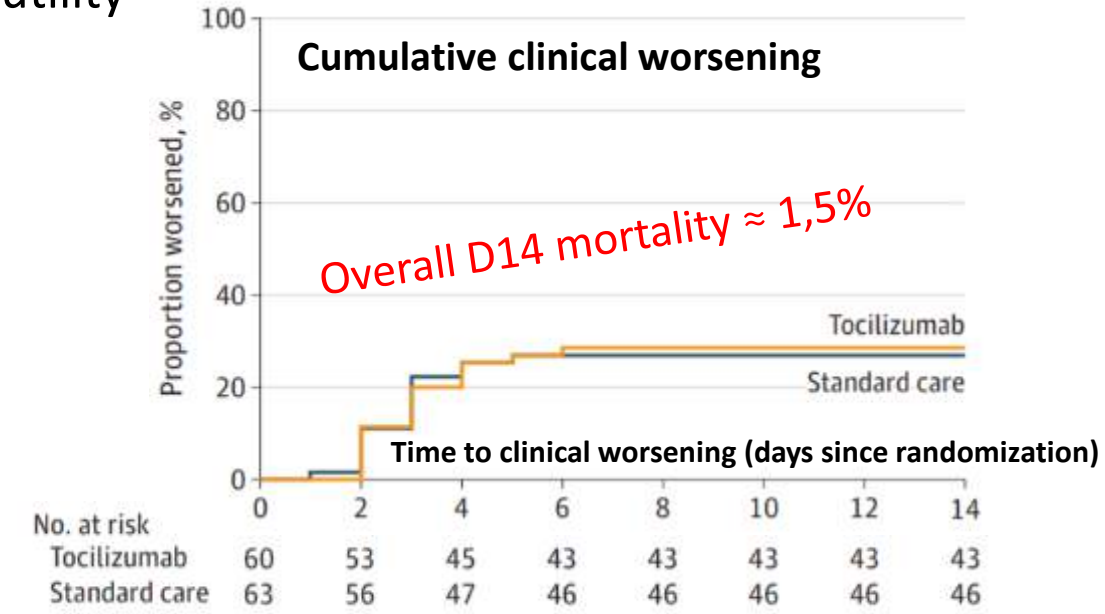
Characteristics	TCZ (N=60)	SoC (N=66)	Overall (N=126)
Age (y) – median (IQR)	61,5 (51,5-73,5)	60,0 (54,0-69,0)	60,0 (53,0-72,0)
Male sex – no (%)	40 (66,7)	37 (56,1)	77 (61,1)
BMI ≥ 30 kg/m² – no (%)	16 (28,1)	22 (36,1)	38 (32,2)
Coexisting conditions			
Diabetes – no (%)	10 (16,7)	9 (13,6)	19 (15,1)
Hypertension – no (%)	27 (45)	29 (43,9)	56 (44,4)
COPD – no (%)	2 (3,3)	13 (16)	42 (17)
Others			
Median time from symptom onset to randomization (IQR) - days	7,0 (4,0-11,0)	8,0 (6,0-11,0)	8,0 (6,0–11,0)
Median time from hospital admission to randomization (IQR) - days	2,0 (1,0-3,0)	2,0 (1,0-4,2)	2,0 (1,0-3,2)
C-Reactive protein - median (IQR) - mg/L	105 (50-146)	65 (32-118)	82 (37-135)
Patients who received steroids during the trial – no (%)	6 (10)	7 (10,6)	13 (10,3)

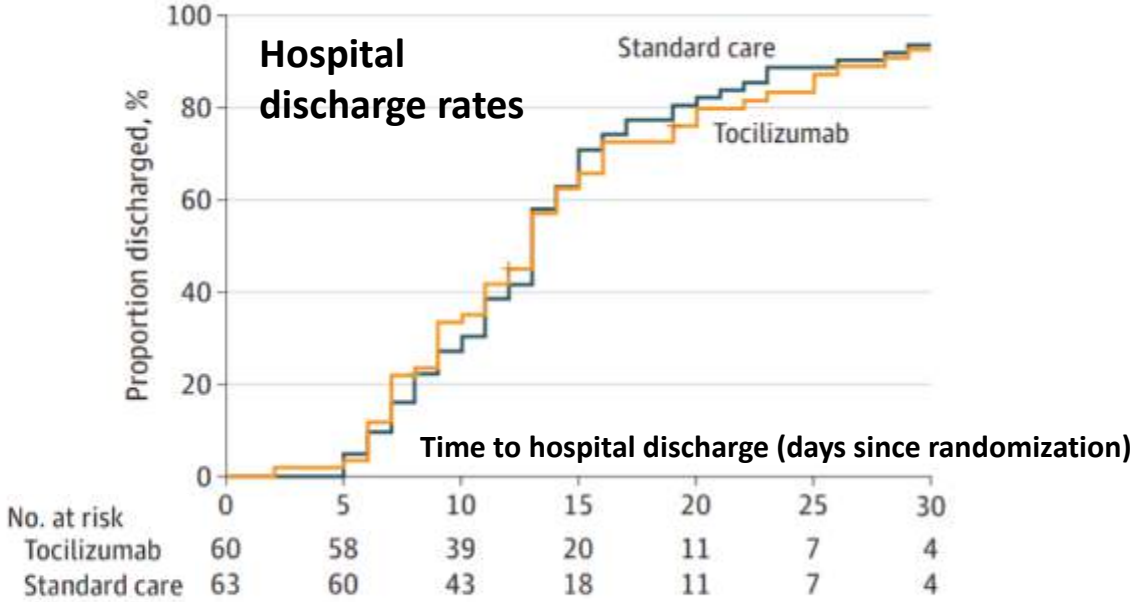
Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 3

- **Clinical worsening within 14 days since randomization**: 17/60 (28,3%) TCZ group *vs.* 17/63 (27%) SoC group, Rate ratio 1,05; $CI_{95\%}$[0,59-1,86] p=0,87, **no difference**
- **Hospital discharge rates** : 54/60 (90%) TCZ group *vs.* 58/63 (92,1%) SoC group. Rate ratio 0,98; $CI_{95\%}$[0,87-1,09], **no difference**
- **Limits:** not a double-blind placebo-controlled trial, prematurely interrupted after an interim analysis for futility





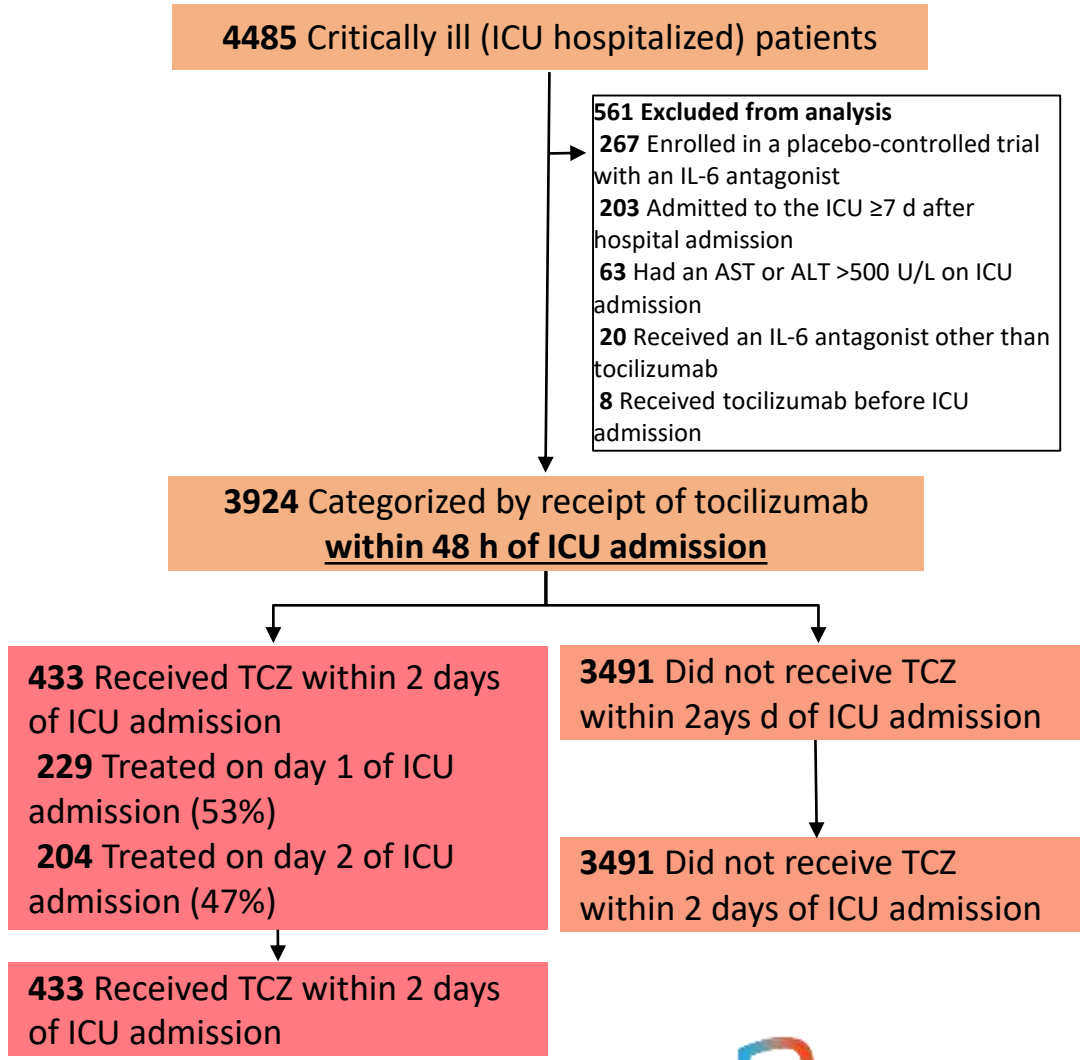
Salvarani C *et al. JAMA Int Med* Oct 2020

Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 4

- Multicenter cohort, academic study, USA (STOP-COVID trial)
- **Inclusion criteria**: ICU hospitalized patients, age ≥ 18 yo, laboratory confirmed COVID-19
- **Exclusion criteria**: hospitalization for 1 week or more before ICU admission, liver dysfunction, got IL-6 antagonist other than TCZ during the first 2 days of ICU, got TCZ before ICU admission
- **Primary outcome**: in-hospital death
- **Secondary outcome**: incidence of secondary infection, transaminitis, arrhythmias, and thrombotic complications occurring within 14 days after ICU admission
- 3 924 participants; **433 TCZ group, 3491 no TCZ group**



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

Gupta S *et al. JAMA Int Med* Oct 2020

Immunomodulatory effect

Tocilizumab (TCZ) - 4

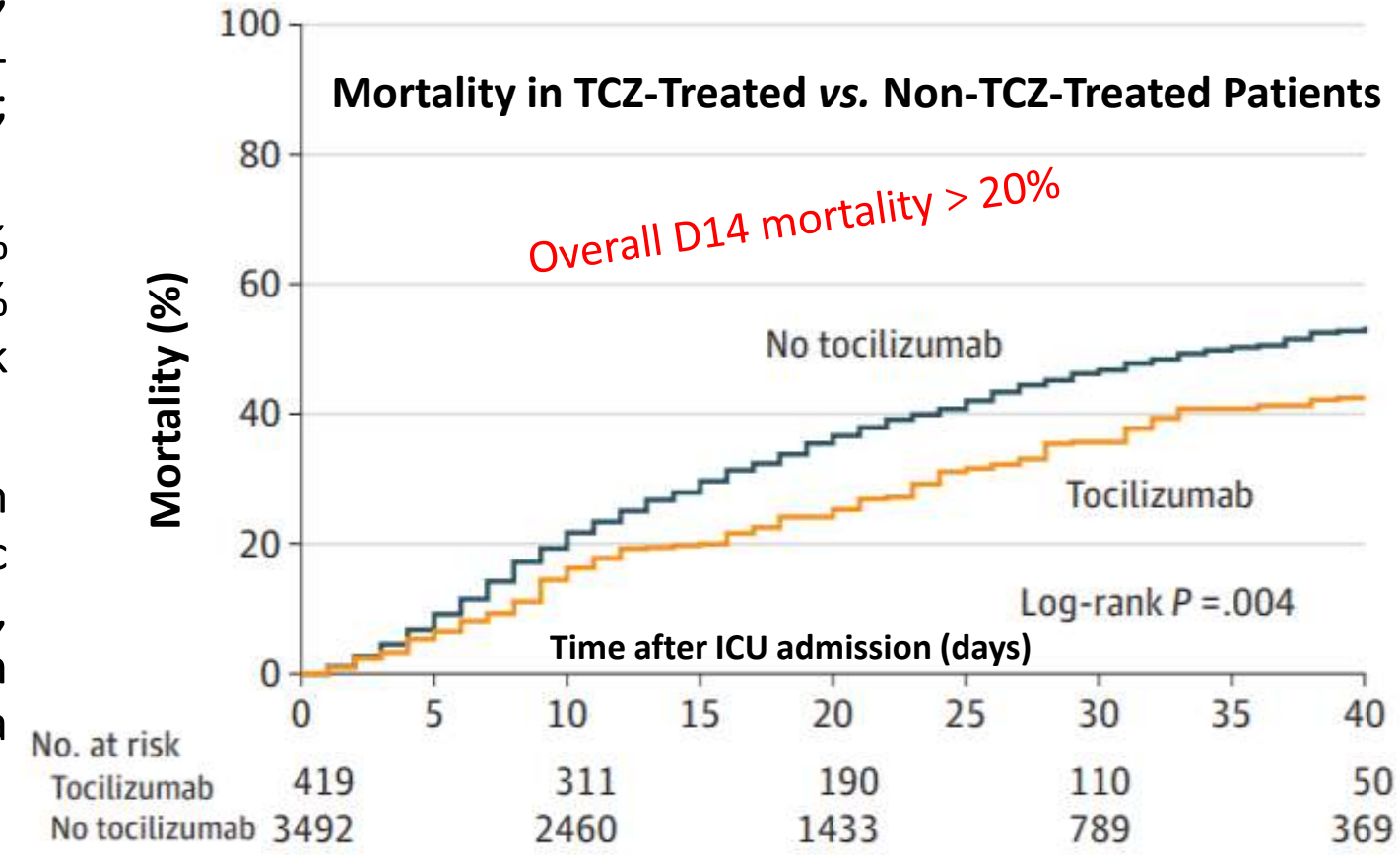
Characteristics	TCZ (N=433)	No TCZ (N=3 491)
Age (y) – median (IQR)	58 (48-65)	63 (52-72)
Male sex – no (%)	299 (69,1)	2165 62)
BMI (kg/m²) – median (IQR)	31,6 (27,5-37,0)	30,4 (26,3-35,9)
Coexisting conditions		
Diabetes – no (%)	165 (38,1)	1464 (41,9)
Hypertension – no (%)	234 (54)	2186 (62,6)
Coronary artery disease – no (%)	39 (9)	504 (14,4)
Others		
PiO_2/FiO_2 < 200 (mmHg) — no (%)	205 (47,3)	1322 (37,9)
Time from symptom onset to ICU admission ≤ 3 days – no	58 (13,4)	835 (23,9)
Fever (>38 °C) on ICU admission — no (%)	207 (47,8)	1647 (47,2)
Treated with any Steroid (%)	81 (18,7)	440 (12,6)

Immunomodulatory effect

Monoclonal antibody

Tocilizumab (TCZ) - 4

- **In hospital death**: 1544 patients (39.3%) died; 125/433 (28,9%) TCZ group *vs.* 1419/3491 (40,6%) no TCZ group, adjusted HR: 0,71; $_{95\%}$CI[0,56-0,92]
- **Estimated 30-day mortality:** 27.5% $_{95\%}$CI[21.2%-33.8%] TCZ group *vs.* 37.1% $_{95\%}$CI[35.5%-38.7%] no TCZ group; risk difference: 9.6%; $_{95\%}$CI[3.1%-16.0%]
- **Limits:** TCZ group patient were younger with fewer comorbidities, were more hypoxemic with more elevated inflammatory markers, corticosteroids could have been concomitantly administrated to TCZ, data missed for some key variables



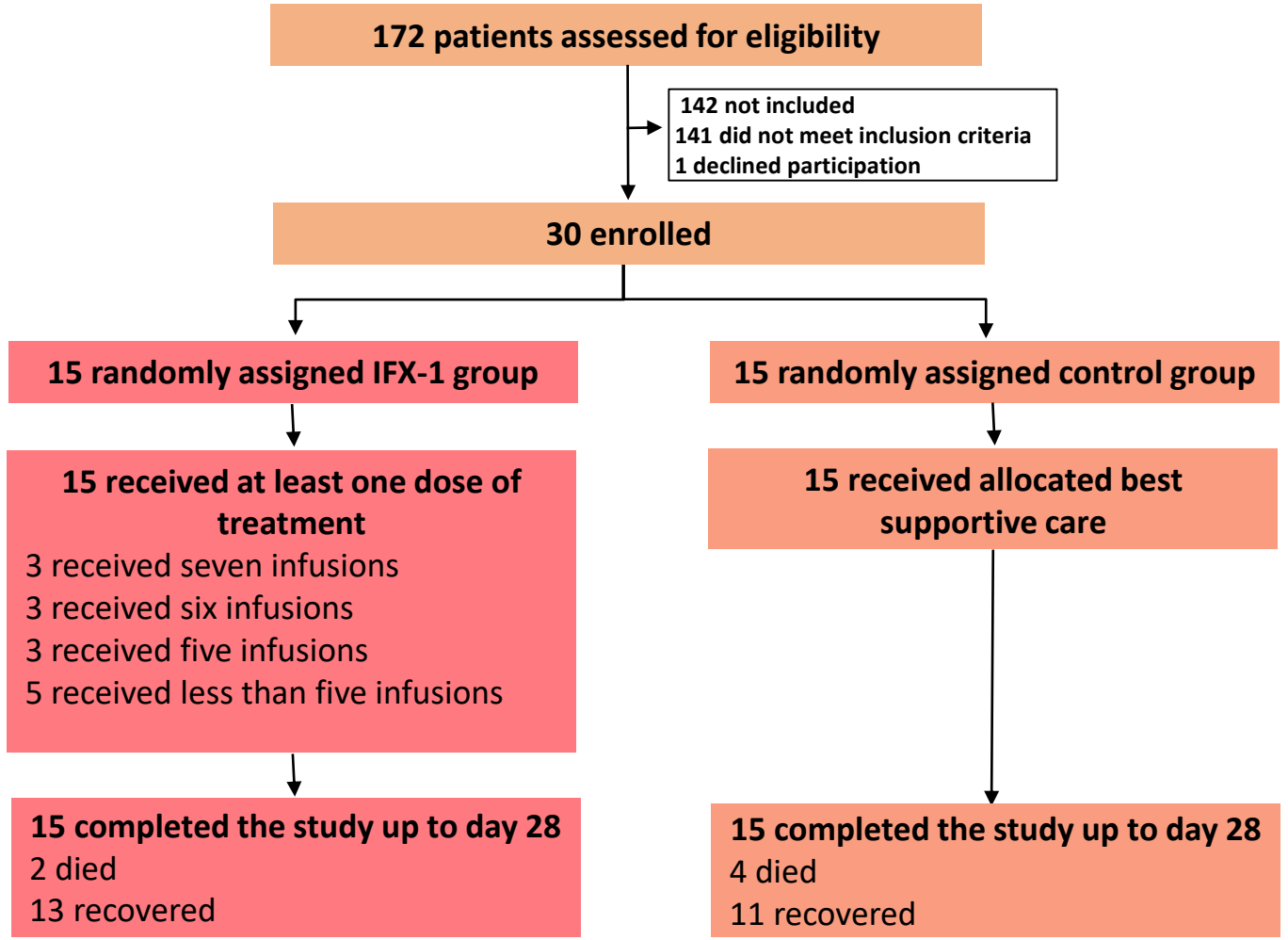
Gupta S *et al. JAMA Int Med* Oct 2020

Immunomodulatory effect

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)

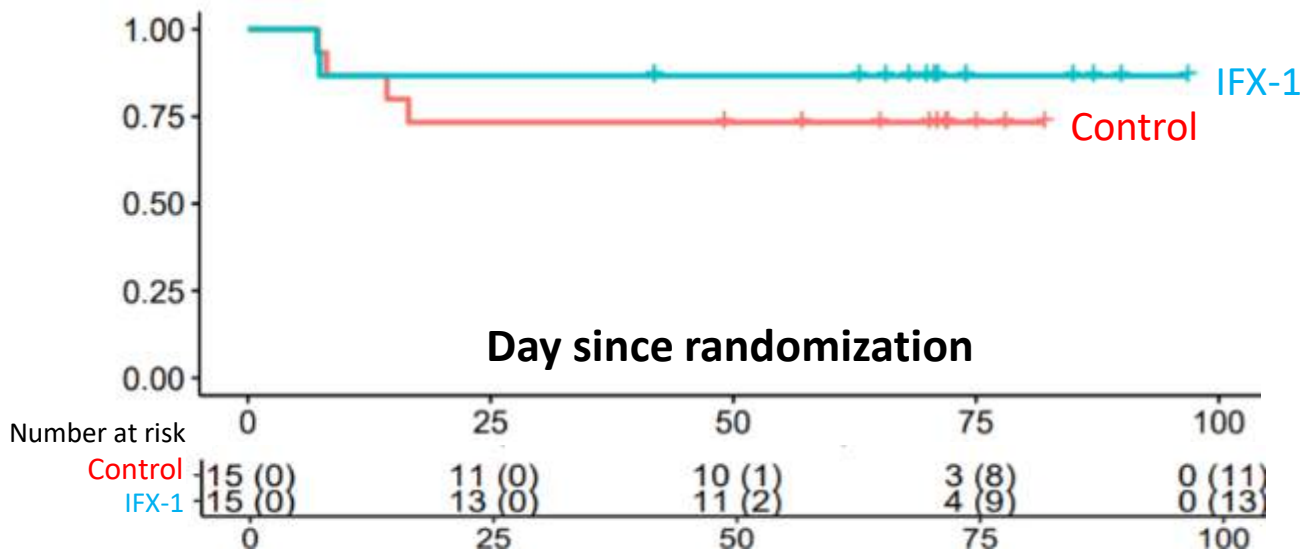


Immunomodulatory effect

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

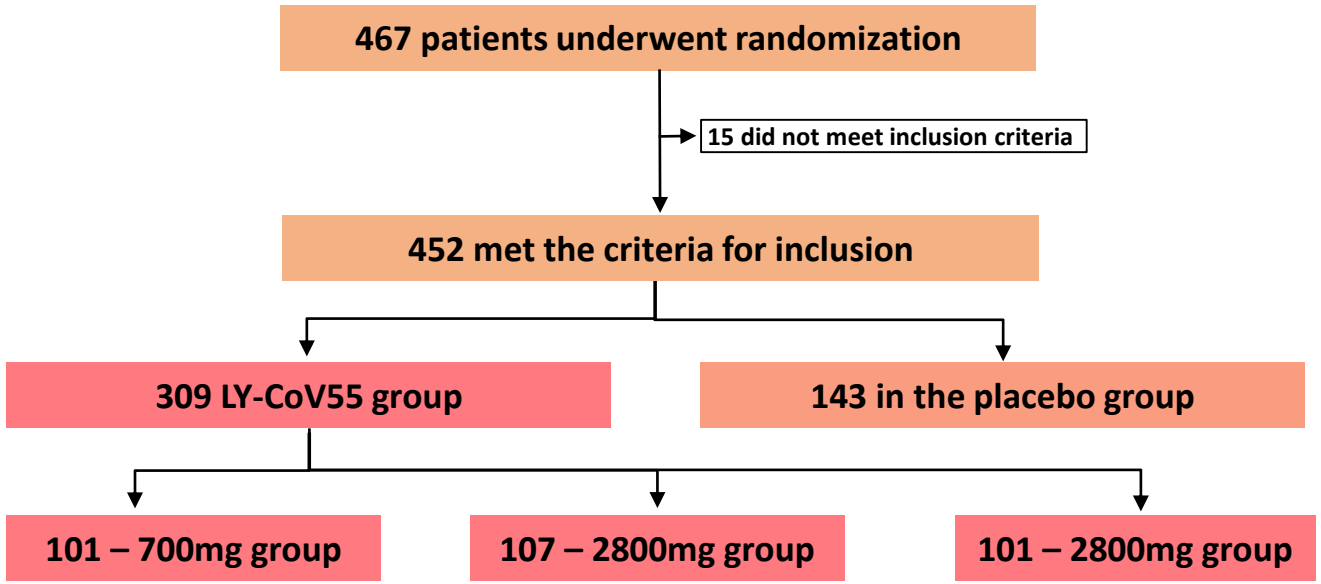
Characteristics	IFX-1 (N=15)	Control (N=15)
Age, mean (SD) - yr	58 (9)	63 (8)
Male sex – no (%)	11 (73)	11 (73)
Coexisting conditions		
Hypertension – no (%)	6 (40)	3 (20)
Diabetes – no (%)	4 (27)	4 (27)
Obesity – no (%)	2 (13)	4 (27)
Respiratory support		
Intubated at randomization – no (%)	8 (53)	10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

Immunomodulatory effect

Monoclonal antibody

LY-CoV555 - 1

- **LY-CoV555**: potent antispike neutralizing monoclonal antibody
- Randomized, double-blind, placebo-controlled, multicenter, United States (BLAZE)
- **Inclusion criteria** : age ≥ 18yo, not hospitalized, at least one mild or moderate COVID-19 symptoms, first positive SARS-CoV-2 viral infection ≤3 days prior to start of the infusion
- **Primary outcome**: change from baseline in the SARS-CoV-2 viral load at day 11 (±4 days) after positive results on testing
- **Secondary outcome**: safety
- 467 participants; **317 LY-CoV55 group, 150 placebo group** (1:1)



Immunomodulatory effect

Monoclonal antibody

LY-CoV555 - 1

Characteristics	LY-CoV555 (N=309)	Placebo (N=143)
Age (y) – median (IQR)	45 (18-86)	46 (18-77)
Female sex – no (%)	171 (55,3)	78 (54,5)
BMI (kg/m²) – median	29,4	29,1
Coronary artery disease – no (%)	39 (9)	504 (14,4)
Days since onset of symptoms – median	4,0	4,0
Viral load - mean (Ct value)	23.9	23.8
Disease status		
Mild – no (%)	232 (75,1)	113 (79,0)
Moderate – no (%)	77 (24,9)	30 (21,0)

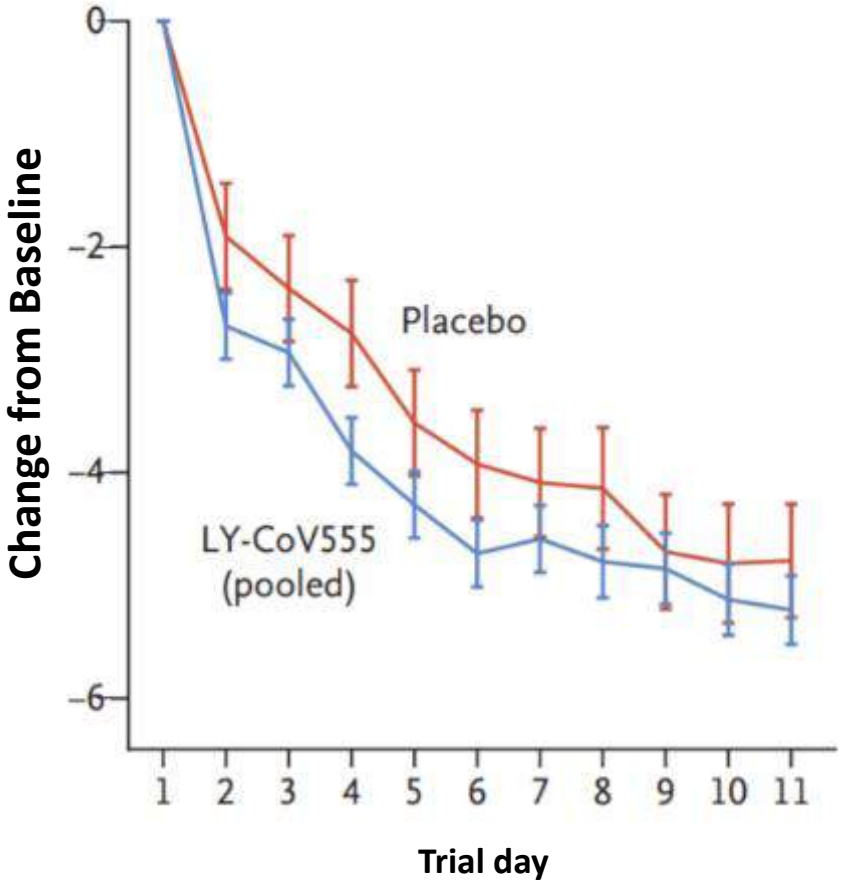
Immunomodulatory effect

Monoclonal antibody

LY-CoV555 - 1

- **D11 change from baseline SARS-CoV-2 viral load**: observed mean decrease from baseline in the log viral load (entire population) −3.81; elimination of more than 99.97% of viral RNA
- **2800-mg group**: difference from placebo in the decrease from baseline: −0.53; viral load was lower by a 3,4 factor
- One of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11.
- **Safety:** Serious adverse events: none LY-CoV555 group *vs.* 0,7% (1/143) placebo group
- **Limits:** interim analysis

Symptoms scores from Day 2 to Day 11



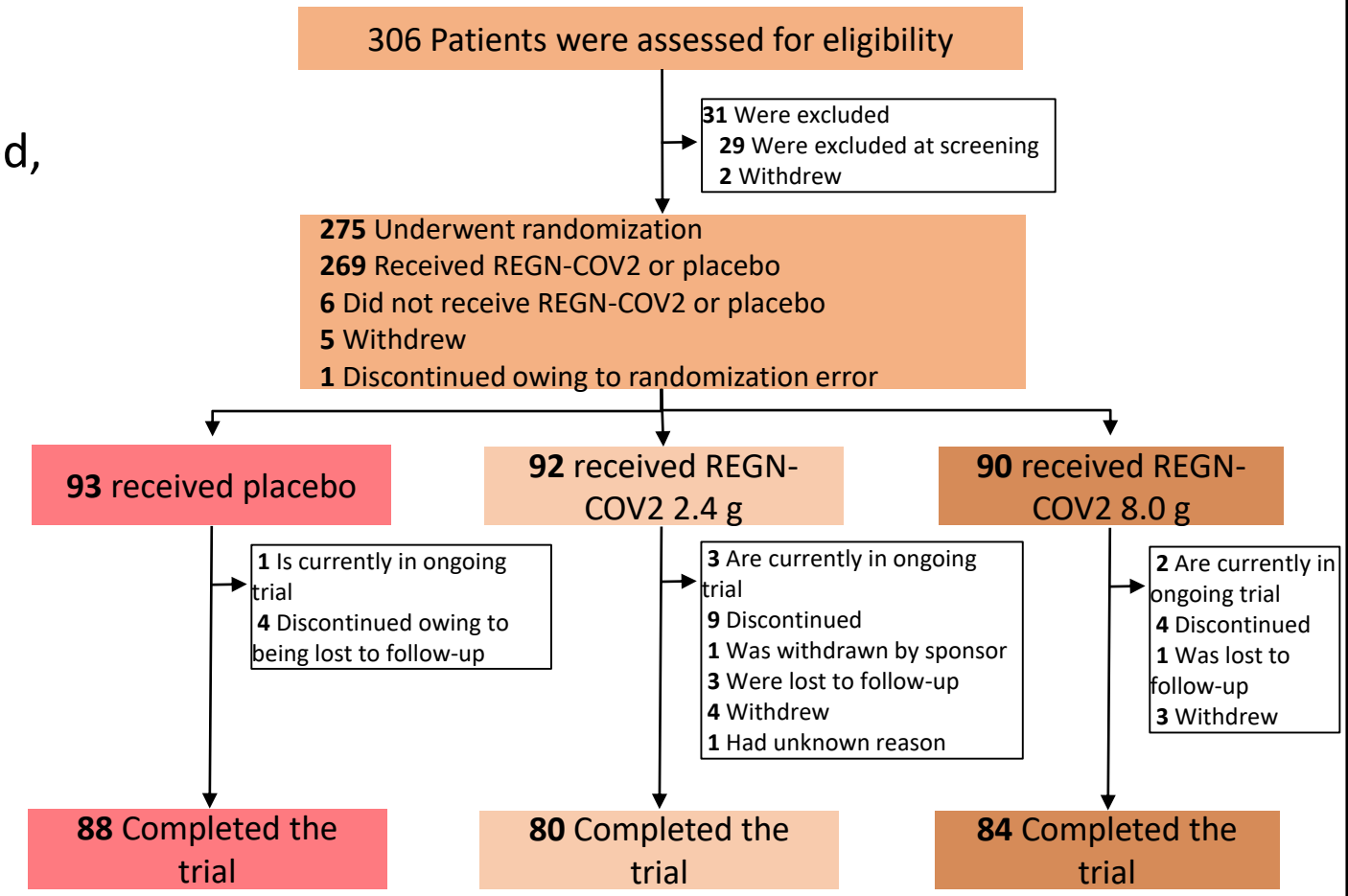
	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

Immunomodulatory effect

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)



Weinreich DM *et al. NEJM* Dec 2020

Immunomodulatory effect

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)

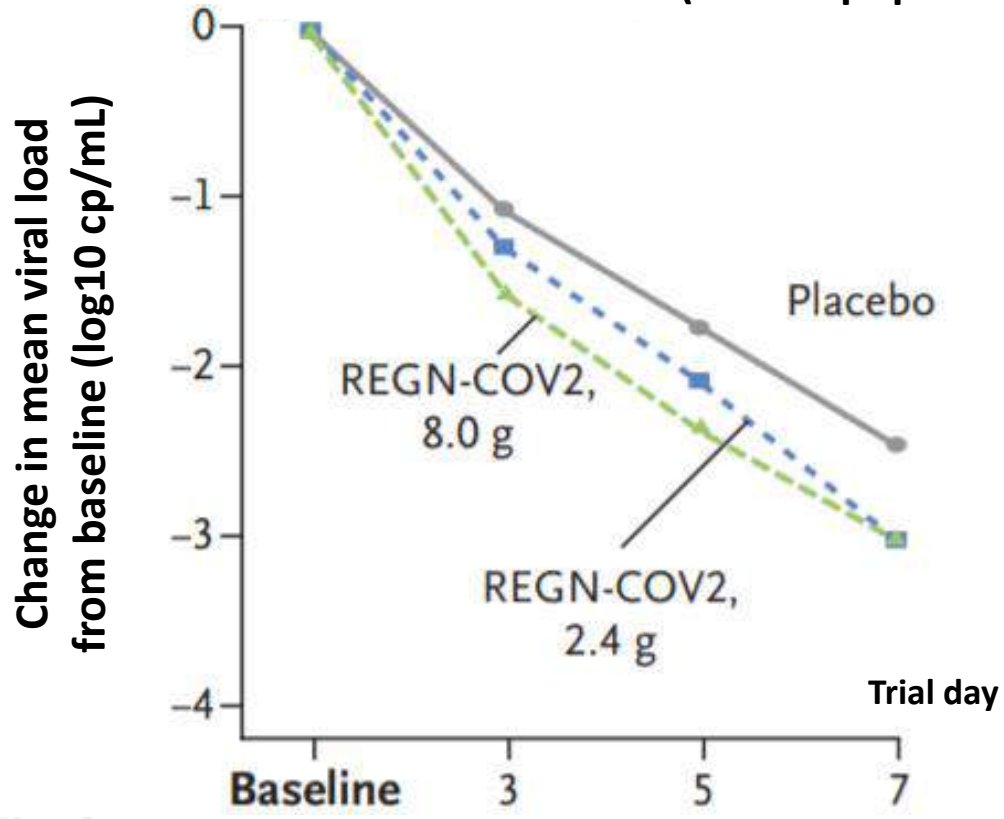
Immunomodulatory effect

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)



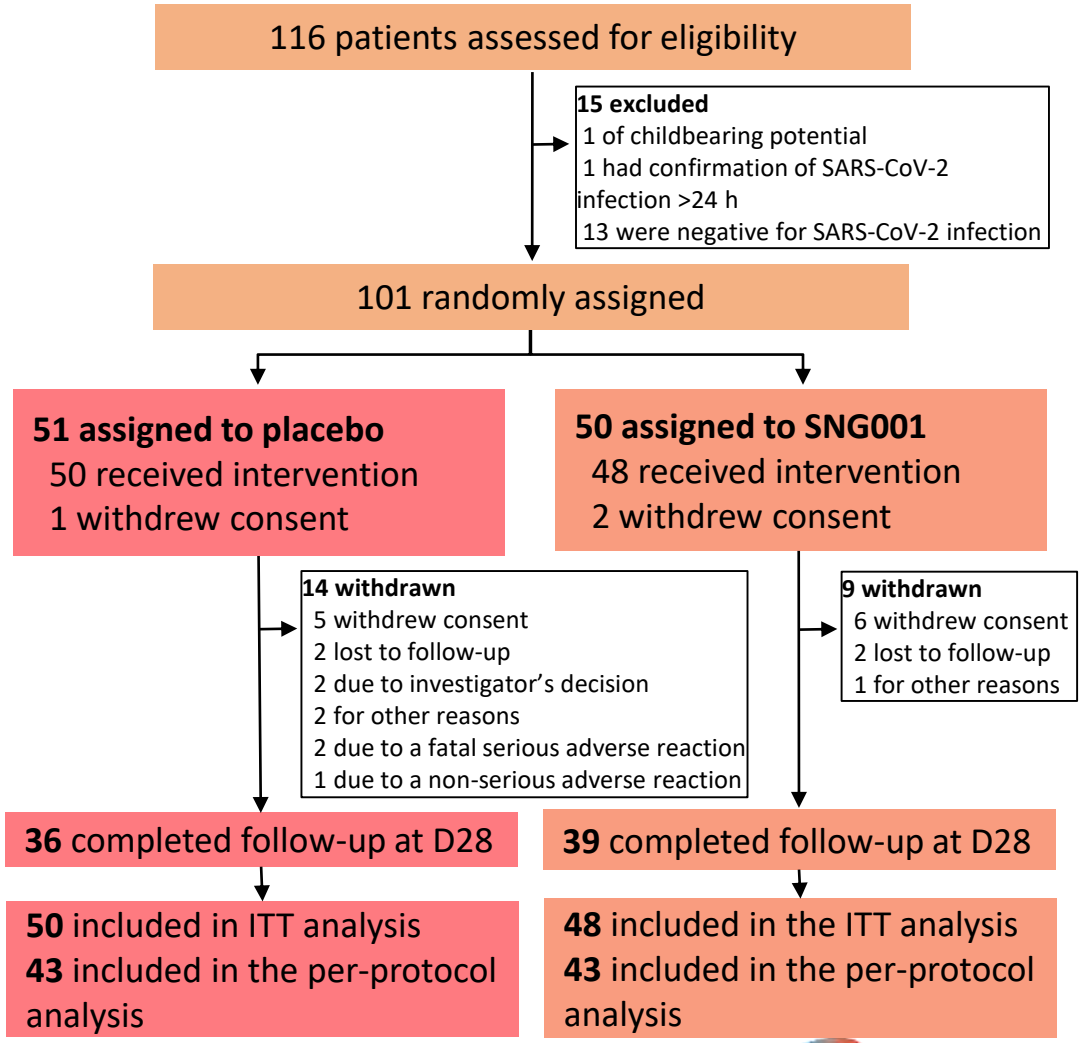
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

Weinreich DM *et al. NEJM* Dec 2020

Immunomodulatory effect

Interferon beta 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

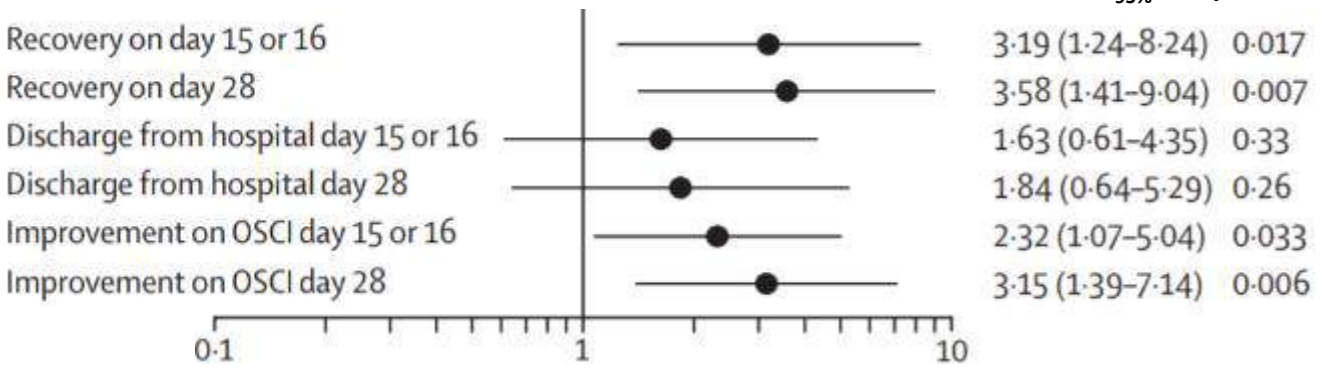
Characteristics	SNG001 (N=50)	Placebo (N=51)
Age (y) – mean (SD)	57,8 (14,6)	56,5 (11,9)
Male sex – no (%)	27 (56)	31 (62)
Coexisting conditions		
Hypertension – no (%)	18/26 (69)	11/27 (41)
Diabetes – no (%)	3/26 (12)	9/27 (33)
Cardiovascular disease – no (%)	5/26 (19)	8/27 (30)
Chronic lung condition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

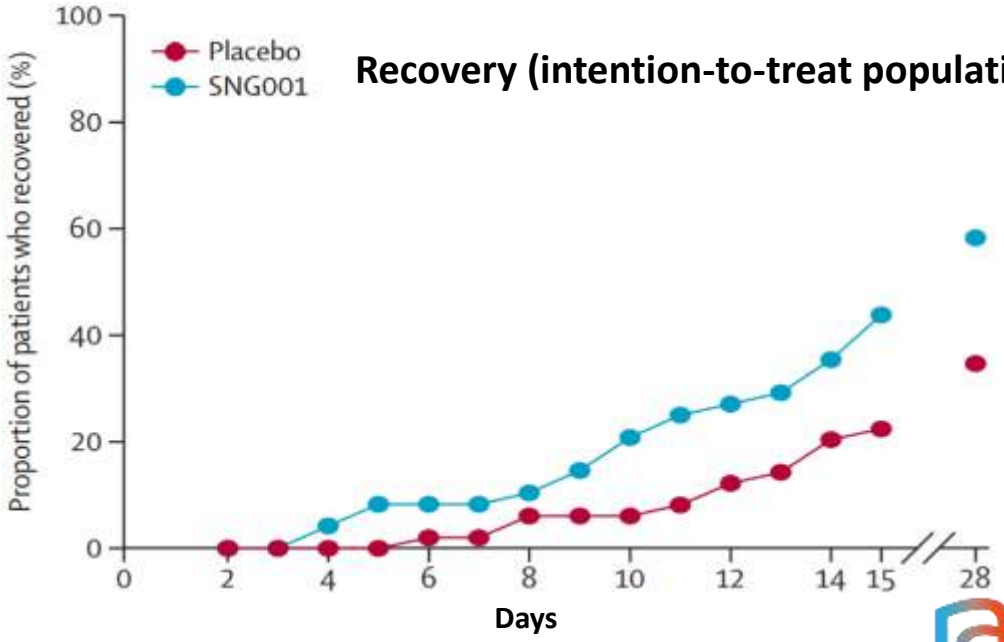
Immunomodulatory effect

Interferon beta 1a

- **Clinical condition change (D15 or D16 OSCI improvement):** 36/48 (75,0%) SNG001 group *vs.* 35/50 (70%) placebo group; OR: 2,32; $CI_{95\%}$[1,07-5,04], p=0,033
- **D14 BCSS score:** difference between SNG001 group and placebo group: -0,8; $CI_{95\%}$[-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

ITT population



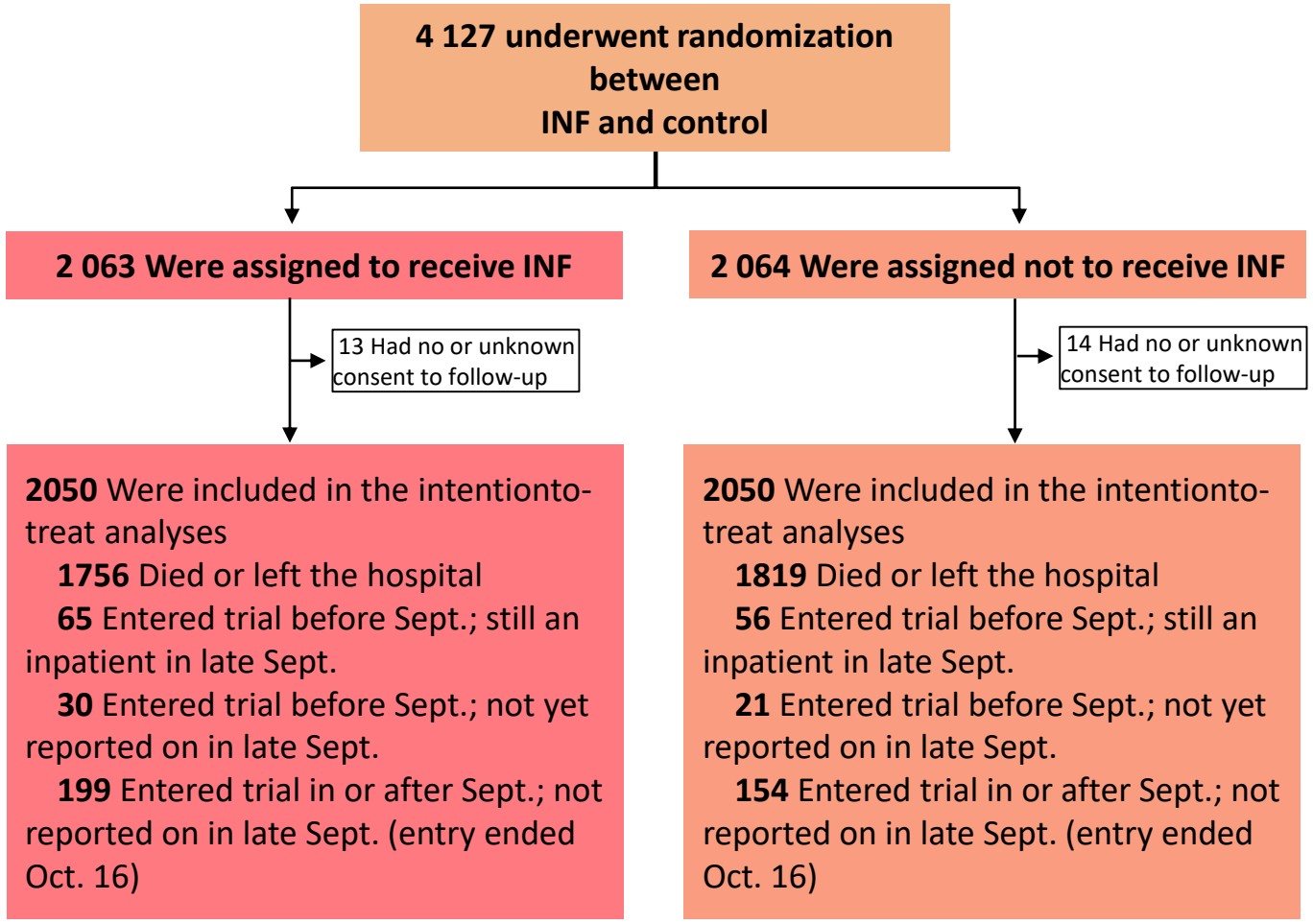


Monk PD *et al. Lancet Resp Med* Nov 2020

Immunomodulatory effect

Interferon beta 1a (IFNβ-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 **IFN** group, 2064 **control** group (1:1)



Immunomodulatory effect

Interferon beta 1a (IFNβ-1a)

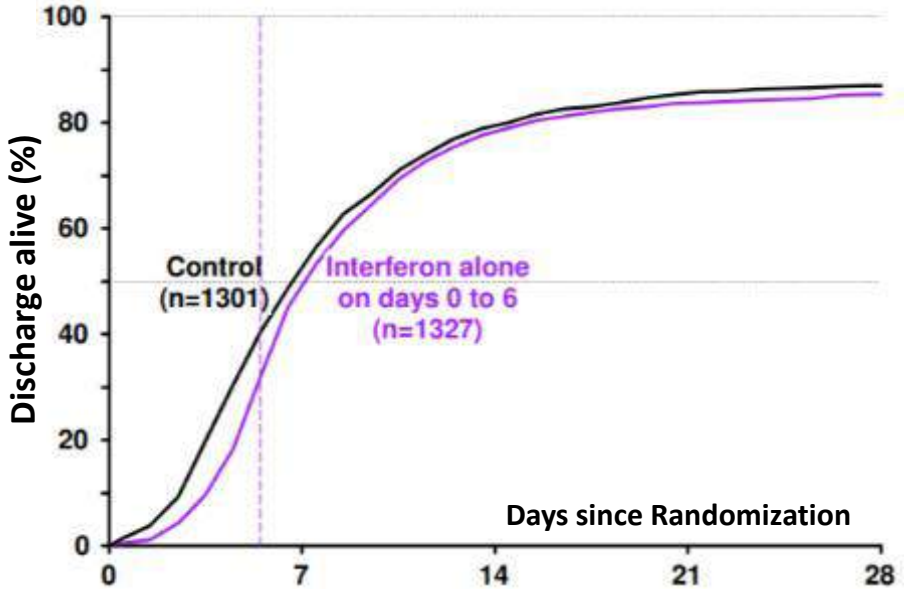
Characteristics		All (N= 11 266)	INF (N= 2 050)	Control (N=2 050)
Age	< 50 yr – no (%)	3995 (35)	720	697
	50-69 yr – no (%)	5125 (45)	934	973
	≥ 70 yr – no (%)	2146 (19)	396	380
Sex	Male sex – no (%)	6985 (62)	1303	1278
Co existing conditions	Diabetes – no(%)	2768 (25)	489	537
	Heart disease – no (%)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

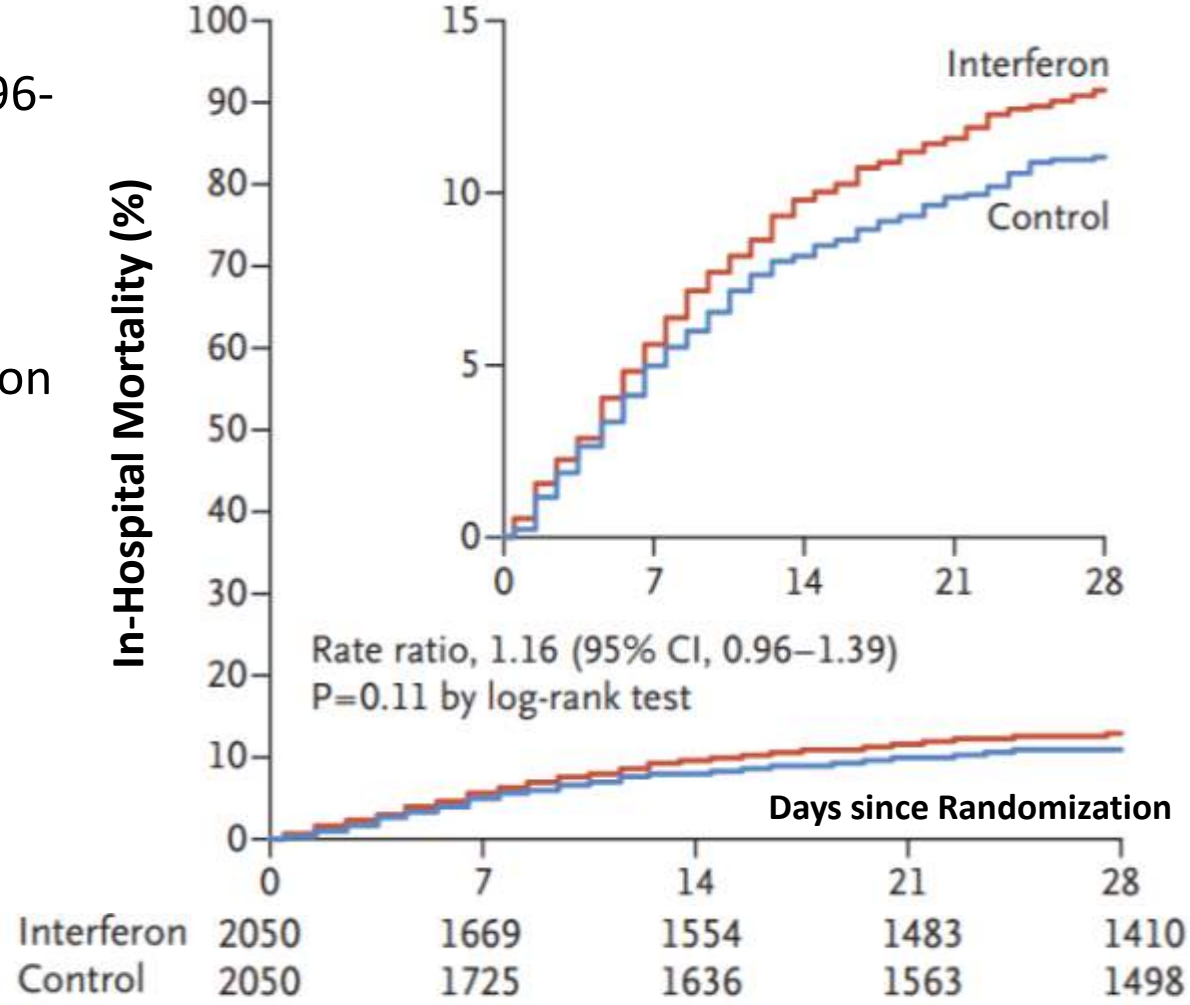
Immunomodulatory effect

Interferon beta 1a (IFNβ-1a)

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

Study stopped for futility on 16th October



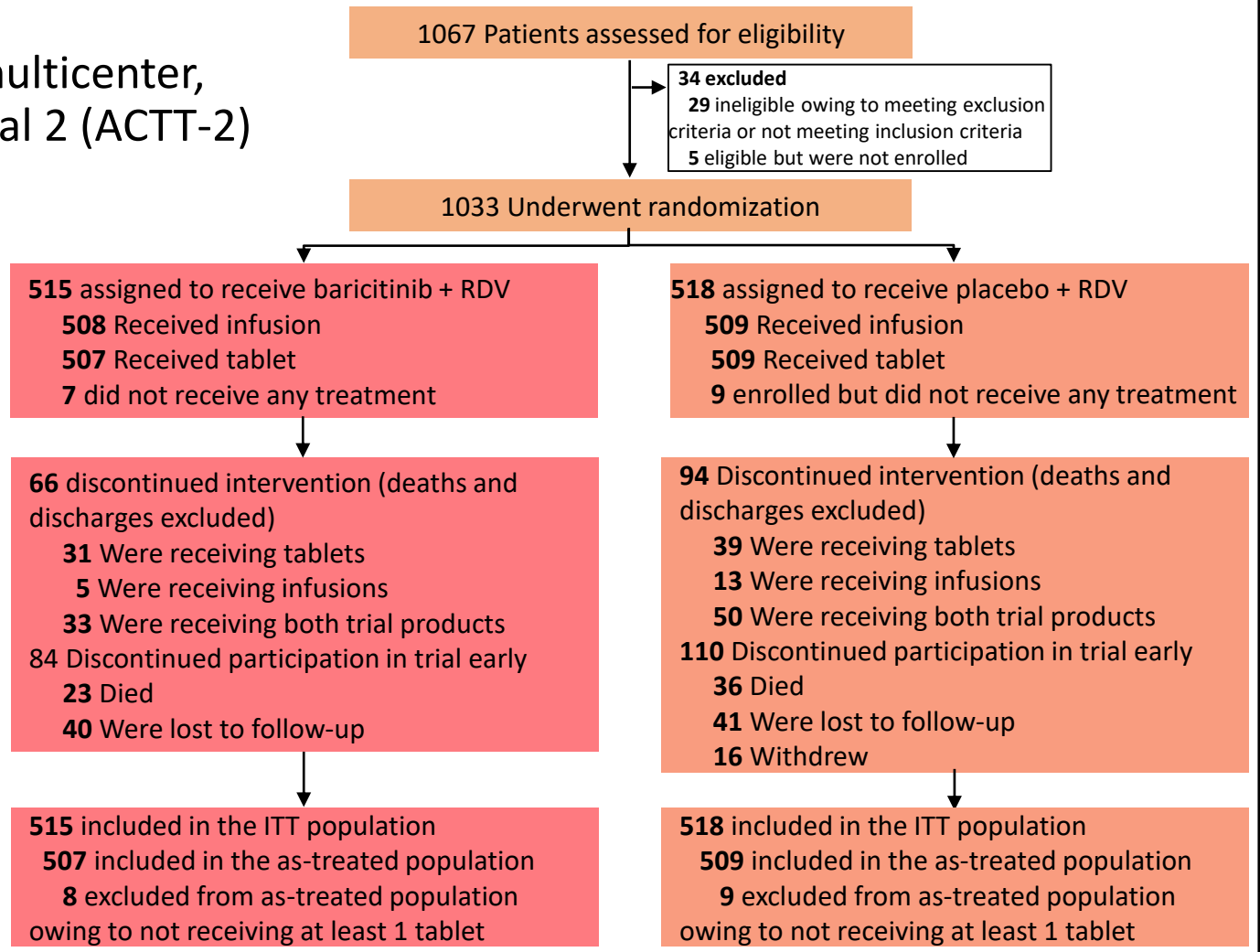


SOLIDARITY *NEJM* Dec 2020

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)



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)

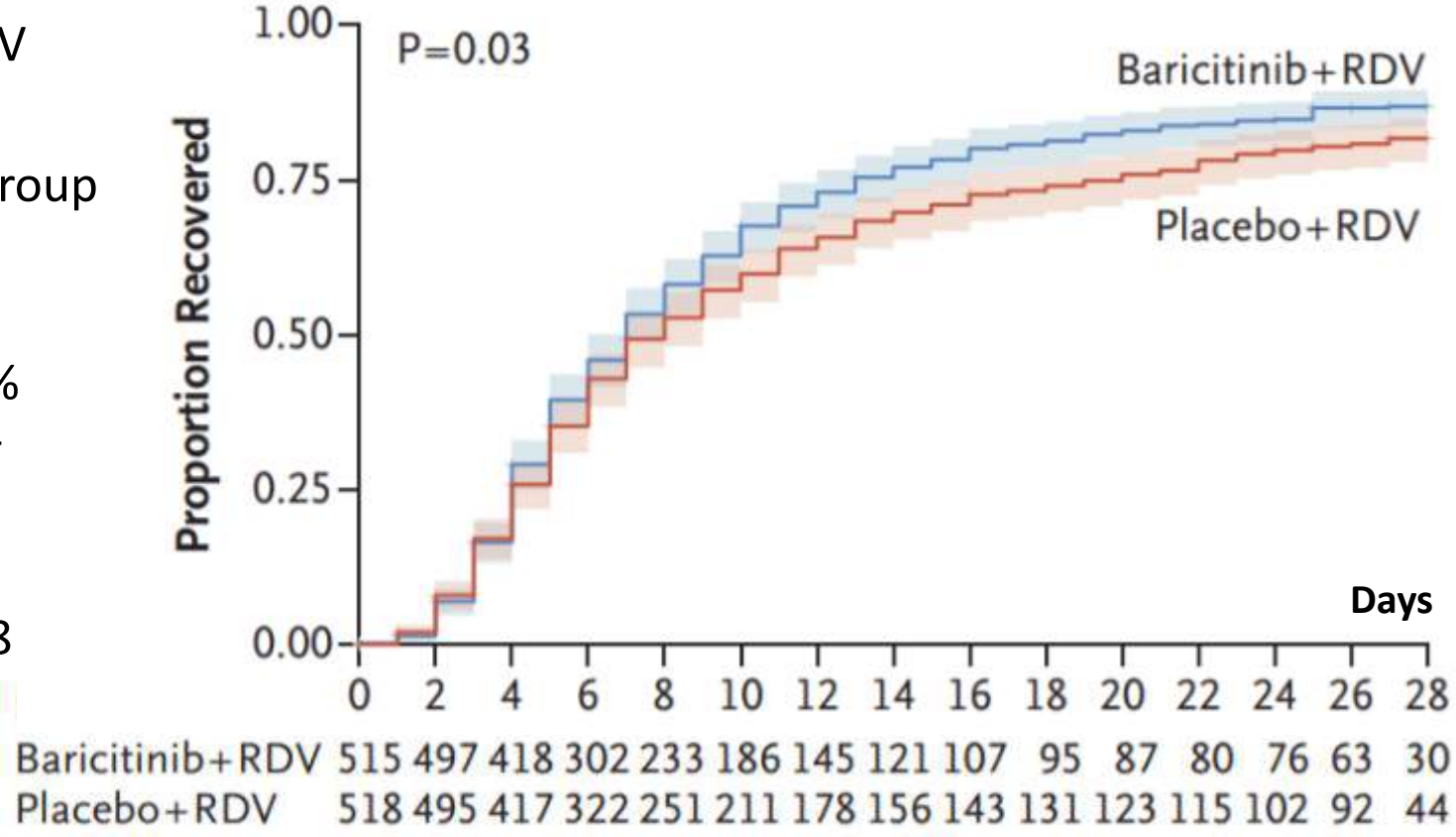
NIV: Non invasive ventilation
MV: mechanical ventilation

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

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Agarwal	Open label, parallel arm, multicenter, RCT	CP + SoC group *vs.* SoC group	**N= 464** Moderate COVID-19 illness	D28 all cause mortality	15% (34/235) CP group *vs.* 14% (31/229) control group, RR: 1,04 $CI_{95\%}$[0,66-1,63]
Joyner	Open label, multicenter	CP	**N= 5 000** High risk of progression to severe or life-threatening COVID-19	Determine the safety of transfusion of COVID-19 CP	Incidence of SAEs in the first four hours after transfusion: < 1% Three severe allergic transfusion reactions, 4 deaths, 18 TACO&TRALI (2 definitely related to CP)

SAEs: serious adverse events

Agarwal A *et al. BMJ* Oct 2020
Joyner M *et al. J Clin Invest* Jun 2020

Passive immunity

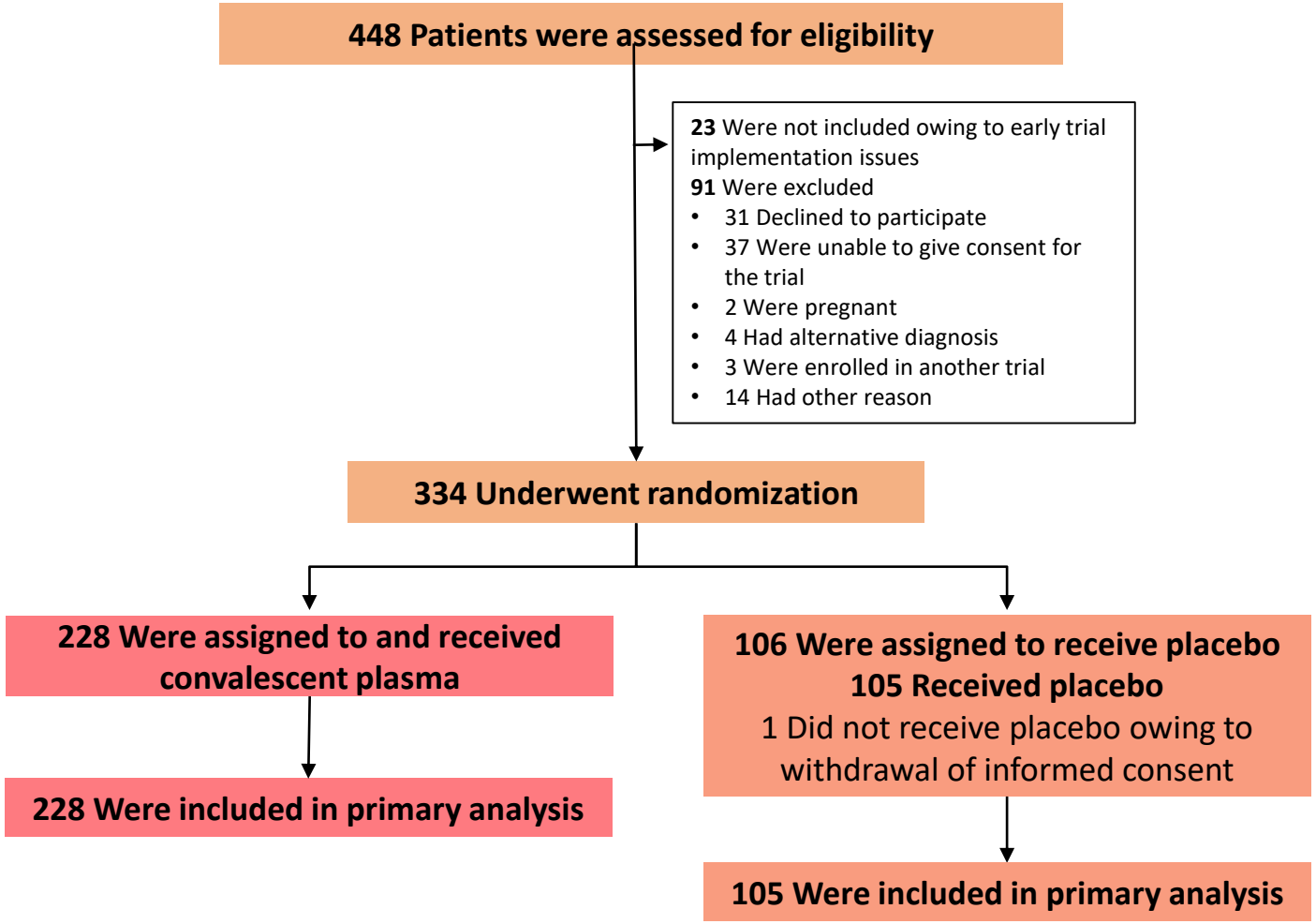
Convalescent plasma (CP) - 2

1st Author	Design	Groups	Participants	Primary outcome	Main results (Primary outcome)
Li	Open-label, multicenter, randomized	CP + SoC group *vs.* SoC group	**N= 103** Severe pneumonia (≥30 breaths/min, $SpO_2 \leq 94\%$ or $PaO_2/FiO_2 \leq 300$)	Time to clinical improvement within 28 days	51,9% (27/52) CP group *vs.* 43,1% (22/51) control group, HR: 1,40 CI $_{95\%}$[0,79-2,49]; p = 0,26
Liu	Retrospective, propensity score-matched case-control study	CP vs. Control group	**N= 195** Severe or immediately life-threatening COVID-19	D14 oxygen requirement	Worsened in 17,9% of CP recipients *vs.* 28,2% of propensity score matched controls hospitalized with COVID-19

Passive immunity

Convalescent plasma (CP) - 3

- Double-blind, placebo-controlled, multicenter trial, Argentina
- **Inclusion criteria:** hospitalized patients, age ≥ 18yo, positive SARS-CoV-2 RT PCR, severe COVID-19 pneumonia (PaO_2/FiO_2 <300, or SpO_2 ≤ 93% (room air) or SOFA score of two or more points above baseline status)
- **Main outcome**: clinical status 30 days after intervention (ordinal categories on an adapted version of the WHO clinical scale)
- **Other outcomes (some of them)**: D7, D14 and discharge from hospital clinical status on the ordinal scale
- **CP group**: 228 patients *vs.* **placebo group**: 105 patients (2:1)



Passive immunity

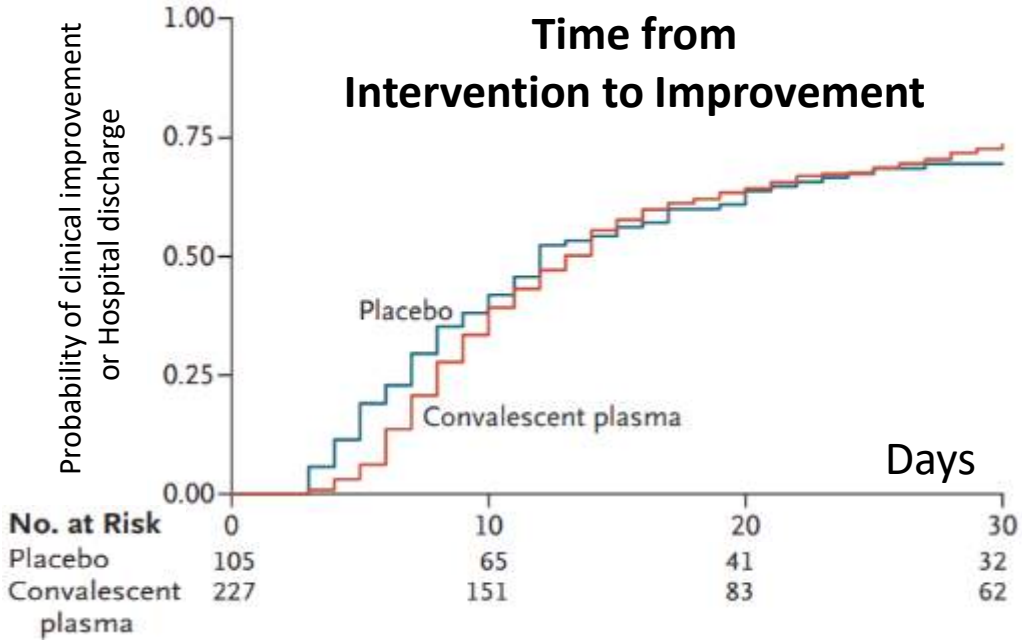
Convalescent plasma (CP) - 3

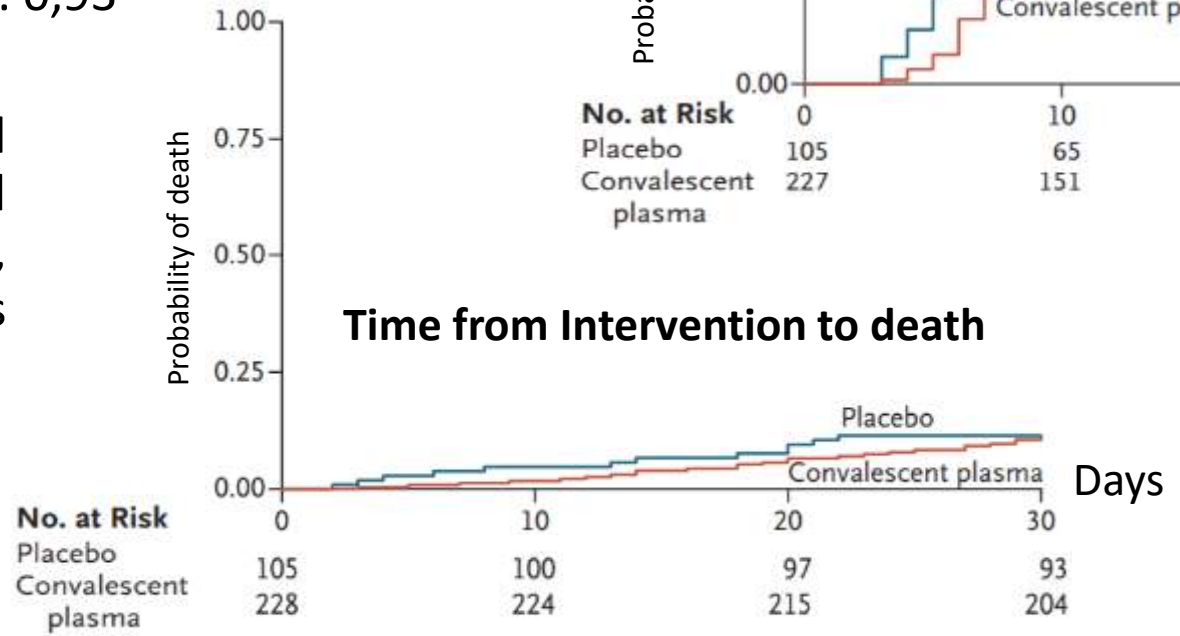
Characteristics	CP group (N=228)	Placebo group (N=105)
Age, median (IQR) – yr	62,5 (53-72,5)	62 (49-71)
Female sex – no (%)	67 (29,4)	41 (39,0)
Time to onset of symptoms, median (IQR) — days	8 (5–10)	8 (5–10)
Co existing conditions		
Diabetes mellitus – no (%)	40 (17,5)	21 (20)
Hypertension – no (%)	111 (48,7)	48 (45,7)
Chronic obstructive pulmonary disease – no (%)	23 (10,1)	2 (1,9)
Obesity – no (%)	104 (45,6)	52 (49,5)
Solid tumors – no (%)	23 (10,1)	11 (10,5)
Clinical and laboratory findings		
Oxygen saturation <93% at FiO_2 0,21 – no (%)	224 (98,2)	100 (95,2)
Low-flow nasal cannula – no (%)	146 (64,0)	70 (66,7)
Venturi or nonrebreather mask – no (%)	49 (21,5)	16 (15,2)

Passive immunity

Convalescent plasma (CP) - 3

- **Clinical status at 30 days:** OR 0,81 $CI_{95\%}$[0,50-1,31], p = 0,396
- **D30 mortality:** 10.96% (25/228) CP group vs. 11.43% (12/105) placebo group, risk difference: −0,46 percentage points $CI_{95\%}$[-7,8-6,8]
- **Median time from intervention to death**: could not be determined in both group; HR: 0,93 $CI_{95\%}$[0,47–1,86]
- **<u>Limits:</u>** trial inclusion criteria limited to severe Covid-19 pneumonia, usual therapy was allowed in both groups, convalescent plasma therapy is intrinsically heterogeneous





Simonovich VA *et al. NEJM* Nov 2020

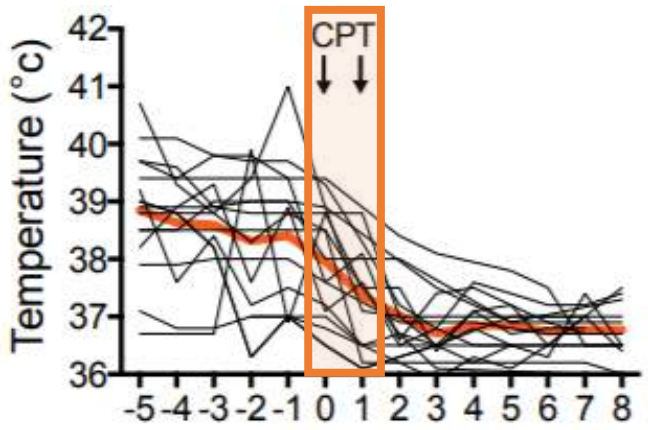
COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

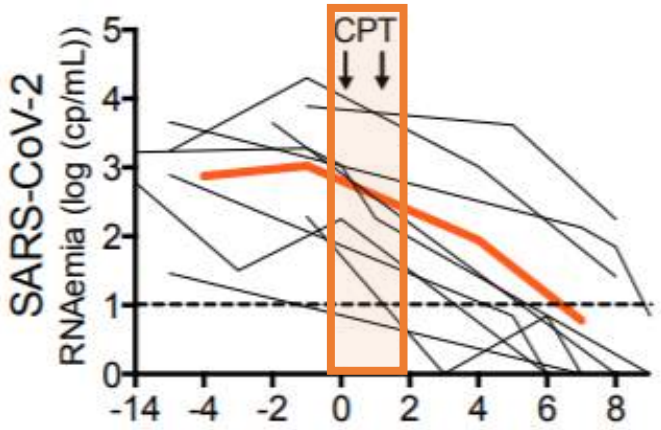
REACTing research & action targeting emerging infectious diseases

Passive immunity

Convalescent plasma (CP) - 4

- 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

THERAPEUTIC (December 21th 2020)

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 nor lopinavir/ritonavir treatment

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