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THERAPEUTIC

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MALADIES INFECTIEUSES ÉMERGENTES

# Scientific update on COVID-19

**Updated on February 18th 2021**

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# THERAPEUTIC

**Questions:**

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

# COVID-19 Treatment

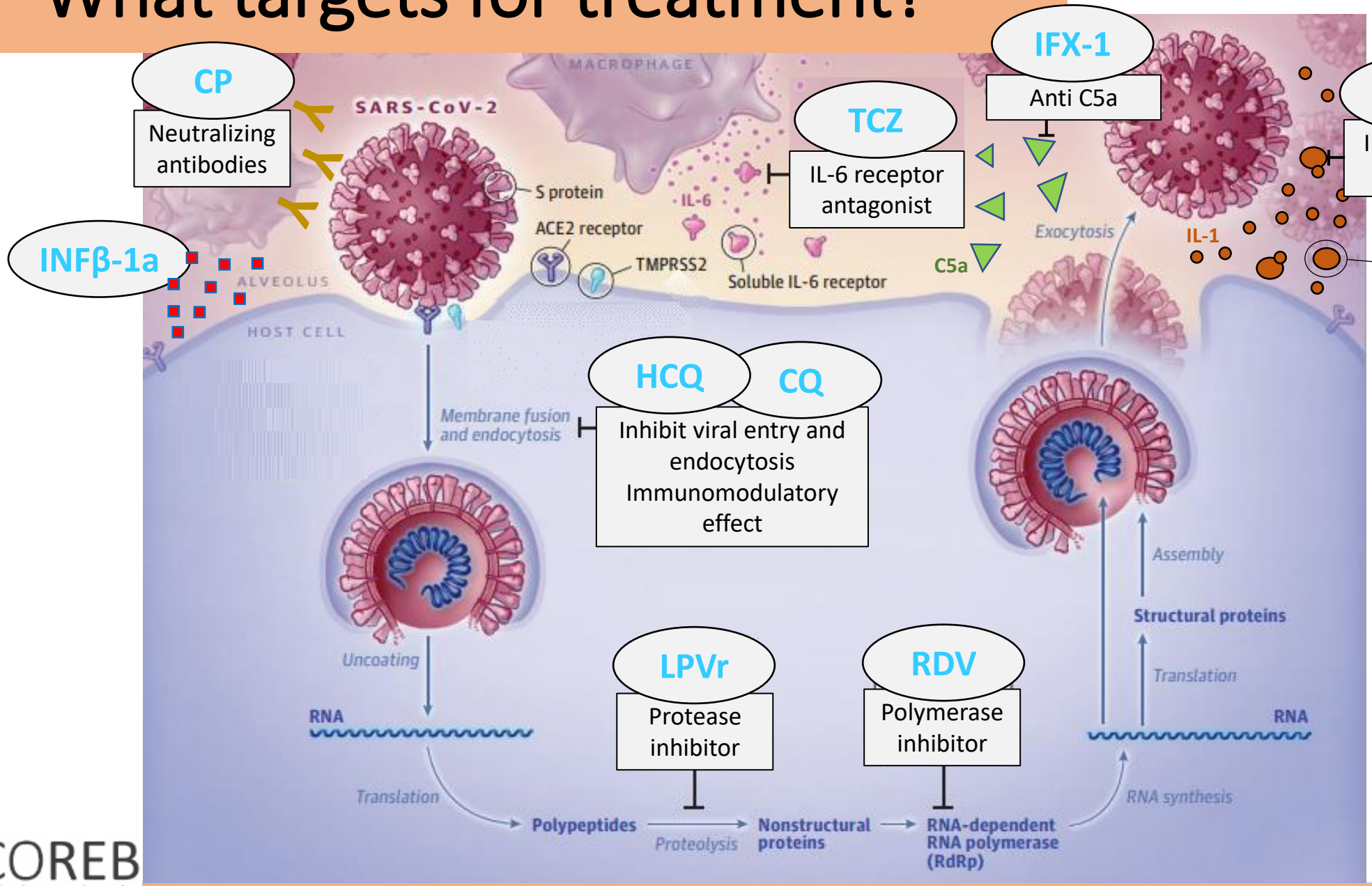
- **Dexamethasone** is the first drug to show life-saving efficacy in patients infected with COVID-19
- More data from clinical trials are needed

## Classes of treatment

| Anti viral effect | Monoclonal antibody | Immunomodulatory effect | Passive immunity |
|---|---|---|---|
| (Hydroxy)chloroquine | Tocilizumab | Corticosteroids | Convalescent plasma |
| Ivermectin | Vilobelimab | INFβ-1a | |
| Lopinavir/ritonavir | LY CoV 555/016 | Janus Kinase (JAK) inhibitor | |
| Remdesivir | Anakinra | | |
| | REG CoV2 | | |

# 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)

| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| Abella | Randomized, double-blind, placebo-controlled | HCQ *vs.* placebo<br><br>(**Pre-exposure prophylaxis**) | **N= 132**<br>Hospital HCW (ED and COVID-19 units) | Incidence of SARS-CoV-2 infection | Early termination of the study<br>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<br>HCQ twice/week *vs.* placebo<br><br>(**Pre-exposure prophylaxis**) | **N= 1483**<br>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 $_{95\%}$CI[0,44-1,16]<br><br>HCQ twice/week group: 29/495 (5,9%) *vs.* placebo group: 39/494 (7,9%); HR: 0,74 $_{95\%}$CI[0,46-1,19] |



No virological data on some studies

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

Rajasingham R *et al*. *CID* Oct 2020
Abella BS *et al. JAMA Int Med* Feb 2021

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<br><br>(**Post exposure prophylaxis**) | **N= 821**<br>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<br><br>(**Post exposure prophylaxis**) | **N= 2314**<br>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 $_{95\%}$IC[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<br><br>(**Non-hospitalized**) | **N= 353**<br>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 $_{95\%}$CI[-0,28- 0,29]<br>D7 VL$^{\S}$: HCQ group: -3,44 *vs.* placebo group: -3,37 $Log_{10}$ copies/mL; difference: 0,07 $_{95\%}$CI[-0,44- 0,29] |
| Skipper | Randomized, double-blind, placebo-controlled | HCQ *vs.* placebo<br><br>(**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;<br>absolute difference: 0,27 $_{95\%}$CI[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<br><br>(**Hospitalized**) | **N= 667**<br>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 $_{95\%}$CI[0,57-1,73]; HCQ *vs.* control: OR: 1,21 $CI_{95\%}$ [0,69-2,11]; HCQ + AZ *vs.* HCQ: OR: 0,82 $_{95\%}$CI[0,47-1,43] |
| RECOVERY | Randomized, controlled, open-label | HCQ *vs.* usual care<br><br>(**Hospitalized**) | **N= 4717**<br>Median of days since symptom onset:<br>9 days | D28 mortality | HCQ group: 421/1561 (27,0%) vs. usual care group: 790/3155 (25,0%) RR: 1,09; $_{95\%}$CI[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<br><br>(**Hospitalized**) | **N= 479**<br>supplemental oxygen to maintain $SpO_2$ ≥92%<br>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 $_{95\%}$CI[0,73-1,42] |
| SOLIDARITY (WHO) | Multicenter, randomized, open-label, non-placebo-controlled | HCQ *vs.* control<br><br>(**Hospitalized**) | **N= 1 863**<br><br>Study stopped for futility | All-cause mortality | HCQ group: 104/947 (10,2%) *vs.* placebo group: 84/906 (8,9%); rate ratio: 1,19; $_{95\%}$CI[0,89-1.59]; p= 0,23 |



No virological data on some studies

§ Median duration
+ Mean duration

Self *et al*. *JAMA* Nov 2020
SOLIDARITY *NEJM* Dec 2020

Anti viral effect

# Hydroxychloroquine (HCQ)

| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| Tang | Randomized, controlled, multicenter, open label | HCQ + SoC *vs.* SoC<br><br>(**Hospitalized**) | **N= 150**<br>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%, $_{95\%}$CI[73,8% - 93,8%] *vs.* SoC: 81,3%, $_{95\%}$CI[71,2%-89,6%] |
| Ulrich | Multicenter, double-blind randomized | HCQ *vs.* placebo<br><br>(**Hospitalized**) | **N= 128**<br>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

Tang W *et al. BMJ* May 2020
Ulrich *et al*. *Open Forum Infect Dis* Sep 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<br>(**Hospitalized**) | **N= 199**<br>$SaO_2 \leq 94\%$ or $PaO_2/FiO_2 < 300$ mm Hg | Time to clinical improvement | LPVr group **not associated** with a difference in time to clinical improvement<br>HR: 1,31 $_{95\%}$CI[0,95-1,80] |
| RECOVERY | Randomized, controlled, open-label | LPVr + SoC *vs.* SoC<br>(**Hospitalized**) | **N= 5 040**<br>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<br>(**Hospitalized**) | **N= 8**<br>Non ICU patients | LPVr plasma concentration | Approximately 2-fold higher than HIV patients receiving the same dose (7.1 µg/mL) 60 to 120-fold higher concentrations are required to reach the assumed LPV $EC_{50}$ |



No virological data on some studies

Anti viral effect

# Lopinavir/ritonavir (LPVr)

| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| SOLIDARITY (WHO) | Multicenter, randomized, open-label, non-placebo-controlled | LPVr *vs.* control<br><br>(**Hospitalized**) | **N= 2 791**<br><br>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<br><br>(**Hospitalized**) | **N= 4 023**<br>Not specified | ARDS and Mortality rate | ARDS rate: LPVr group 15,6% *vs.* control group 24,2%; p= 0,49<br>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<br><br>(**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]<br>Oral IVM group *vs.* placebo p=0,02; Oral IVM group *vs.* IVM + doxycycline p=0,27 |
| Camprubí | Retrospective study | IVM *vs.* non-IVM<br><br>(**Hospitalized**) | **N= 26**<br>All patients received HCQ and azithromycin<br>Severe patients | D3-D5 SARS-CoV-2 PCR and clinical improvement | D3-D5 SARS-CoV-2 PCR:<br>IVM group : 5/13 (38,5%) *vs.* non-IVM group : 4/13 (30,8%); p>0,99<br>Clinical improvement:<br>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 |
| 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

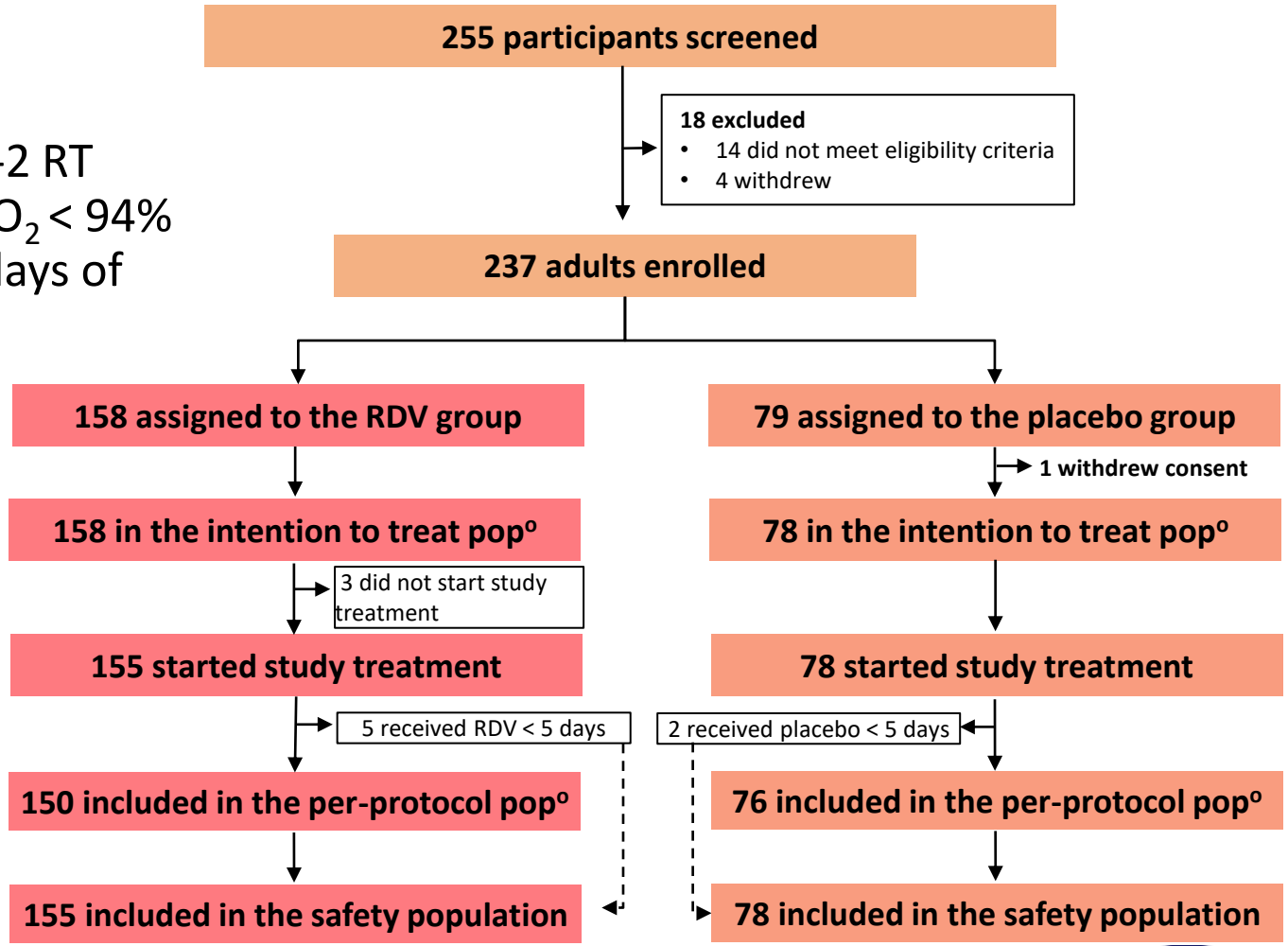
# Ivermectin (IVM)

| 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 |
| Podder | Randomized, controlled, open-label | IVM + usual care *vs.* usual care only (**Hospitalized**) | **N= 62** Mild to moderate patients | Total recovery time from the onset of symptoms to complete resolution of symptoms (days) | IVM group : 10,09 ± 3,24 *vs.* control group : 11,50 ± 5.32 $_{95\%}$CI [-0,86-3,63]; p>0,05 |

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%) |

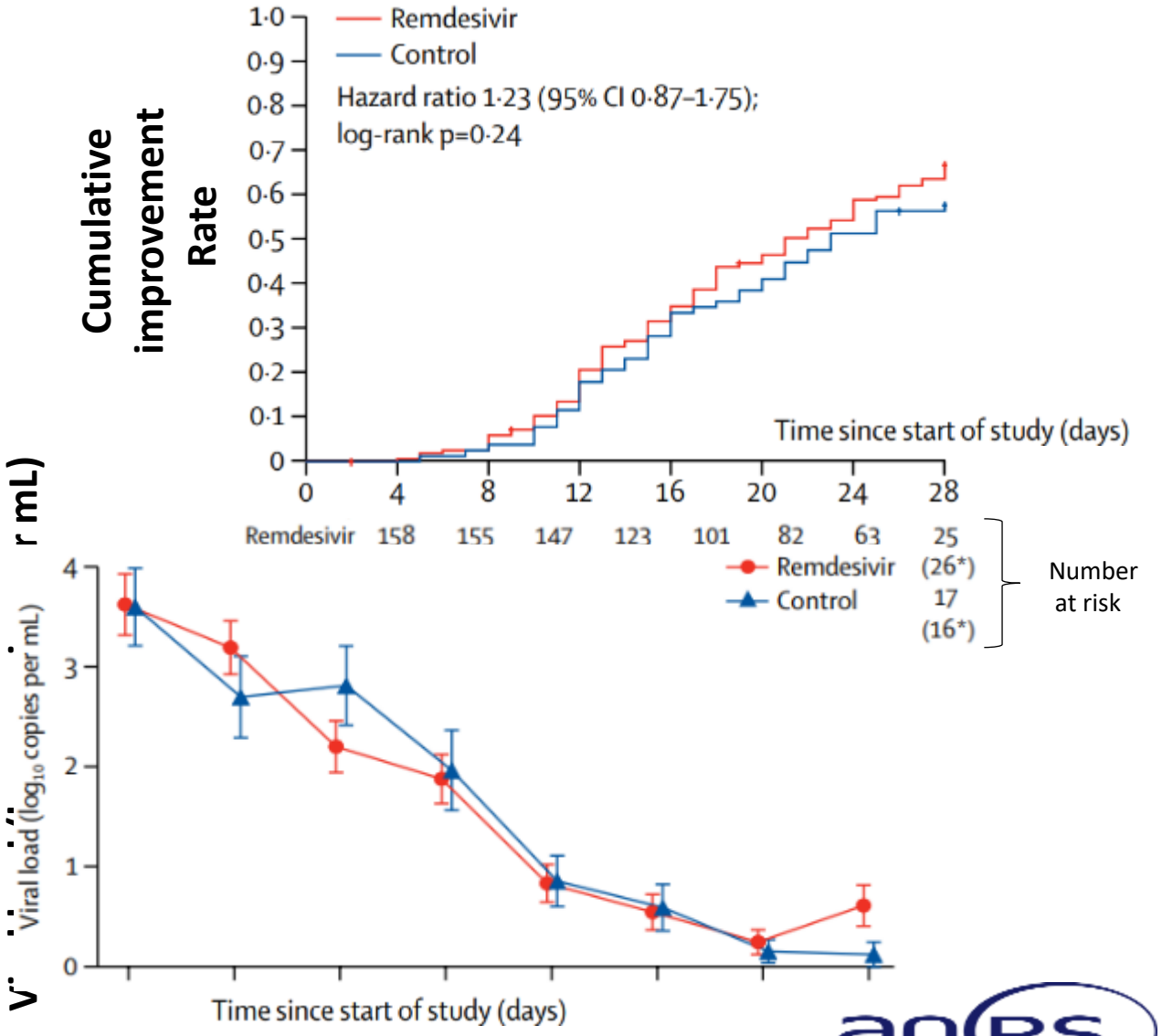
NP: nasopharyngeal
OP: oropharyngeal

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
- **Limits:** 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

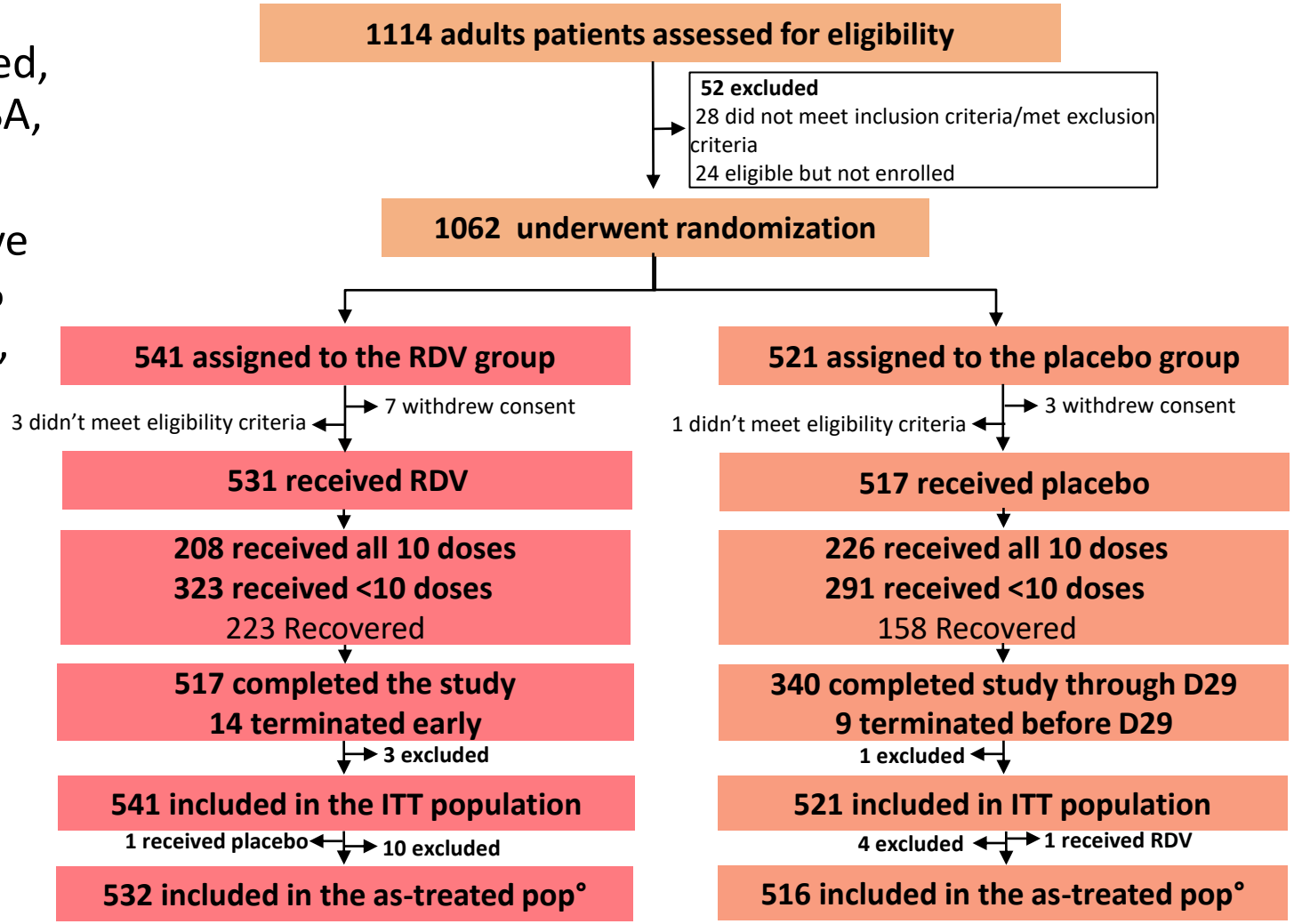



Wang Y *et al*. *Lancet* Apr 2020

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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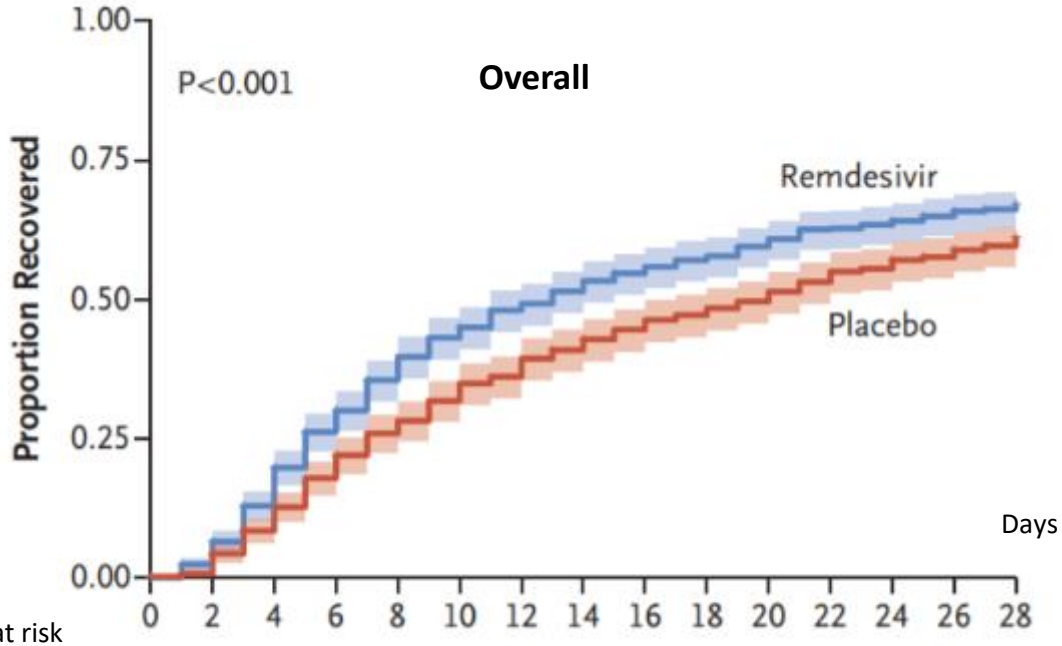
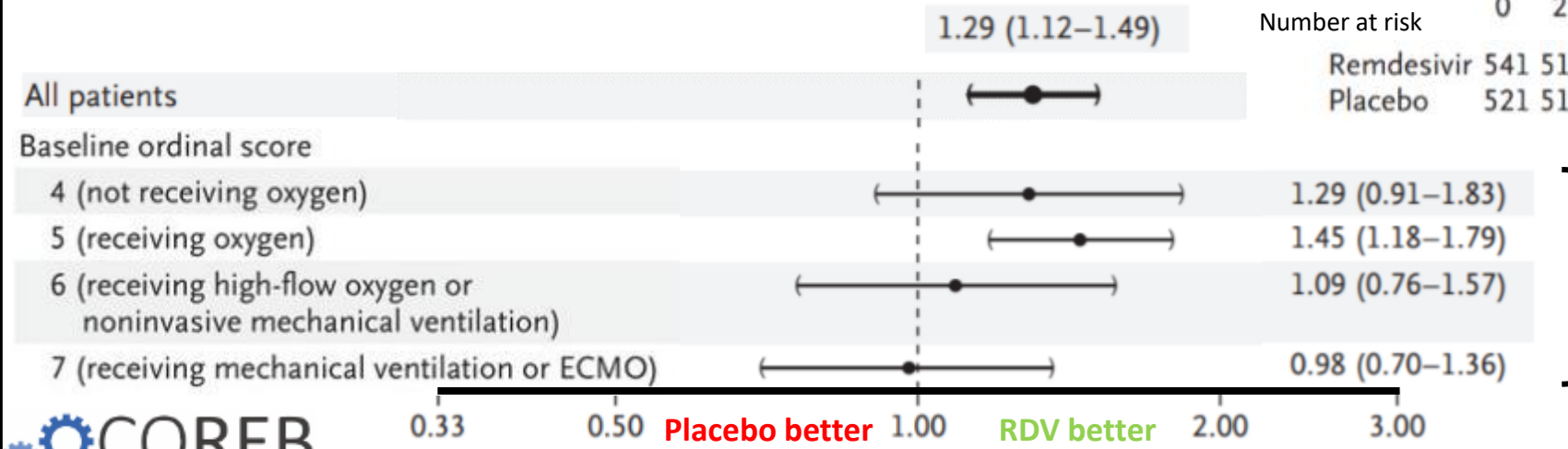
Anti viral effect

# 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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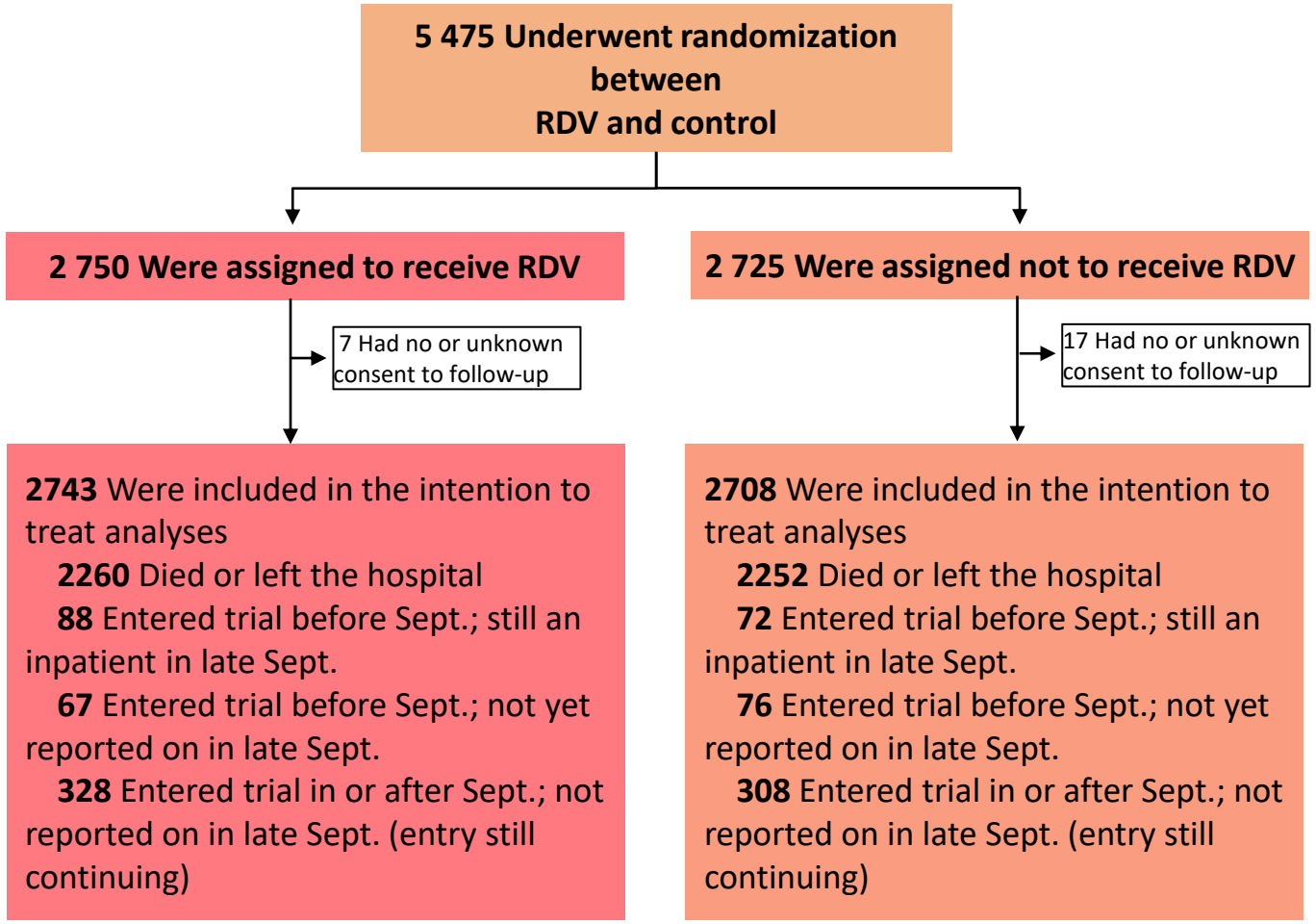
Anti viral effect

# 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

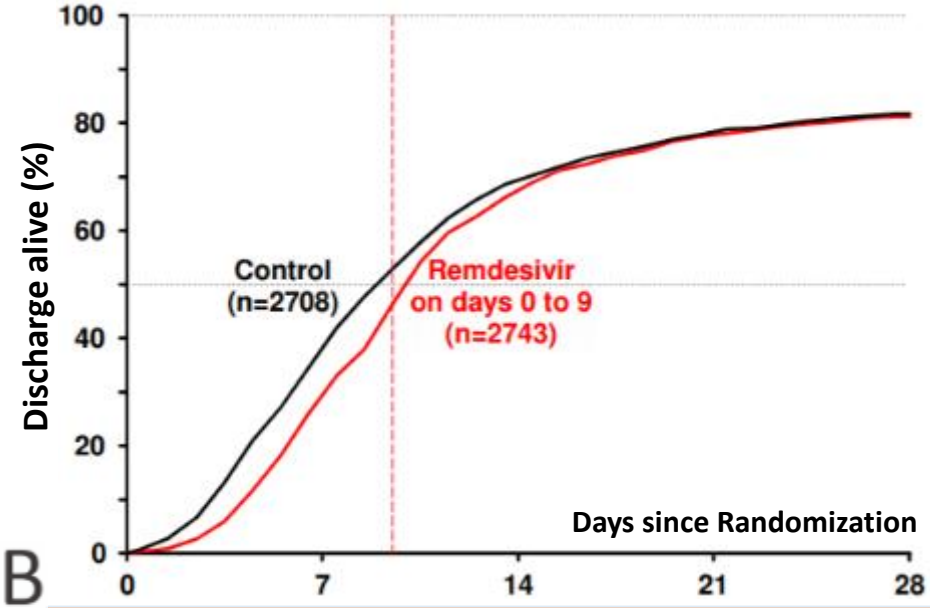
# Remdesivir (RDV) - 3

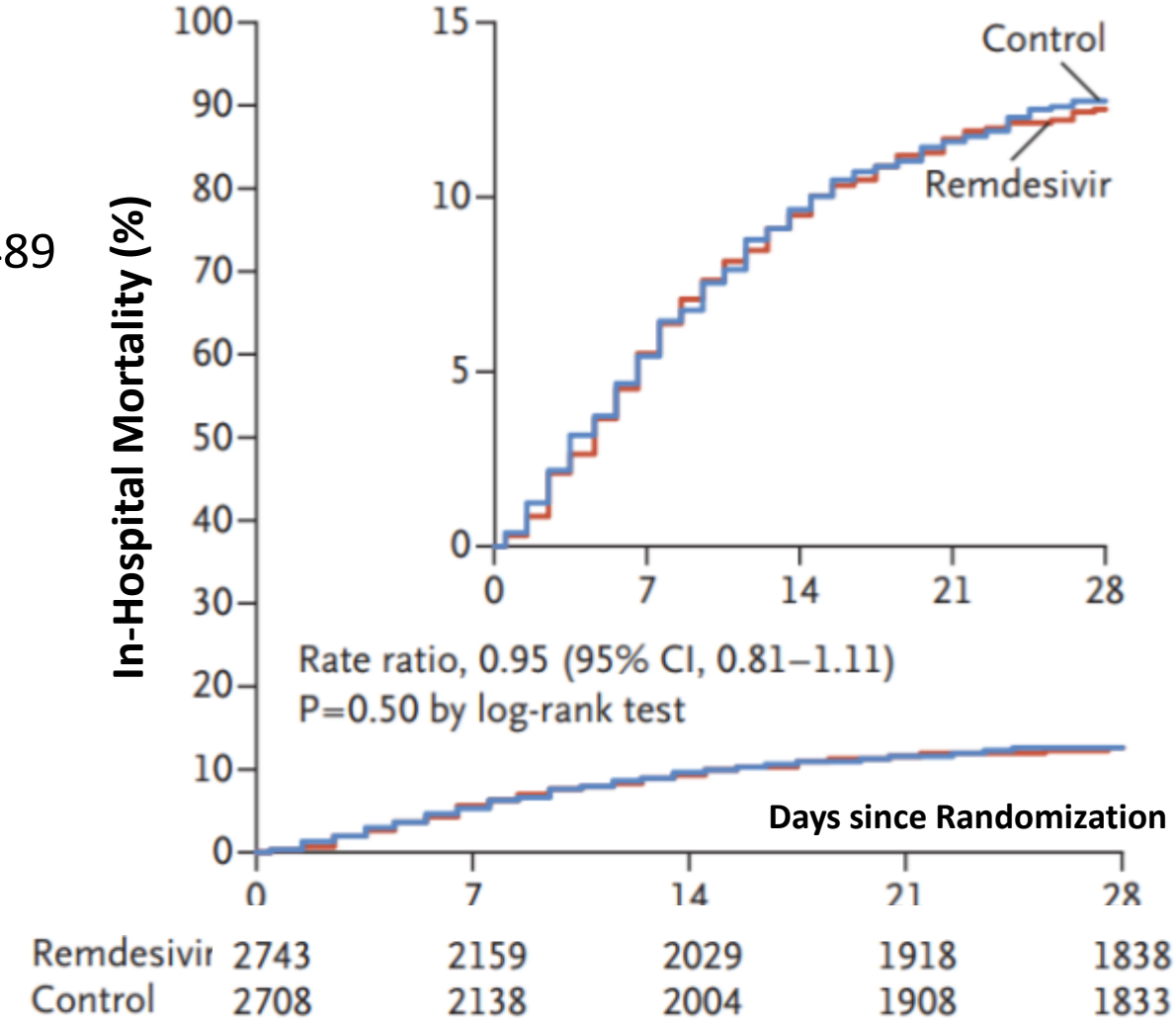
| Characteristics | | All (N= 11 266) | RDV (N= 2 743) | Control (N=2 708) |
|---|---|---|---|---|
| **Age** | < 50 yr – no (%) | 3995 (35) | 961 | 952 |
| | 50-69 yr – no (%) | 5125 (45) | 1282 | 1282 |
| | ≥ 70 yr – no (%) | 2146 (19) | 500 | 469 |
| | | | | |
| **Sex** | Male sex – no (%) | 6985 (62) | 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

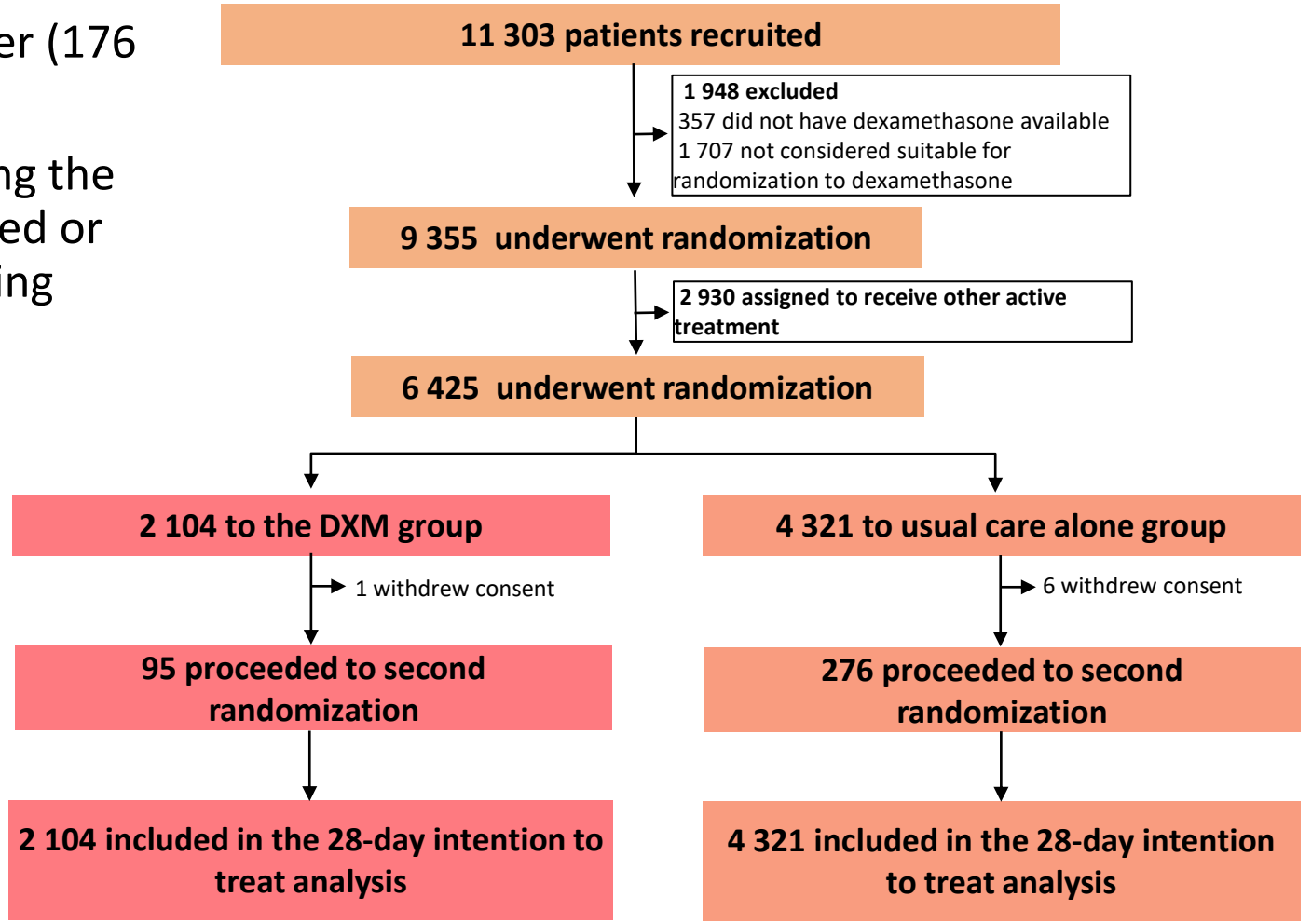
Spinner CD *et al*. *JAMA* Aug 2020
Goldman JD *et al*. *NEJM* Nov 2020

anrs MALADIES INFECTIEUSES ÉMERGENTES

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

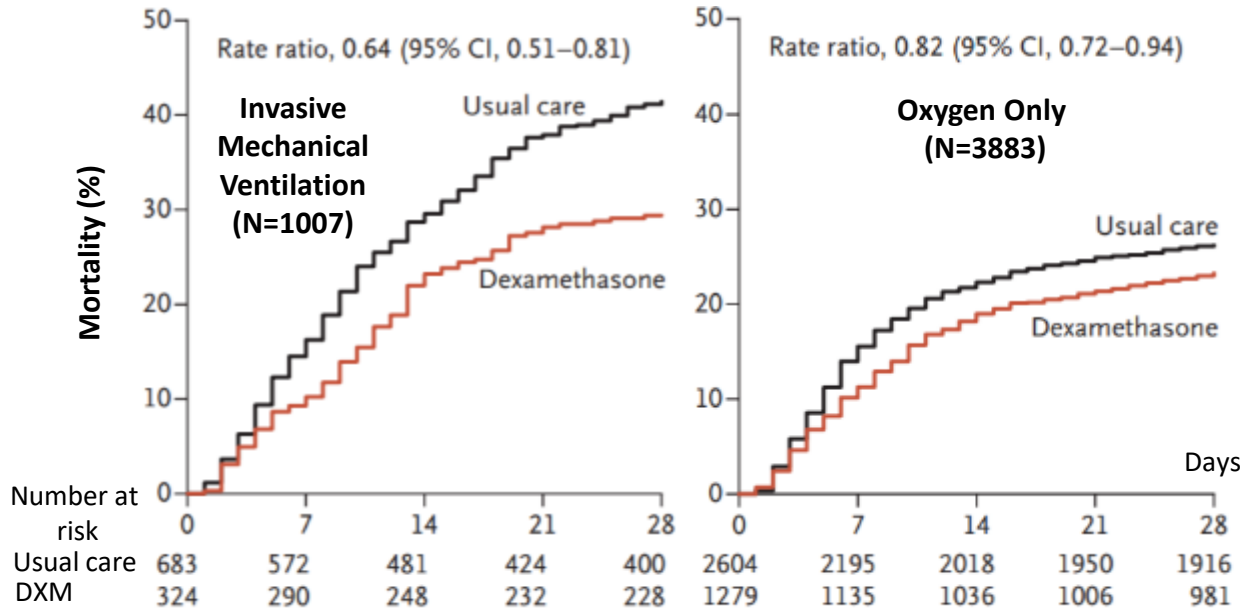
# Corticosteroids (CT) - 1

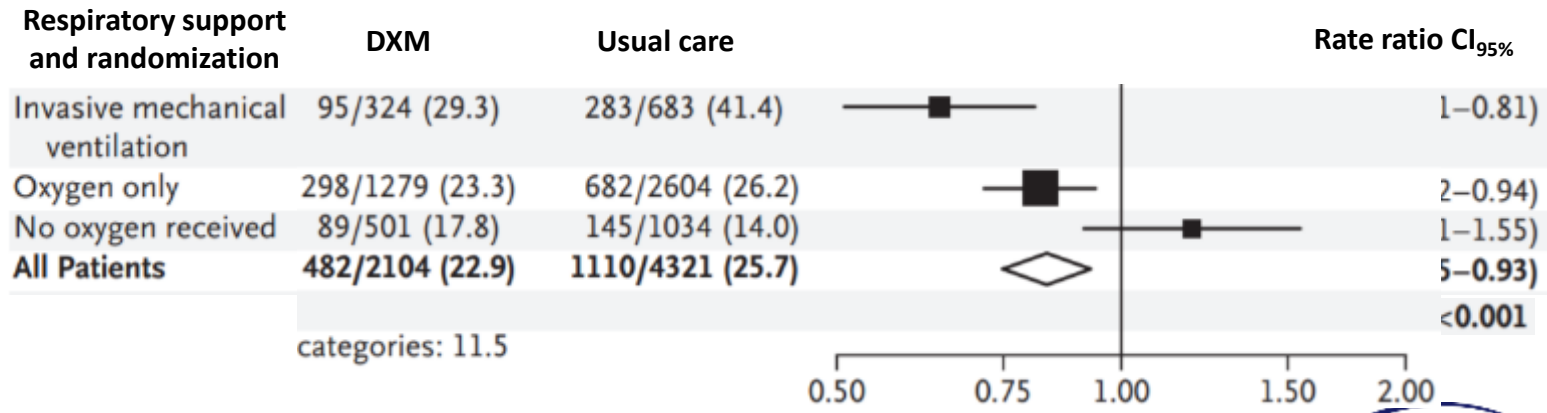
| | Treatment assignment | |
|---|---|---|
| **Characteristics** | **DXM (N=2 104)** | **Usual care (N=4 321)** |
| Age ≥ 70 yr – no (%) | 963 (45) | 1817 (42) |
| Female sex – no (%) | 766 (36) | 1572 (36) |
| **Coexisting conditions** | | |
| Diabetes – no (%) | 521 (25) | 1025 (24) |
| Heart disease – 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



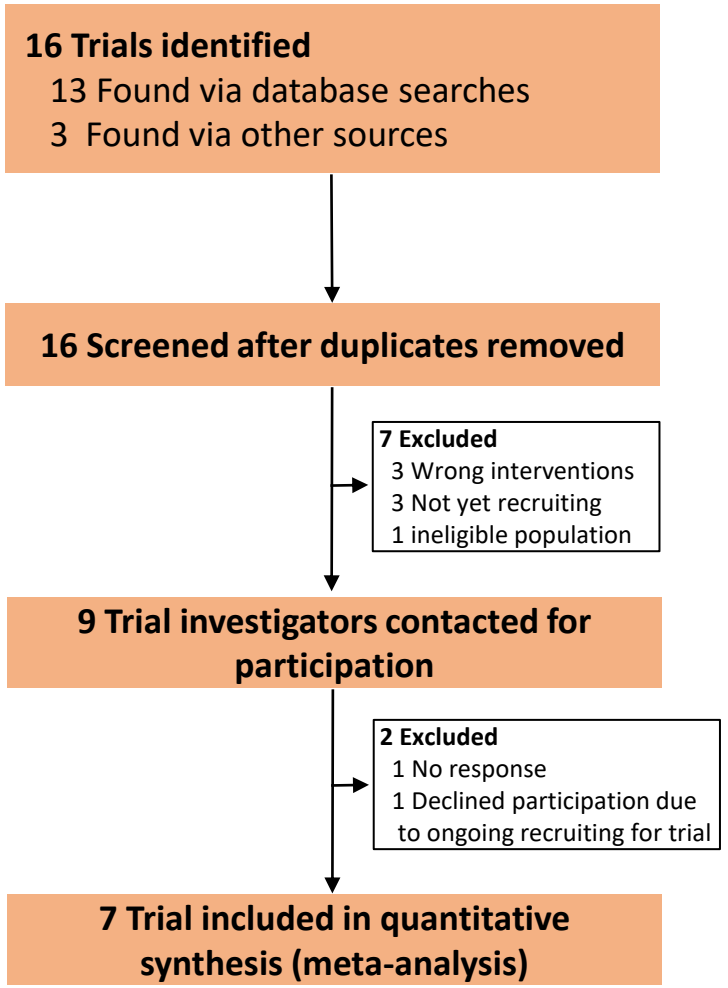




RECOVERY *collaborative group NEJM* Jul 2020

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**



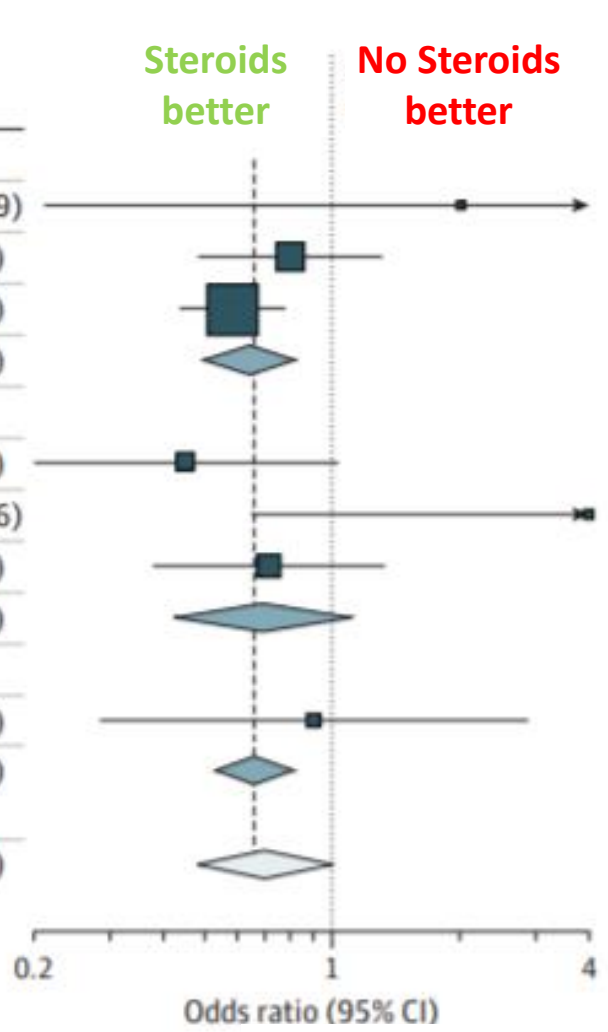

Sterne *et al. JAMA* Sep 2020

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 $_{95\%}$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 |

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 |



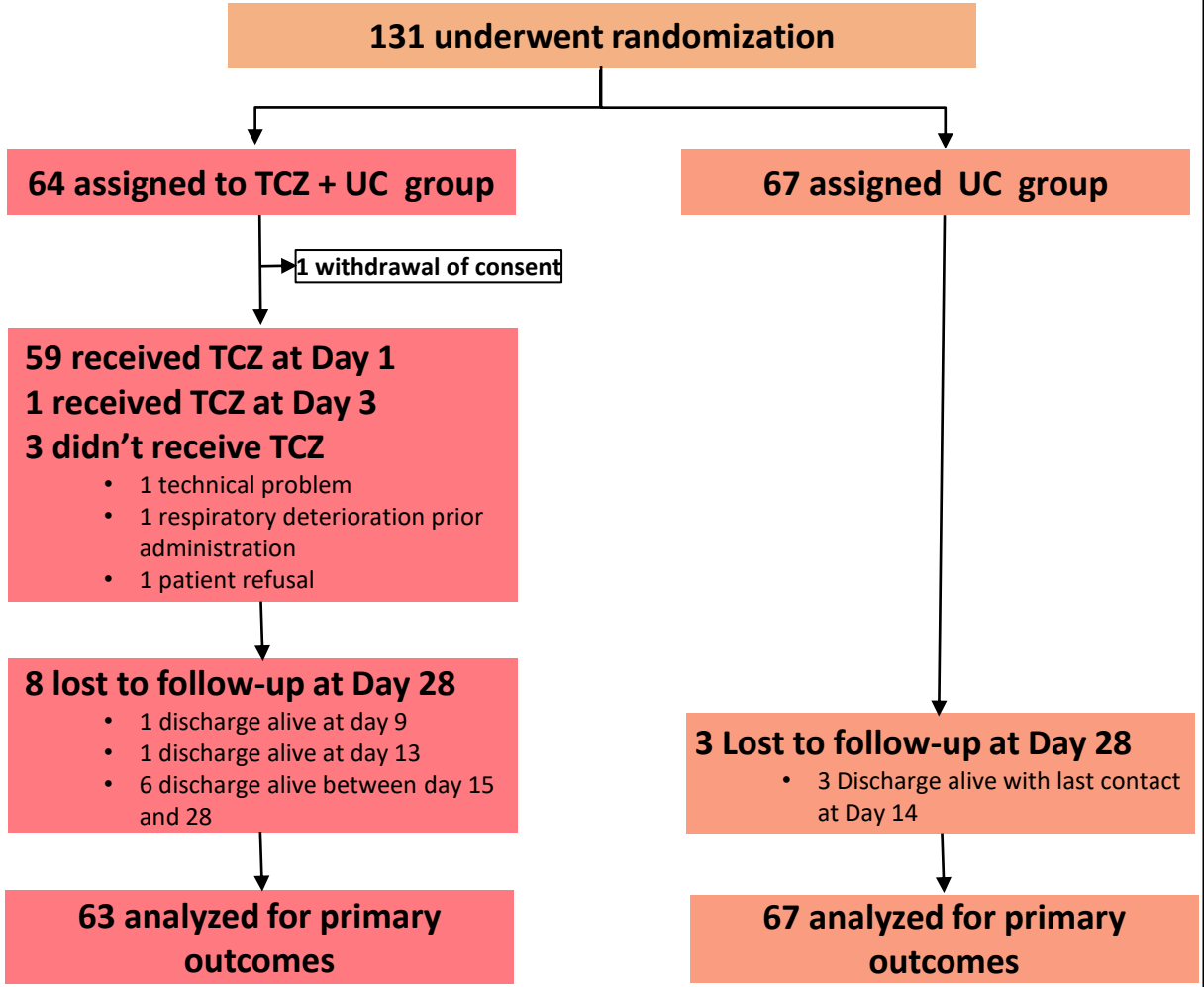
HC: hydrocortisone

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

Monoclonal antibody

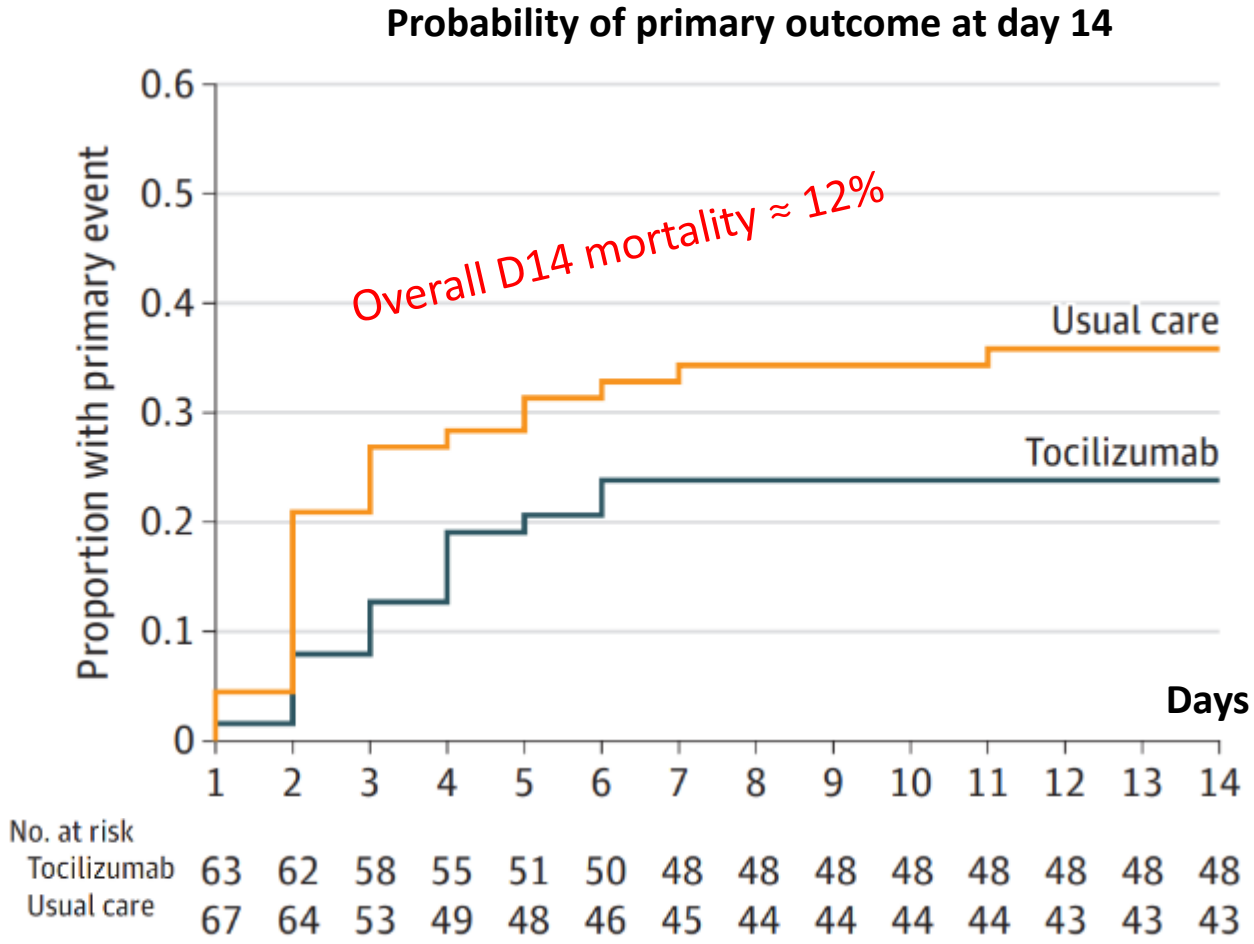
# Tocilizumab (TCZ) - 1

| 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%) |

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, D14 overall mortality ≈ 12%



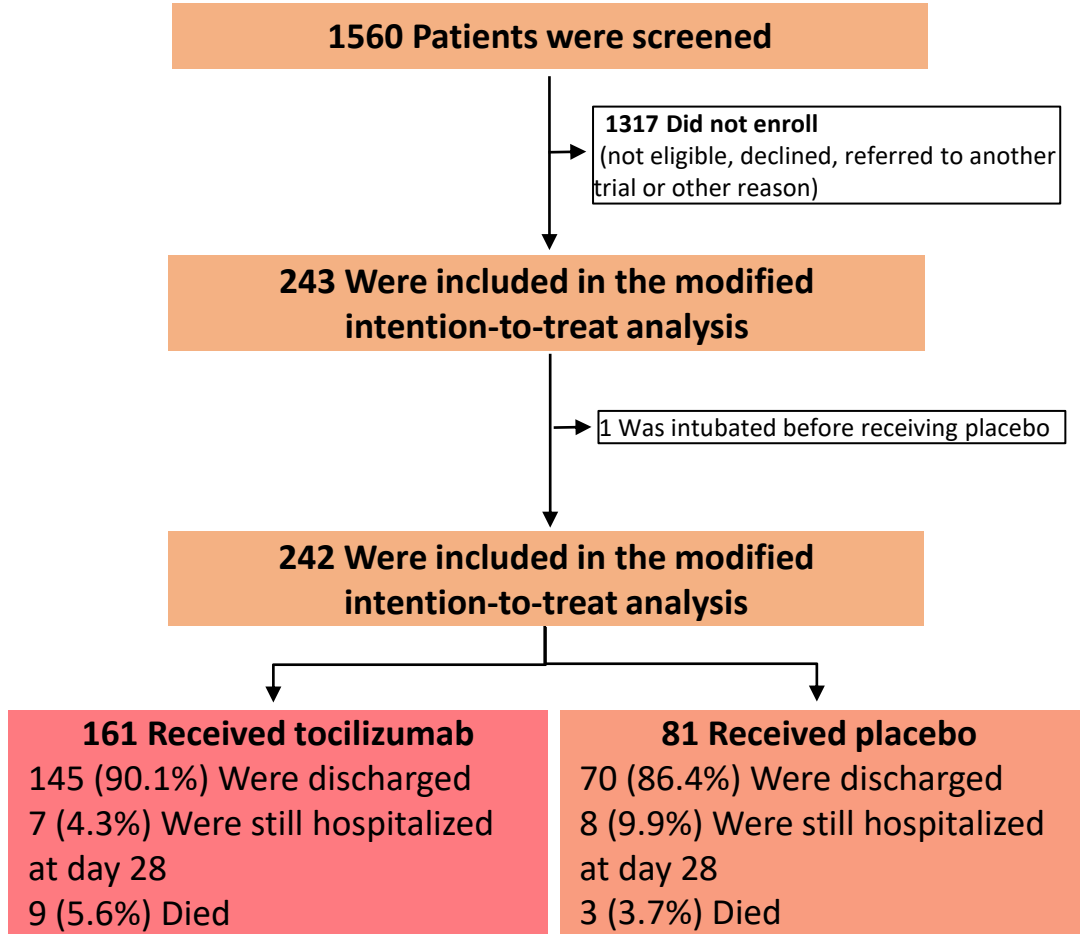

UC: usual care
NIV: non invasive ventilation - MV: mechanical ventilation

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

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

Monoclonal antibody

# 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) |



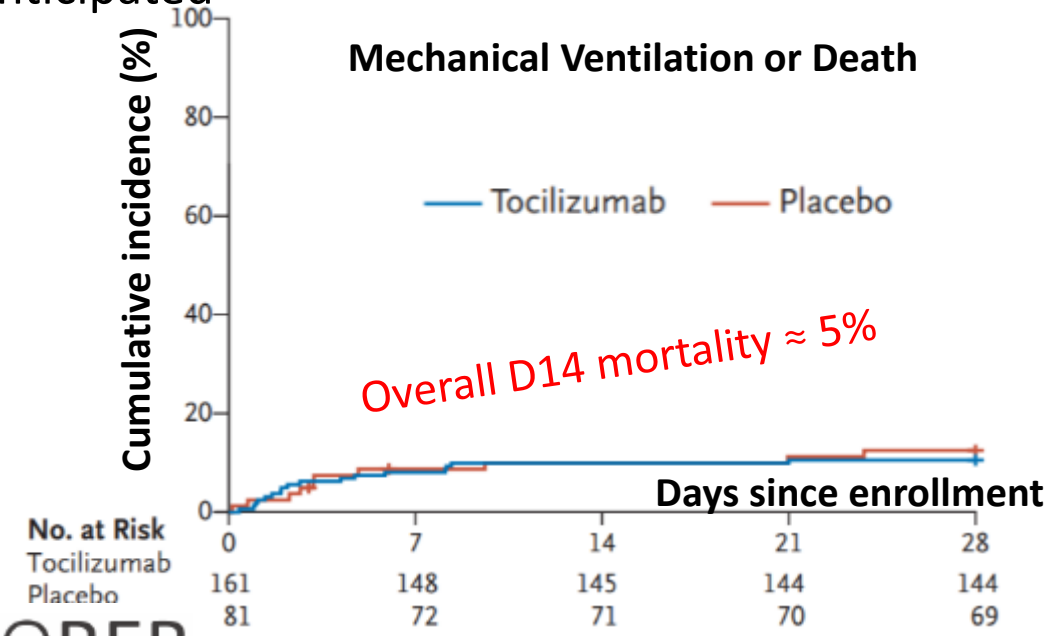
CT: corticosteroids

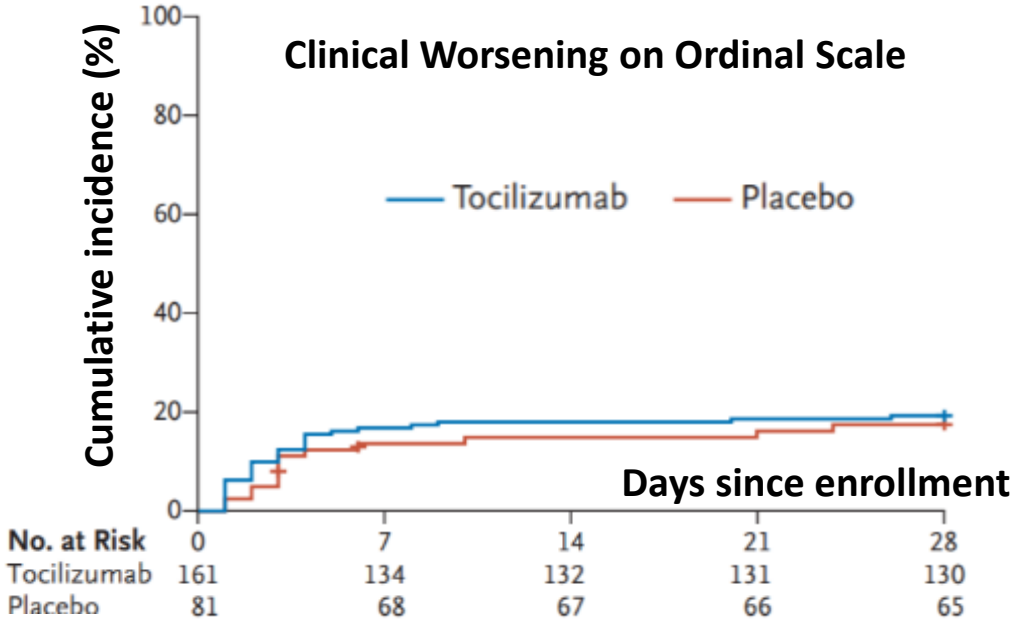
Stone JH *et al. NEJM* Dec 2020

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



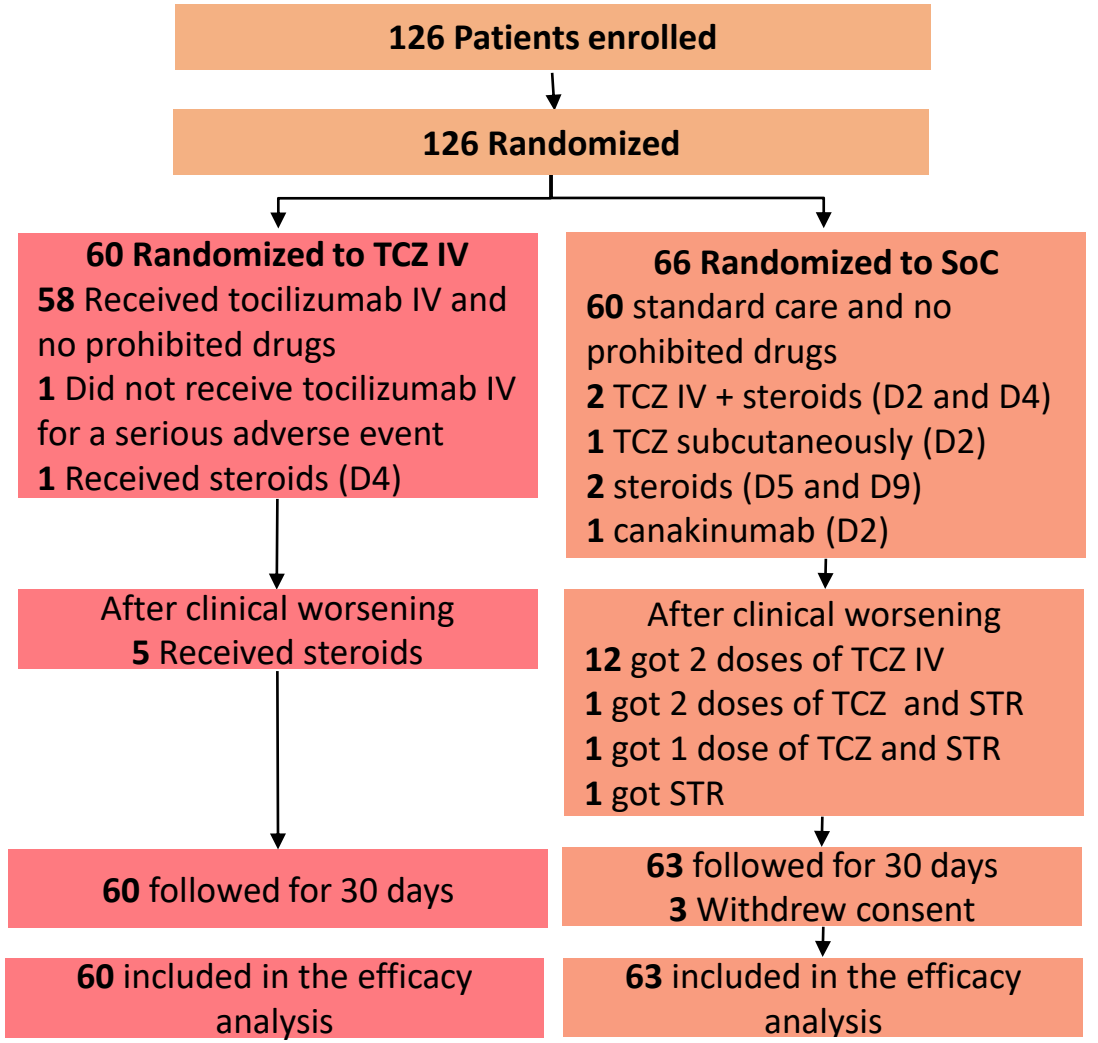




Stone JH *et al. NEJM* Dec 2020

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

Monoclonal antibody

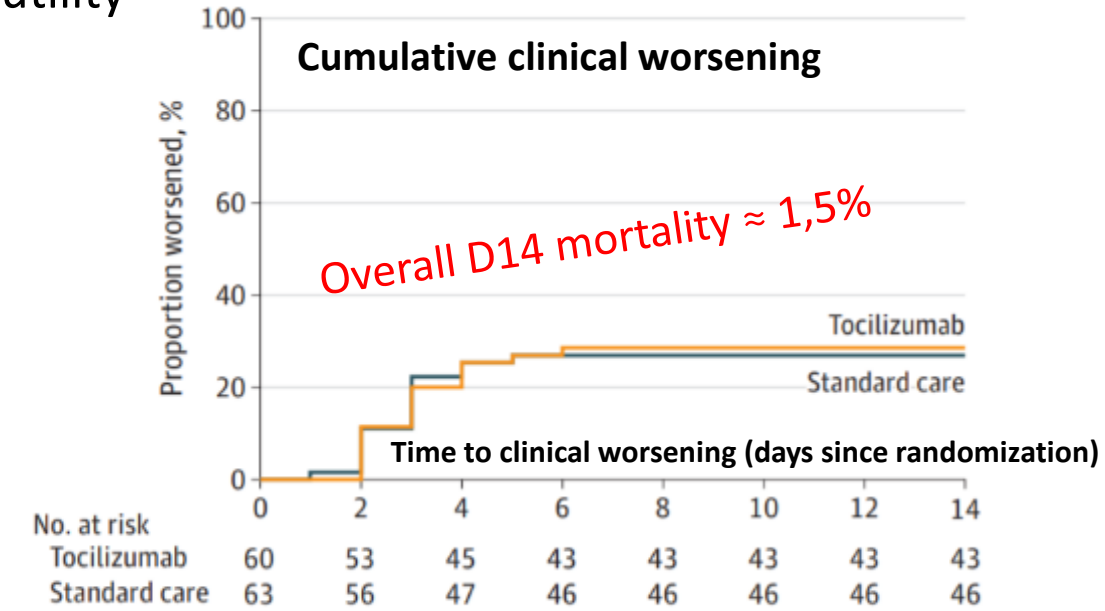
# Tocilizumab (TCZ) - 3

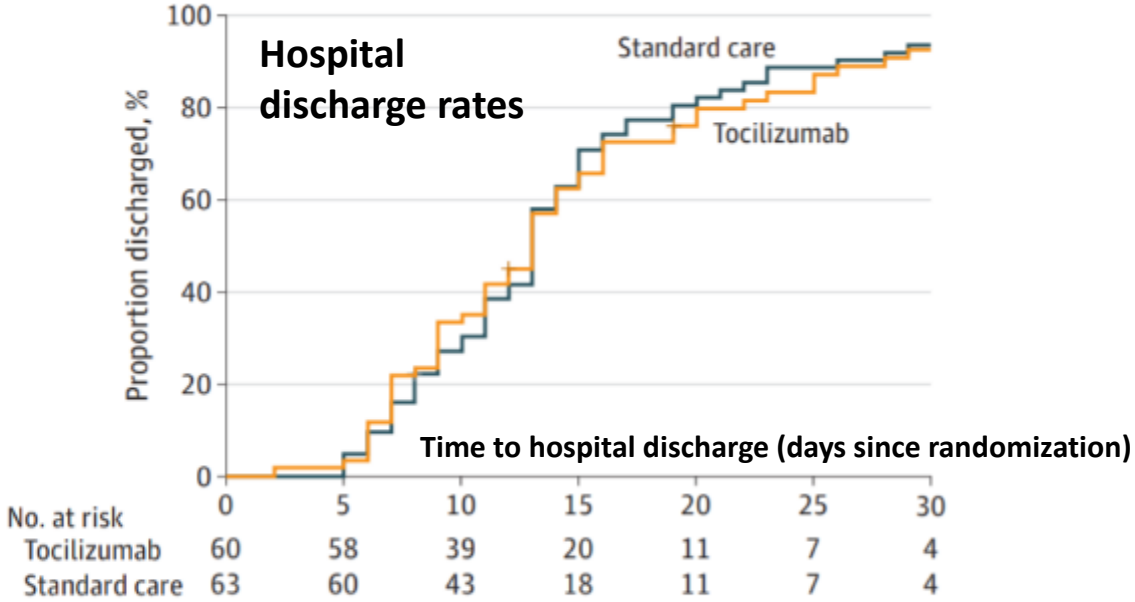
| Characteristics | TCZ (N=60) | SoC (N=66) | Overall (N=126) |
|---|---|---|---|
| Age (y) – median (IQR) | 61,5 (51,5-73,5) | 60,0 (54,0-69,0) | 60,0 (53,0-72,0) |
| Male sex – no (%) | 40 (66,7) | 37 (56,1) | 77 (61,1) |
| BMI ≥ 30 kg/m² – no (%) | 16 (28,1) | 22 (36,1) | 38 (32,2) |
| **Coexisting 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) |

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

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

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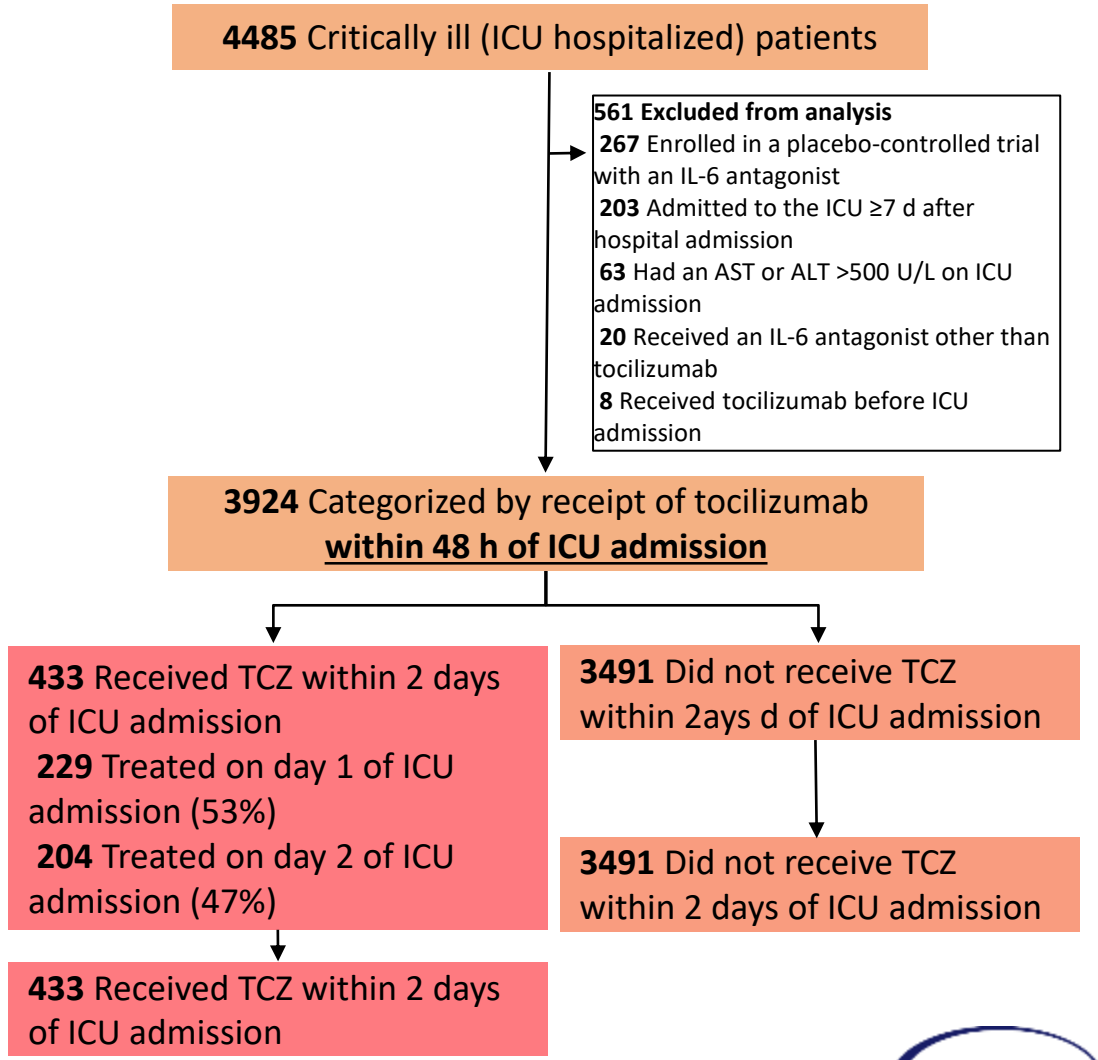
Monoclonal antibody

# 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

Monoclonal antibody

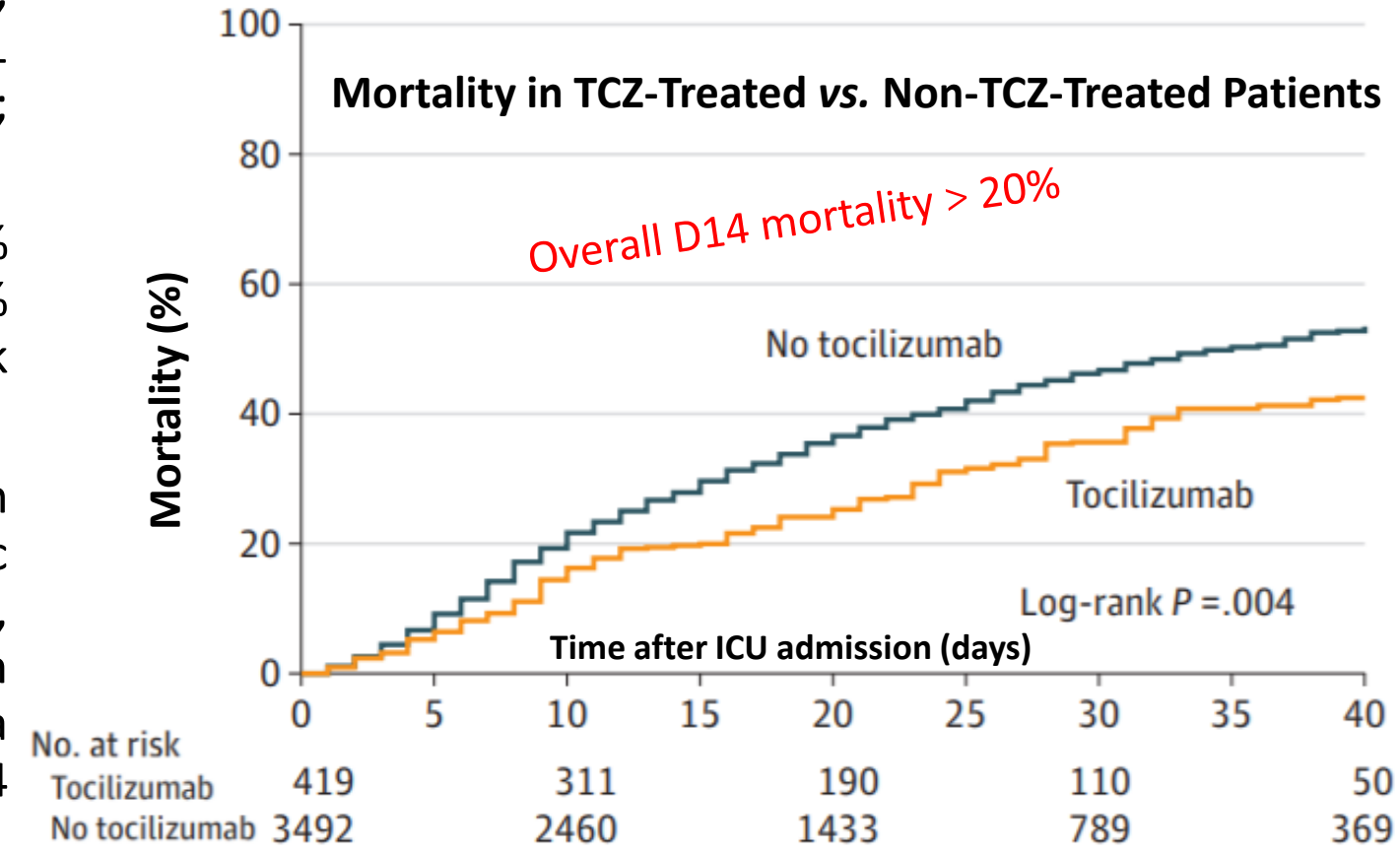
# Tocilizumab (TCZ) - 4

| 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) |

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, high D14 overall mortality >20%

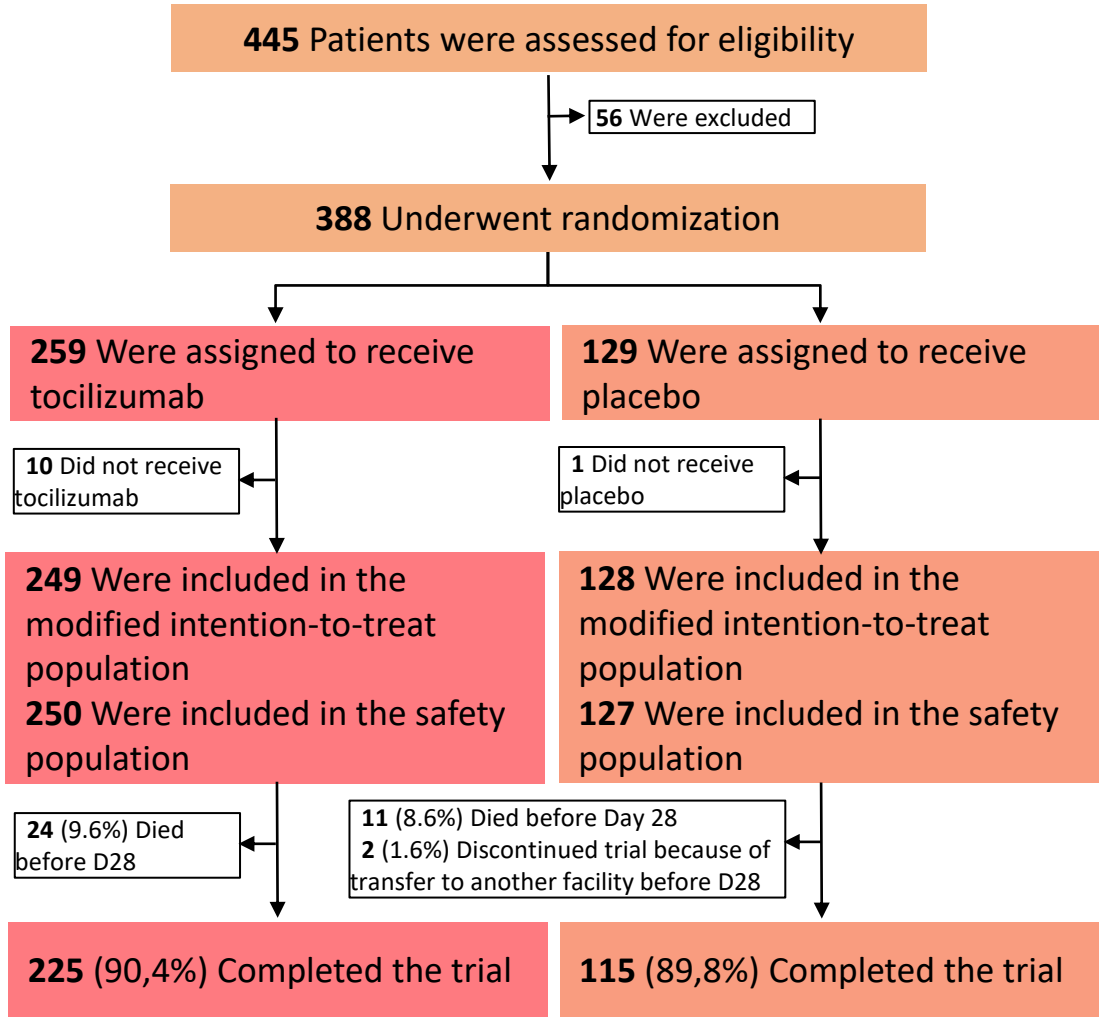



Gupta S *et al. JAMA Int Med* Oct 2020

Monoclonal antibody

# Tocilizumab (TCZ) - 5

- Randomized, double-blind, placebo-controlled, phase 3 trial
- **Inclusion criteria**: age ≥ 18 yo, positive SARS-CoV-2 RT-PCR, radiographic imaging pneumonia
- **Exclusion criteria**: $SpO_2$ < 94% (room air) if receiving continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation, progression of the illness to death was imminent and inevitable within 24 hours, active tuberculosis or suspected active bacterial, fungal, or viral infection (other than SARS-CoV-2)
- **Primary outcome**: mechanical ventilation or death by day 28
- **Secondary outcome** (one of them): Median time to hospital discharge or readiness for discharge
- 388 participants; **249 TCZ group, 128 placebo group** (2:1)




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

Salama C *et al. NEJM* Jan 2021

Monoclonal antibody

# Tocilizumab (TCZ) - 5

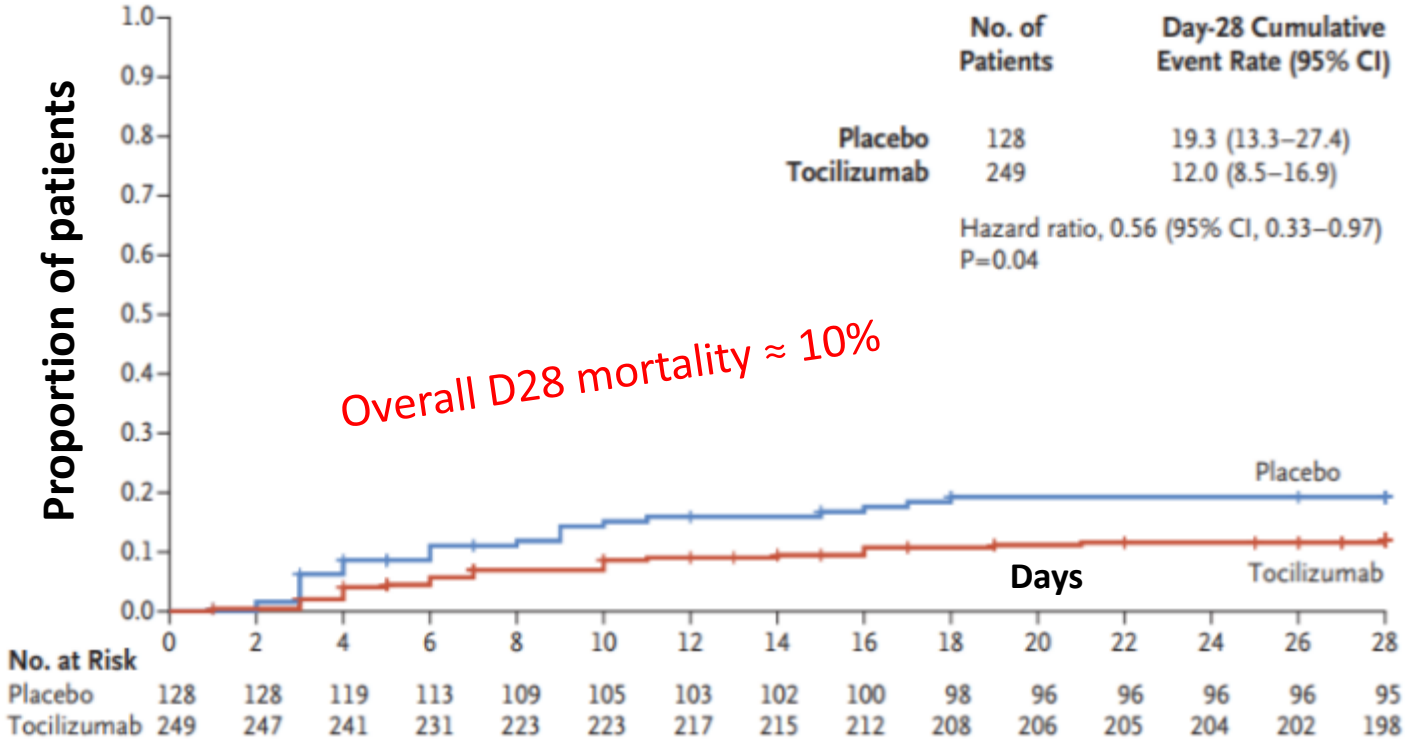
| Characteristics | TCZ (N=249) | Placebo (N=128) |
|---|---|---|
| Age (y) – mean (SD) | 56 (14,3) | 55,6 (14,9) |
| Male sex – no (%) | 150 (60,2) | 73 (57) |
| BMI (kg/m²) – mean (SD) | 32 (7,9) | 33,1 (7,2) |
| **Category on seven-category ordinal scale for clinical status** | | |
| 2 – no (%) | 24 (9,6) | 11 (8,6) |
| 3 – no (%) | 161 (64,7) | 81 (63,3) |
| 4 – no (%) | 64 (25,7) | 36 (28,1) |
| **Others** | | |
| C-reactive protein level ( mg/L) — median (range) | 124,50 (2,5–2099,0) | 143,40 (9,0–3776,0) |
| Ferritin level (pmol/L) — median (range) | 1401,34 (29,2–38 482,1) | 1353,14 (110,1–122 328,9) |

Monoclonal antibody

# Tocilizumab (TCZ) - 5

- **Mechanical ventilation or death by day 28:** 12% $_{95\%}$CI [8,5-16,9] TCZ group *vs.* 19,3% $_{95\%}$CI [13,3-27,4] placebo group; p=0,04 HR: 0,56; $_{95\%}$CI [0,33-0,97]
- **Median time to hospital discharge or readiness for discharge**: 6 days $_{95\%}$CI [6,0-7,0] TCZ group *vs.* 7,5 days $_{95\%}$CI [7,0-9,0] placebo group; HR: 1,16; $_{95\%}$CI [0,91-1,48]
- **Death from any cause:** 26/249 (10.4%) $_{95\%}$CI [7,2-14,9] TCZ group *vs.* 11/128 (8,6%) $_{95\%}$CI [4,9-14,9] placebo group; Weighted Difference: 2 $_{95\%}$CI [-5,2-7,8]

**Time to Mechanical Ventilation or Death by Day 28 in the Modified Intention-to-Treat Population**

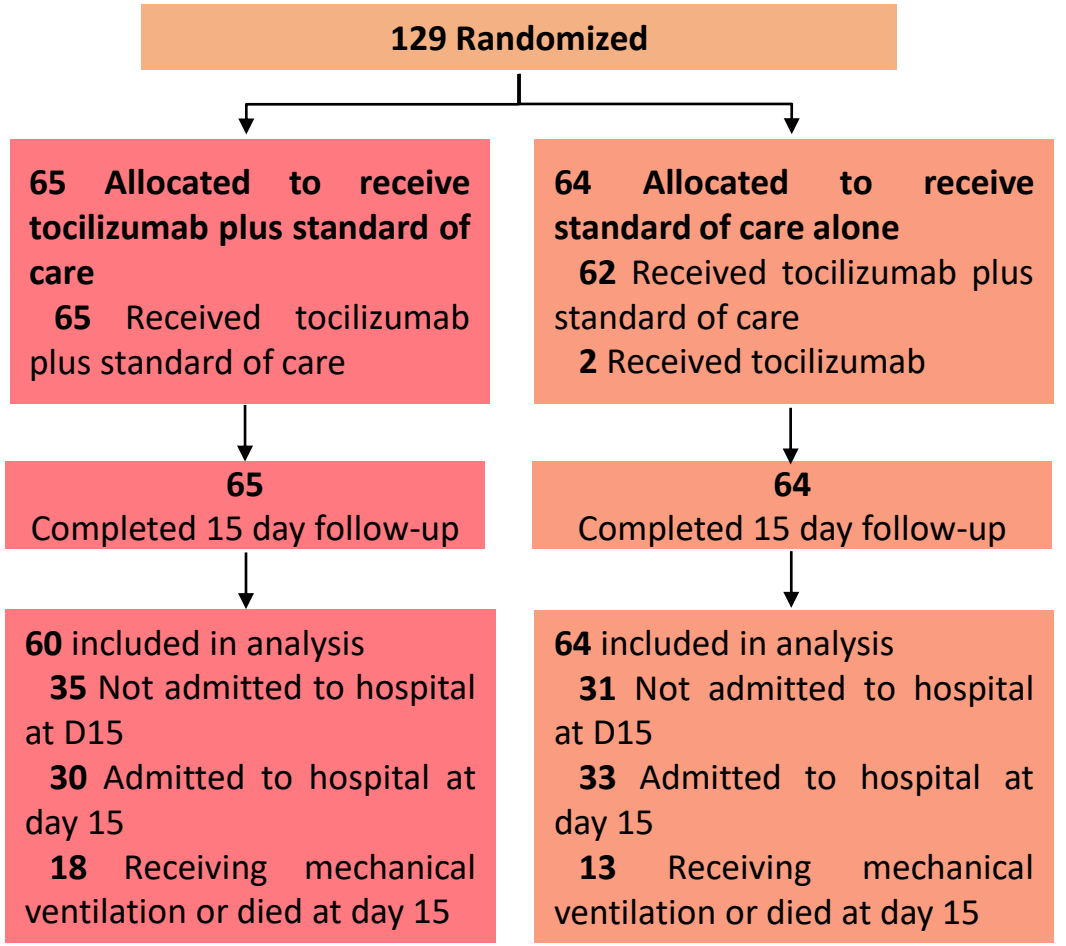



Salama C *et al. NEJM* Jan 2021

Monoclonal antibody

# Tocilizumab (TCZ) - 6

- Randomized, multicenter, open label trial, Brazil
- **Inclusion criteria**: hospitalized patients, age ≥ 18 yo, positive SRAS-CoV-2 PCR, symptoms > 3 days, receiving supplemental $O_2$ or mechanical ventilation, ≥ 2 serum biomarkers abnormal levels (C reactive protein, D dimer, lactate dehydrogenase, or ferritin)
- **Exclusion criteria** : uncontrolled infection, raised ASAT or ALAT > 5 times ULN, renal disease (estimated glomerular filtration of <30 mL/min/1.72 $m^2$)
- **Primary outcome**: D15 clinical status (WHO seven level ordinal scale)
- **Secondary outcome** (one of them): D28 all cause mortality
- 129 participants; **65 TCZ group, 64 control group** (1:1)




ULN: upper limit of normal

Veiga VC *et al. BMJ Jan* 2021

Monoclonal antibody

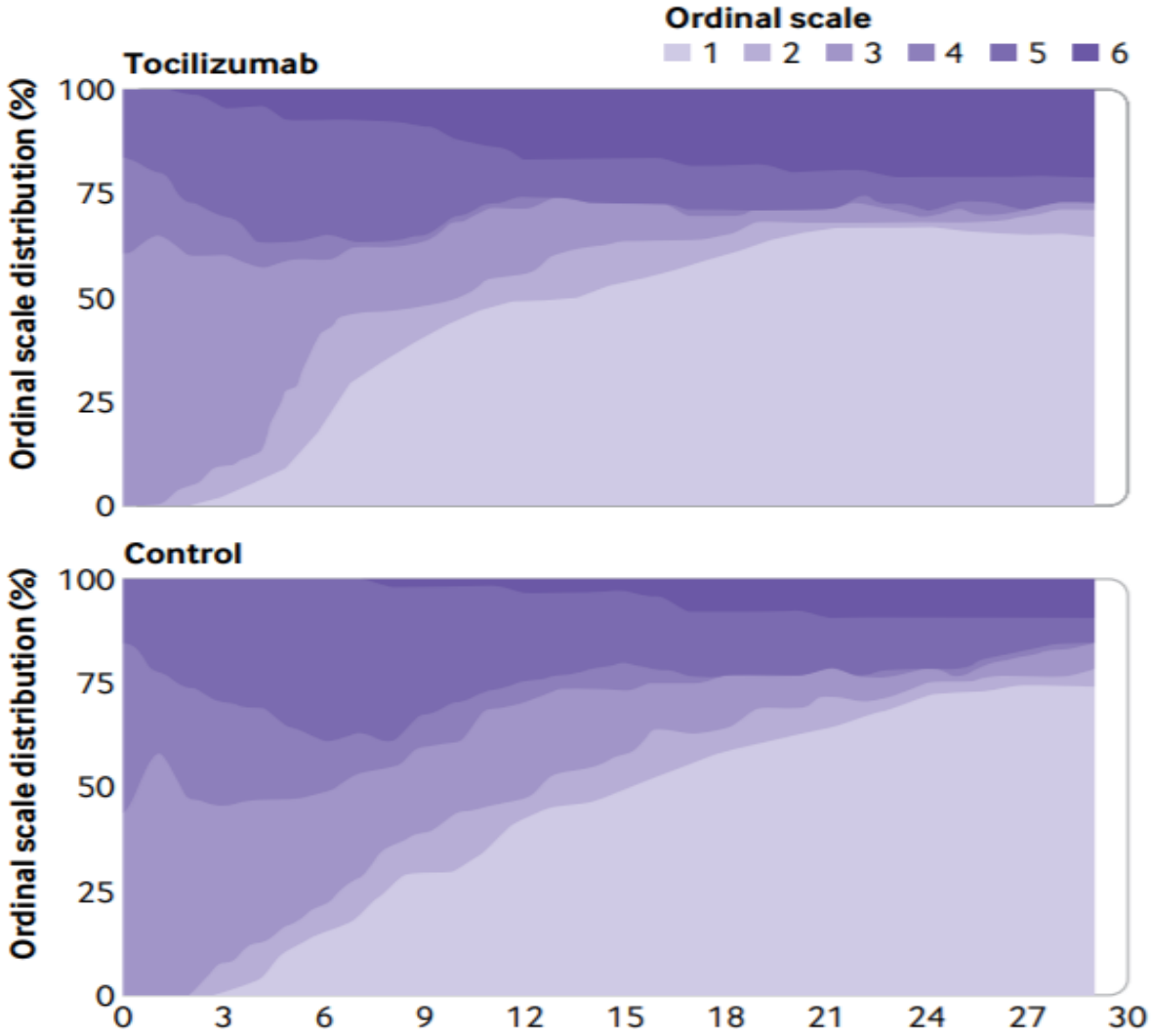
# Tocilizumab (TCZ) - 6

| Characteristics | TCZ (N=65) | Control (N=64) |
|---|---|---|
| Age (y) – mean (SD) | 57,4 (15,7) | 57,5 (13,5) |
| Male sex – no (%) | 44 (68) | 44 (69) |
| **Coexisting conditions** | | |
| Hypertension – no (%) | 30 (46) | 34 (53) |
| Diabetes – no (%) | 22 (34) | 20 (31) |
| Obesity – no (%) | 15 (23) | 16 (25) |
| **Others** | | |
| Days from symptom onset to randomization — mean (SD) | 10 (3,1) | 9,5 (3,0) |
| Respiratory rate (rpm) – median (IQR) | 20 (18-24) | 20 (18-25) |
| Peripheral oxygen saturation (%) — median (IQR) | 95 (92-96) | 95 (93-96) |
| C reactive protein (mg/L) — mean (SD) | 160 (104) | 193 (283) |

Monoclonal antibody

# Tocilizumab (TCZ) - 6

- **Receiving mechanical ventilation or died at day 15:** 18/65 (28%) TCZ group *vs.* 13/64 (20%) placebo group; effect size 1,54 $_{95\%}$CI [0,66-3,66], p= 0,32
- **D15 death**: 11/65 (17%) TCZ group *vs.* 2/64 (3%) placebo group
- **D28 mortality**: 14/65 (21%) TCZ group *vs.* 6/64 (9%) placebo group; OR 2,70 $_{95\%}$CI [0,97-8,35], p= 0,07
- **Mean (SD) D29 ventilator-free days :** 19.4 (12.0) TCZ group *vs.* 20.5 (10.8) placebo group; Rate ratio 1,12 $_{95\%}$CI [0,86-1,99], p= 0,53
- **Limits**: small sample size, investigators did not record the number of patients assessed for eligibility




Veiga VC *et al. BMJ Jan* 2021

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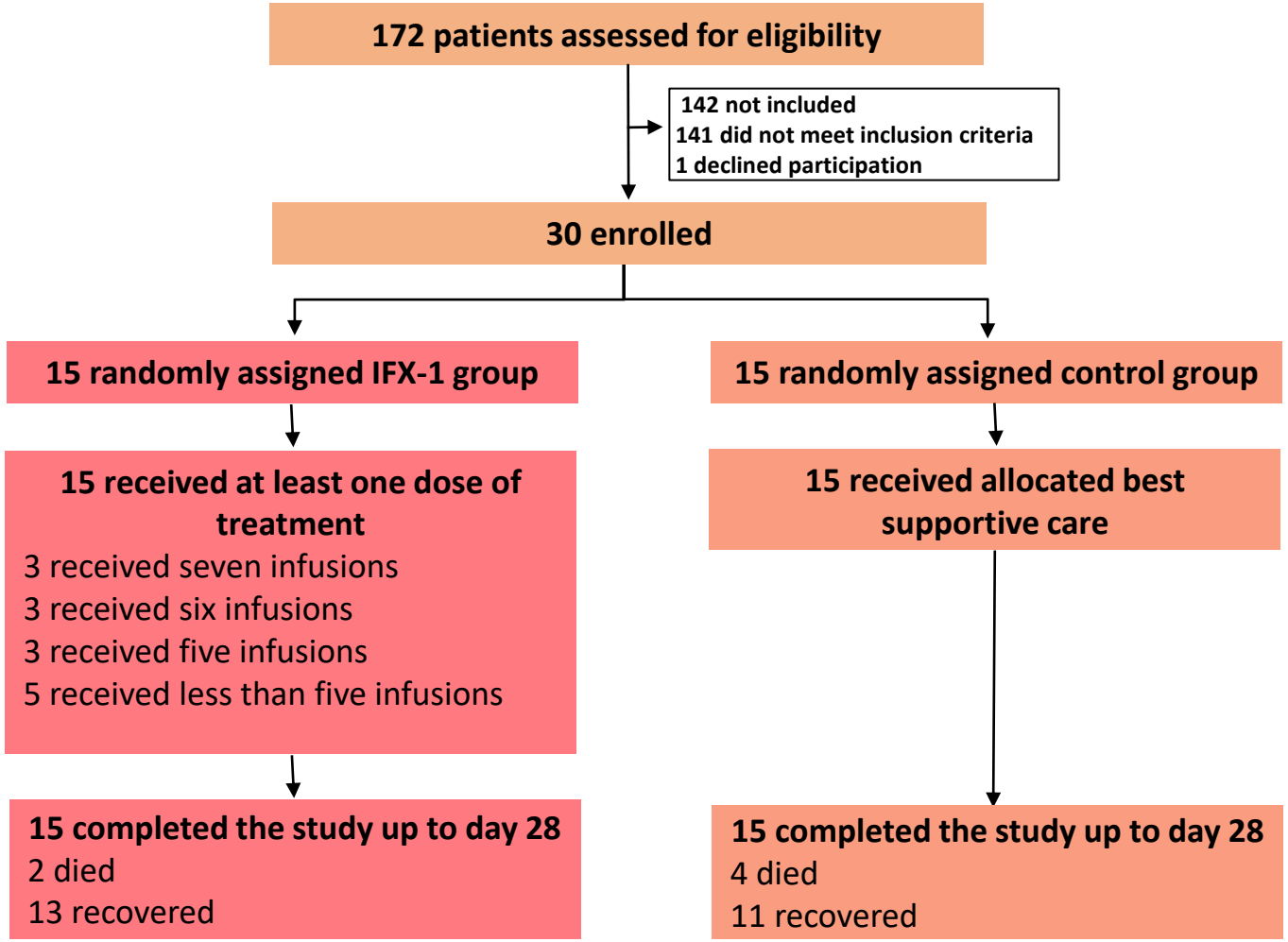
anrs MALADIES INFECTIEUSES ÉMERGENTES

Monoclonal antibody

# Vilobelimab (IFX-1) - 1

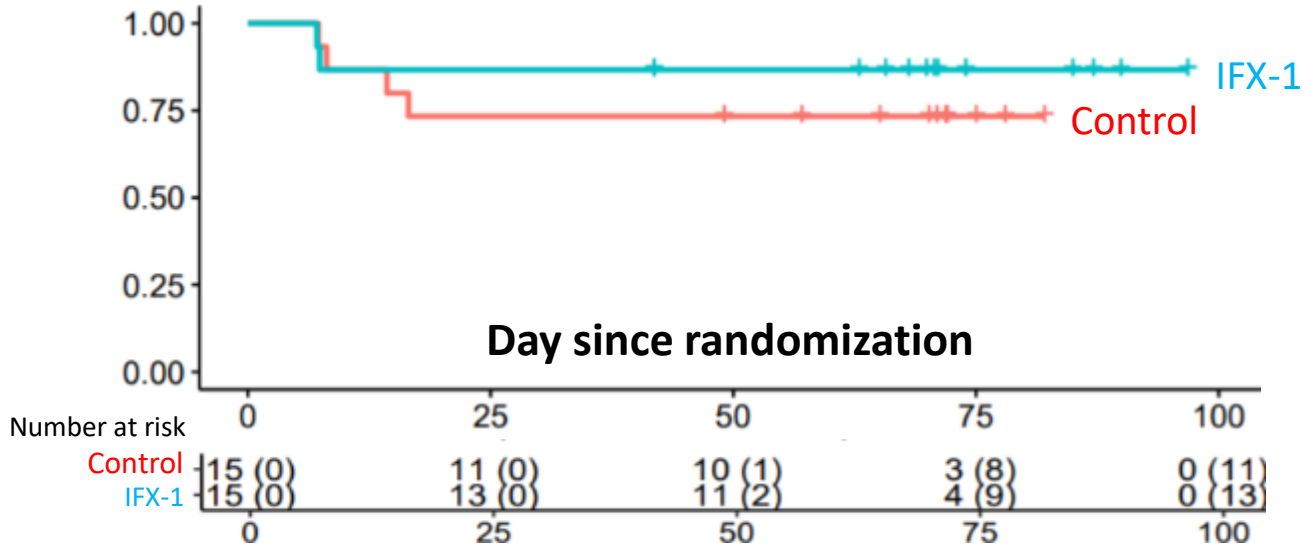
- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria** : age ≥ 18yo, severe pneumonia ($PaO_2/FiO_2$ between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive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



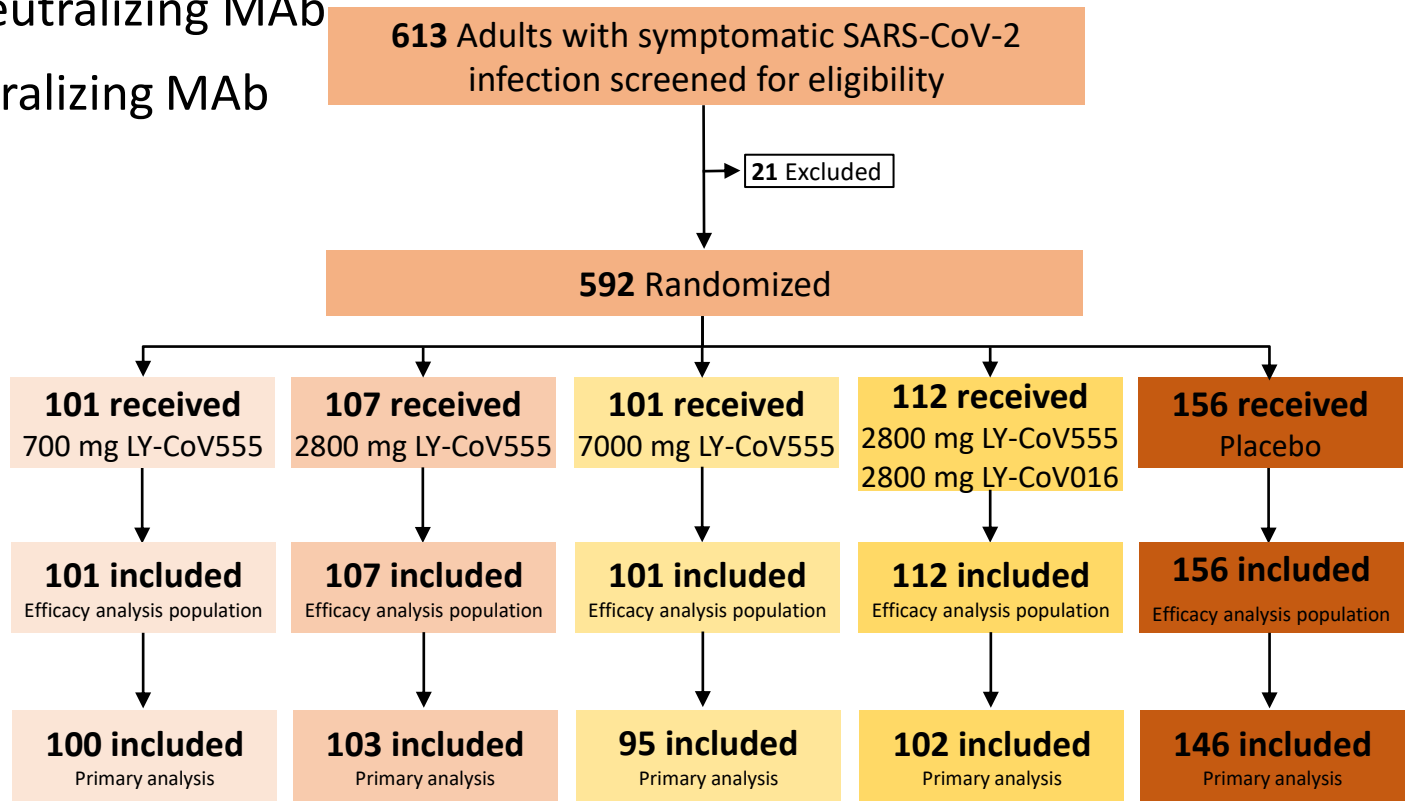

- **Limits**: patient heterogeneity, open label study

| 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

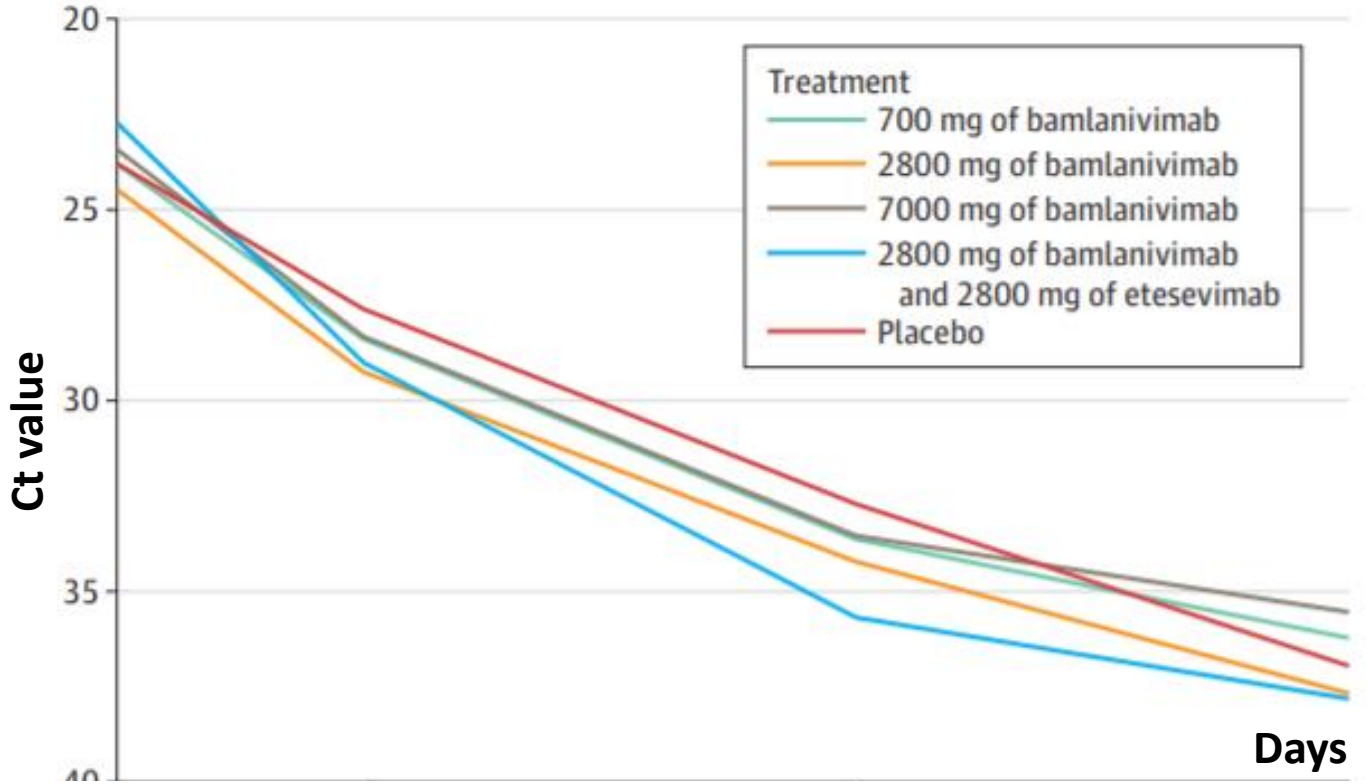
| Characteristics | LY-CoV555 | | | LY-CoV555 + LY-CoV016 | Placebo |
|---|---|---|---|---|---|
| | 700 mg N=101 | 2800 mg N=107 | 7000 mg N=101 | 2800 mg + 2800 mg N= 112 | N= 156 |
| Age (y) – median (IQR) | 39 (31-58) | 45 (31-56) | 46 (34-55) | 44 (30-60) | 46 (35-57) |
| Female sex – no (%) | 63 (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) |

Gottlieb RL *et al. JAMA* Jan 2021

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



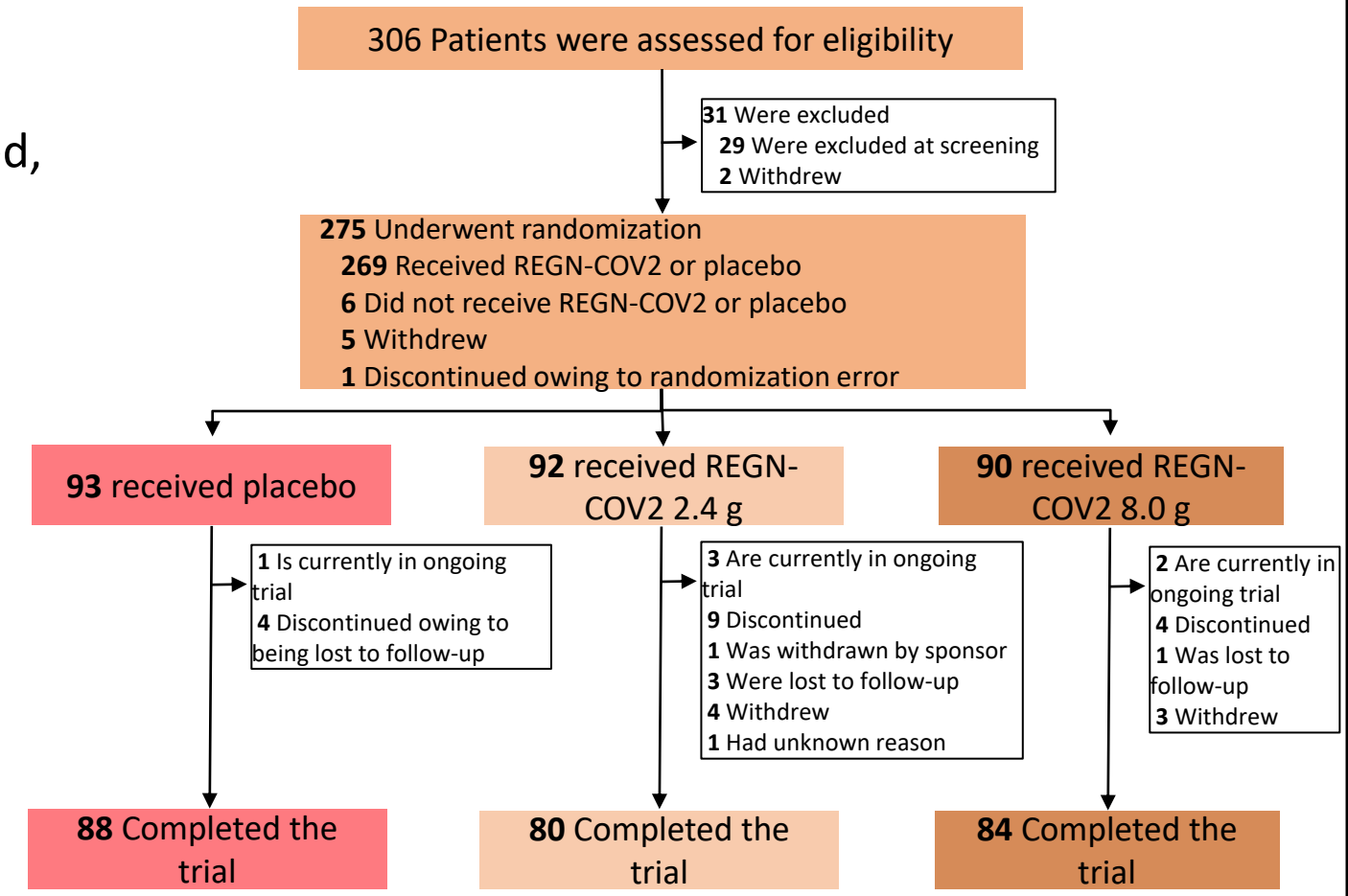

| Treatment, No. | | | | |
|---|---|---|---|---|
| 700 mg of bamlanivimab | 101 | 96 | 98 | 100 |
| 2800 mg of bamlanivimab | 107 | 98 | 101 | 103 |
| 7000 mg of bamlanivimab | 101 | 93 | 95 | 95 |
| 2800 mg of bamlanivimab and 2800 mg of etesevimab | 109 | 96 | 95 | 102 |
| Placebo | 152 | 141 | 142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

Gottlieb RL *et al. JAMA* Jan 2021

Monoclonal antibody

# 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

Monoclonal antibody

# REGN-COV2

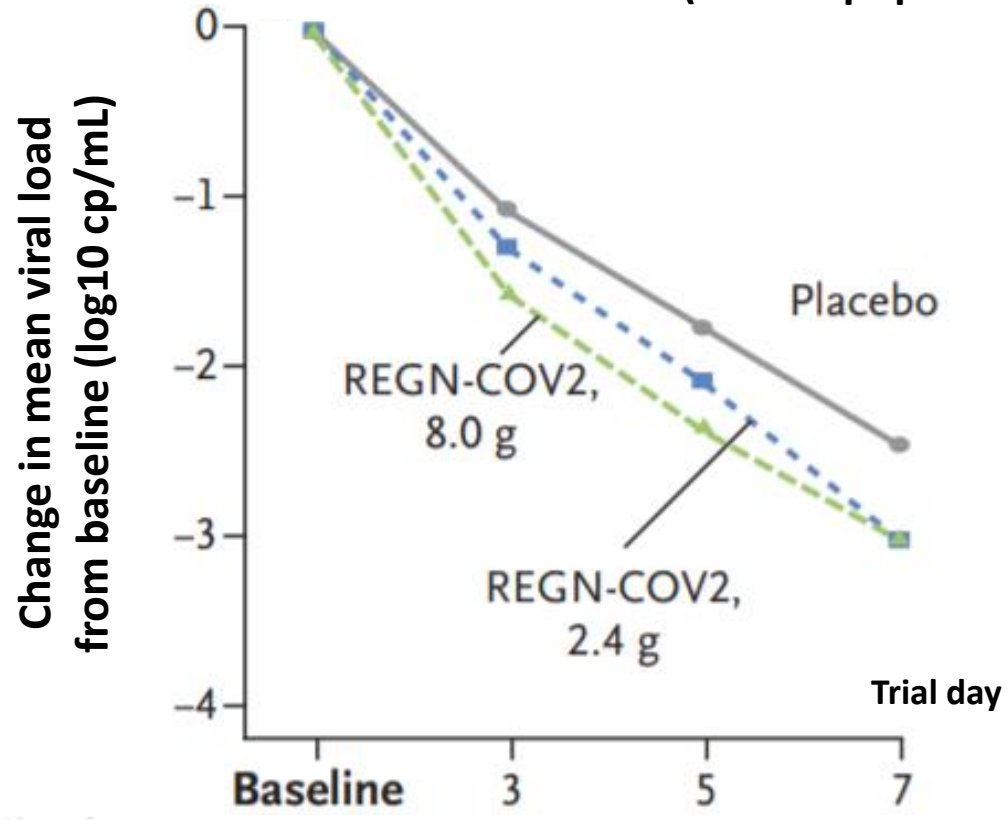
| Characteristics | REGN-COV2 (N=182) | Placebo (N=93) |
|---|---|---|
| Age (y) - median (IQR) | 43,0 (35,0–52,0) | 45,0 (34,0–54,0) |
| Female sex - no (%) | 98 (54) | 43 (46) |
| BMI (kg/m²) - mean (SD) | 30,51 (6,87) | 29,73 (7,15) |
| | | |
| Days from symptom onset to randomization - median (range)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



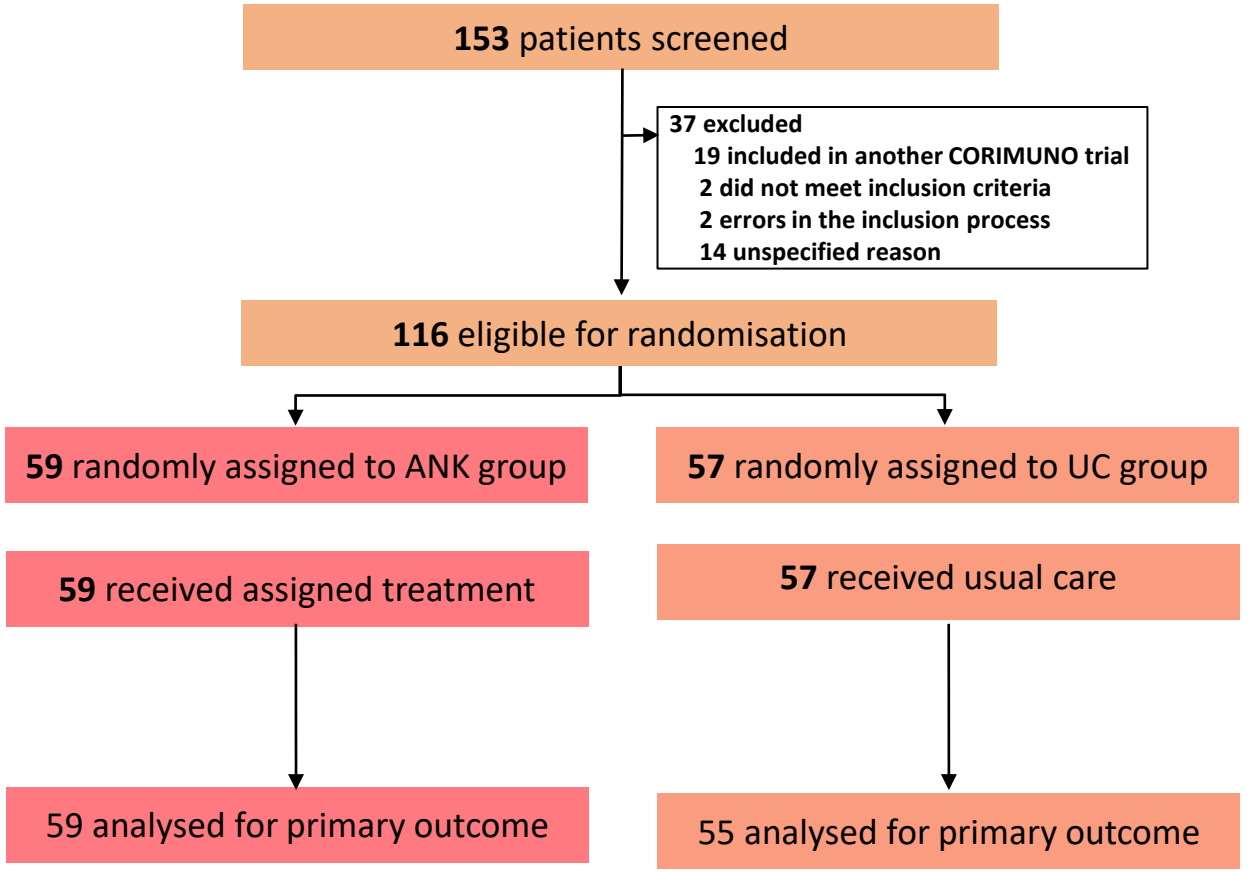

| | | | | |
|---|---|---|---|---|
| Placebo | 81 | 70 | 78 | 78 |
| REGN-COV2, 2.4 g | 73 | 66 | 69 | 70 |
| REGN-COV2, 8.0 g | 74 | 70 | 73 | 73 |

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

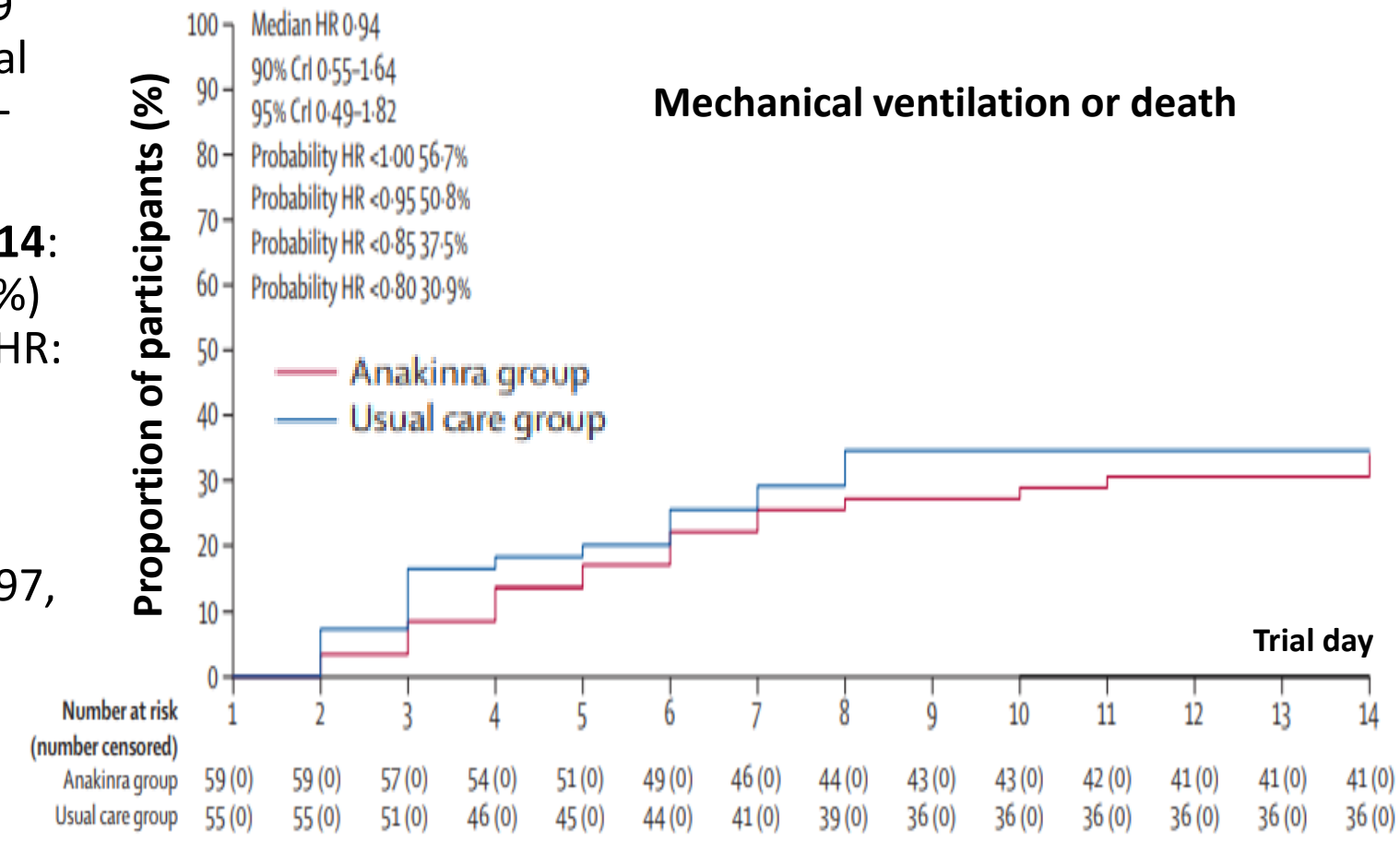
# Anakinra (ANK)

| 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>**

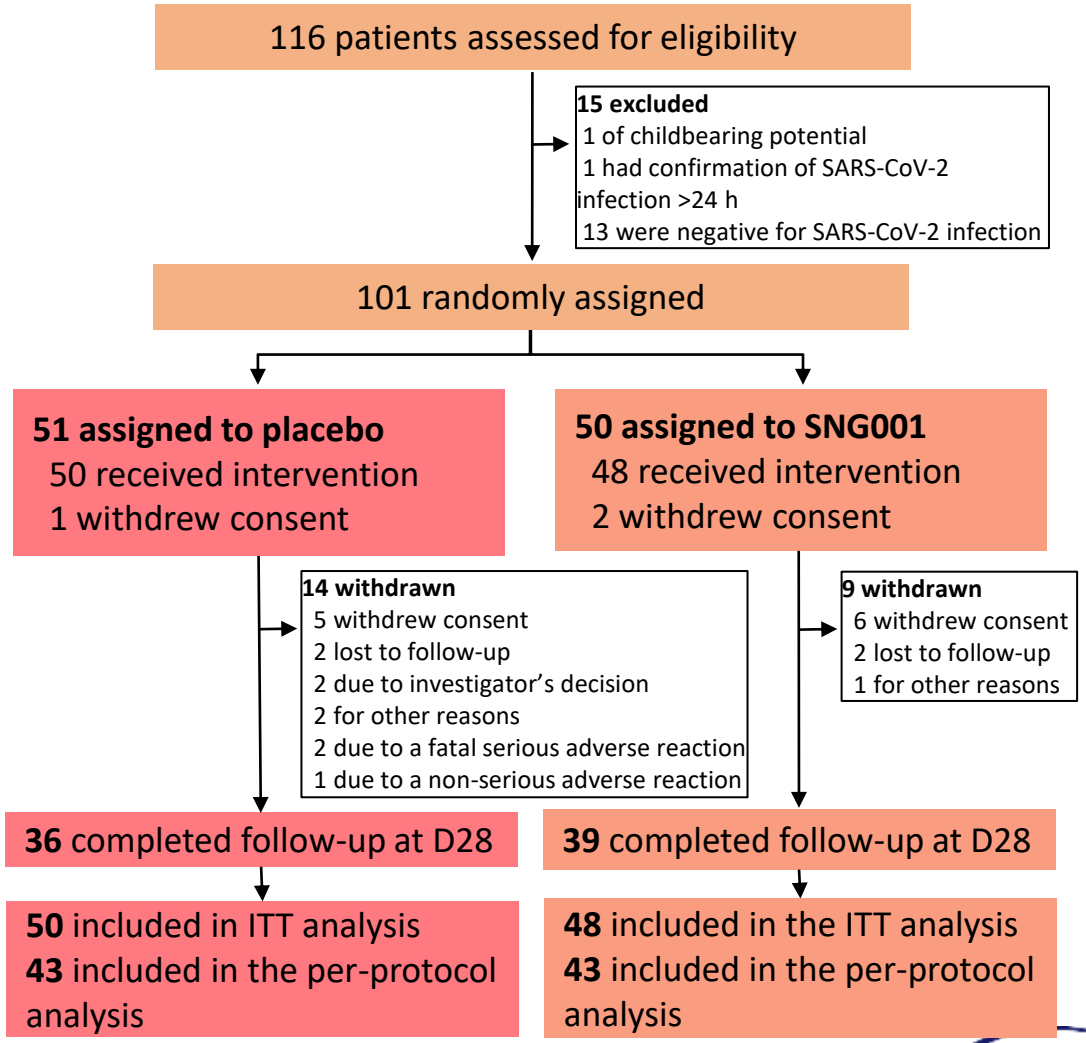



The CORIMUNO-19 Collaborative group. *Lancet Resp Med* Jan 2021

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

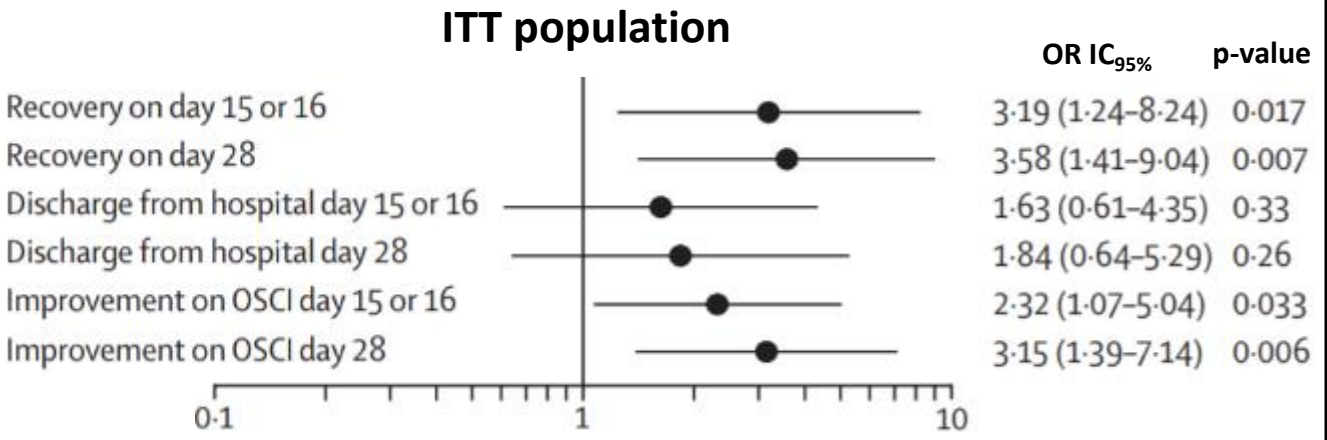
# Interferon beta 1a (INFβ-1a)

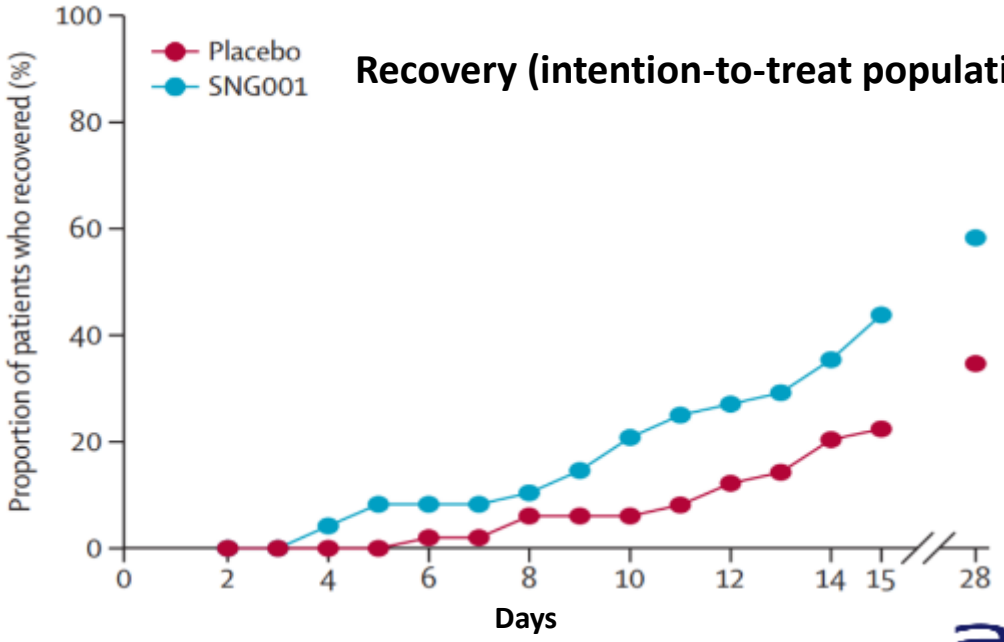
| Characteristics | SNG001 (N=50) | Placebo (N=51) |
|---|---|---|
| Age (y) – mean (SD) | 57,8 (14,6) | 56,5 (11,9) |
| Male sex – no (%) | 27 (56) | 31 (62) |
| **Coexisting conditions** | | |
| Hypertension – no (%) | 18/26 (69) | 11/27 (41) |
| Diabetes – no (%) | 3/26 (12) | 9/27 (33) |
| Cardiovascular 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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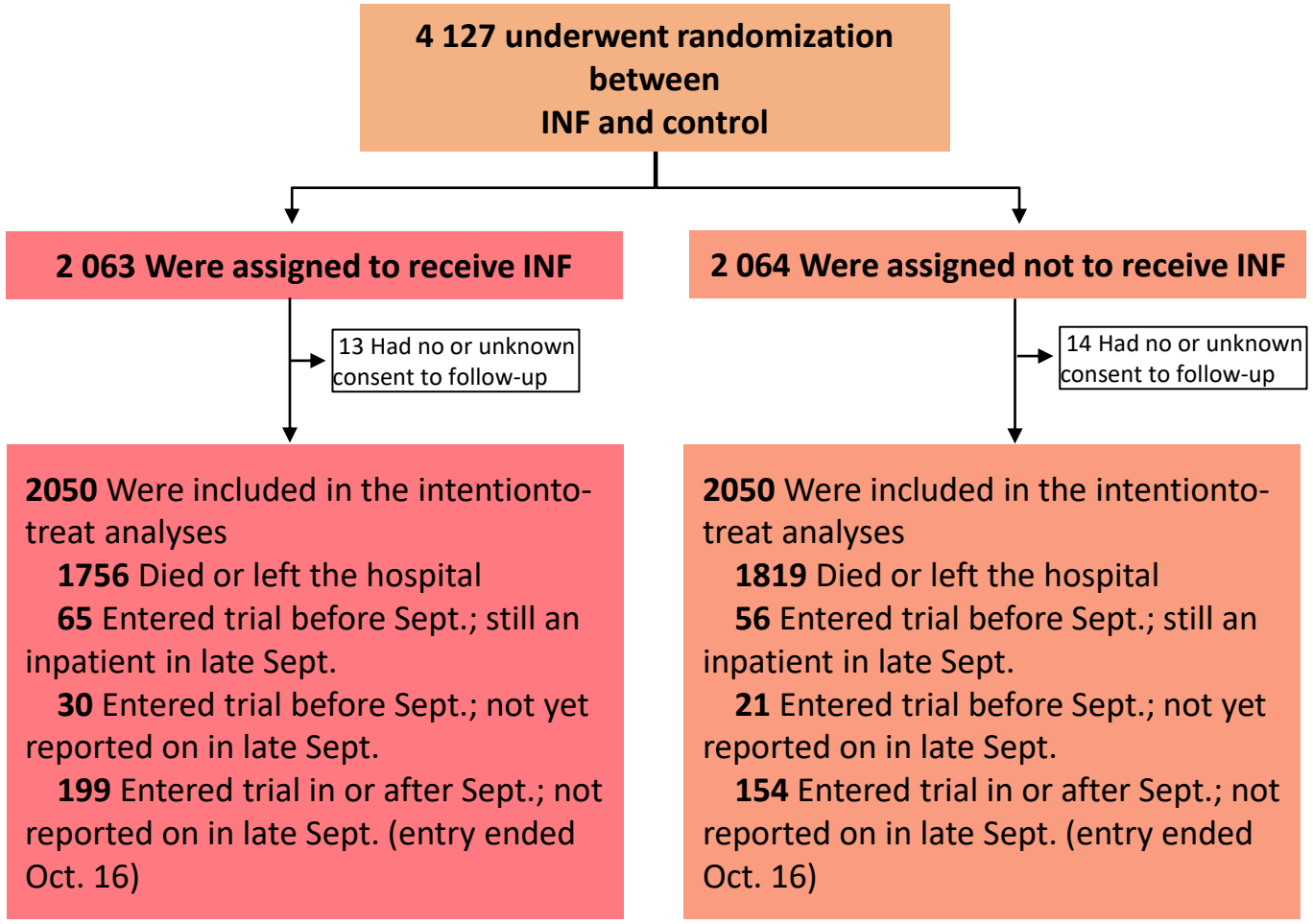
anrs MALADIES INFECTIEUSES ÉMERGENTES

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)

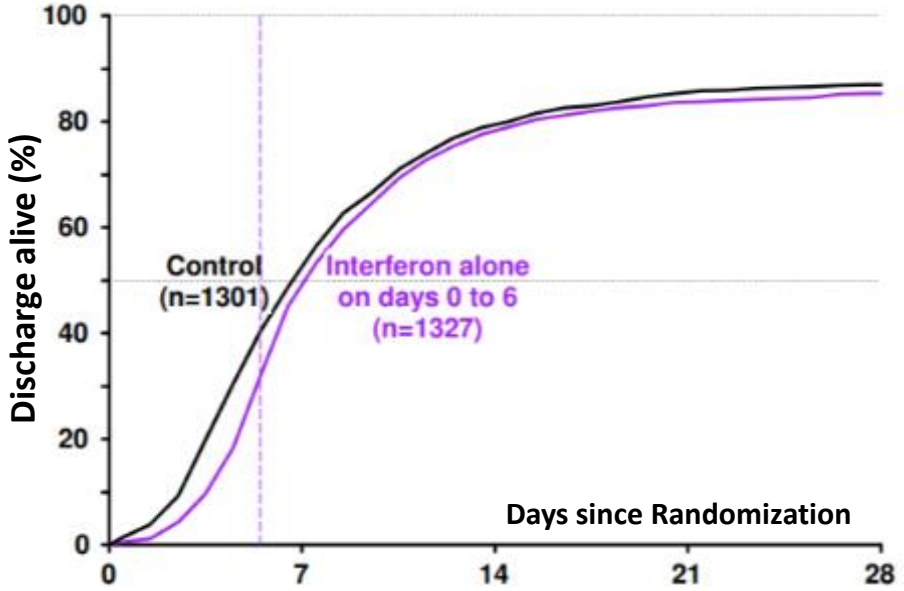
| Characteristics | | All (N= 11 266) | INF (N= 2 050) | Control (N=2 050) |
|---|---|---|---|---|
| **Age** | < 50 yr – no (%) | 3995 (35) | 720 | 697 |
| | 50-69 yr – no (%) | 5125 (45) | 934 | 973 |
| | ≥ 70 yr – no (%) | 2146 (19) | 396 | 380 |
| | | | | |
| **Sex** | Male sex – no (%) | 6985 (62) | 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 |

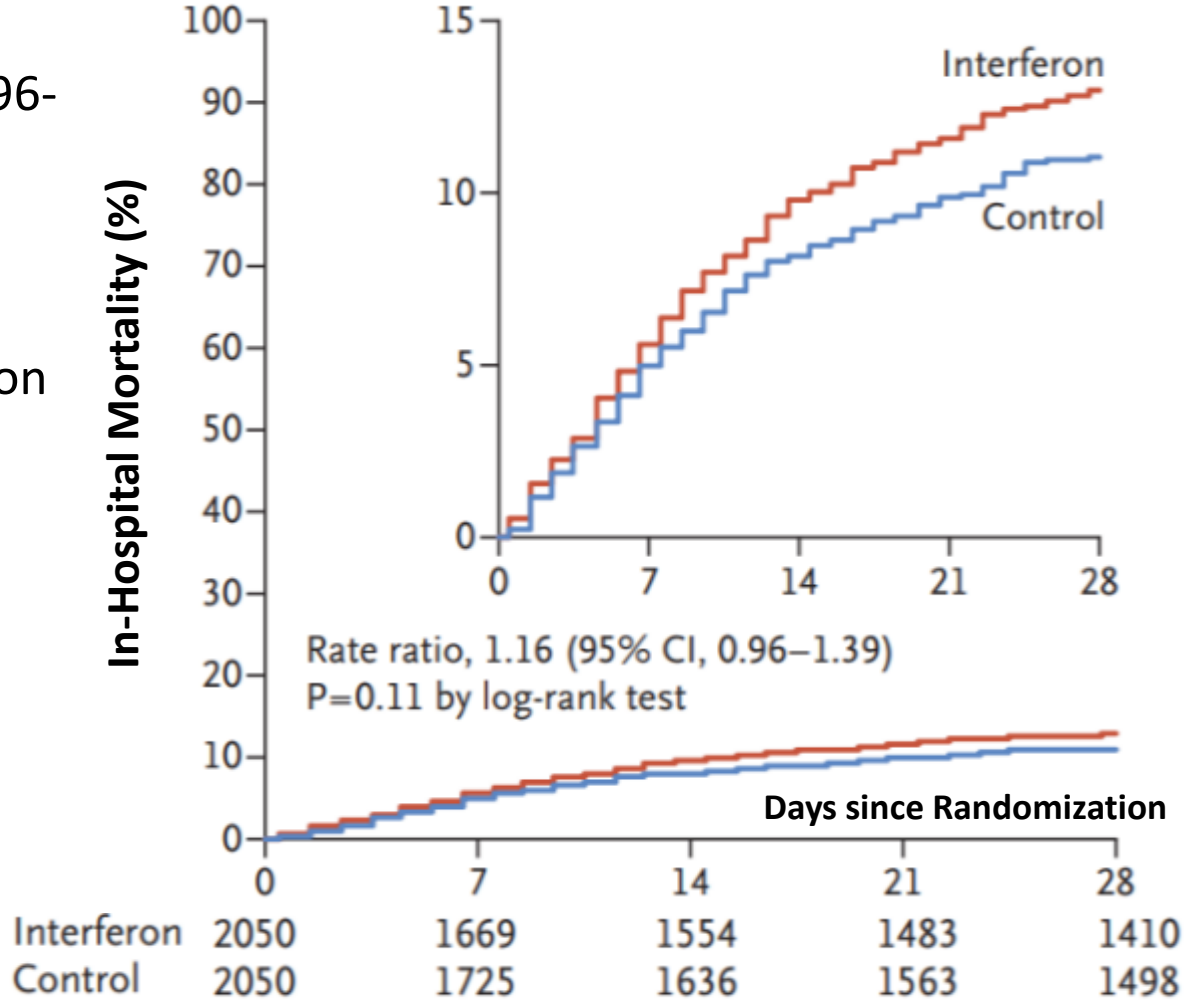
Immunomodulatory effect

# 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**



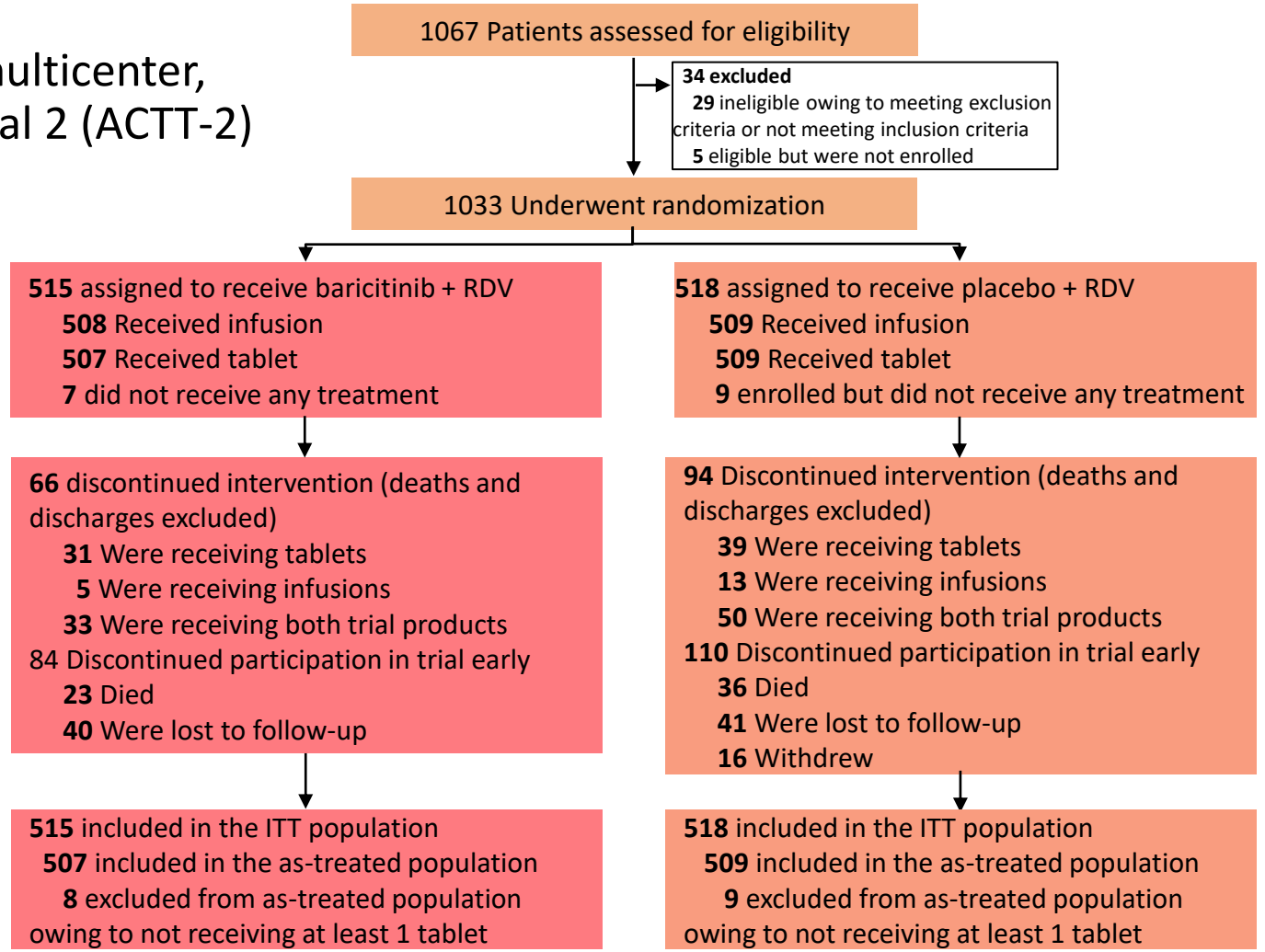




SOLIDARITY *NEJM* Dec 2020

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) |

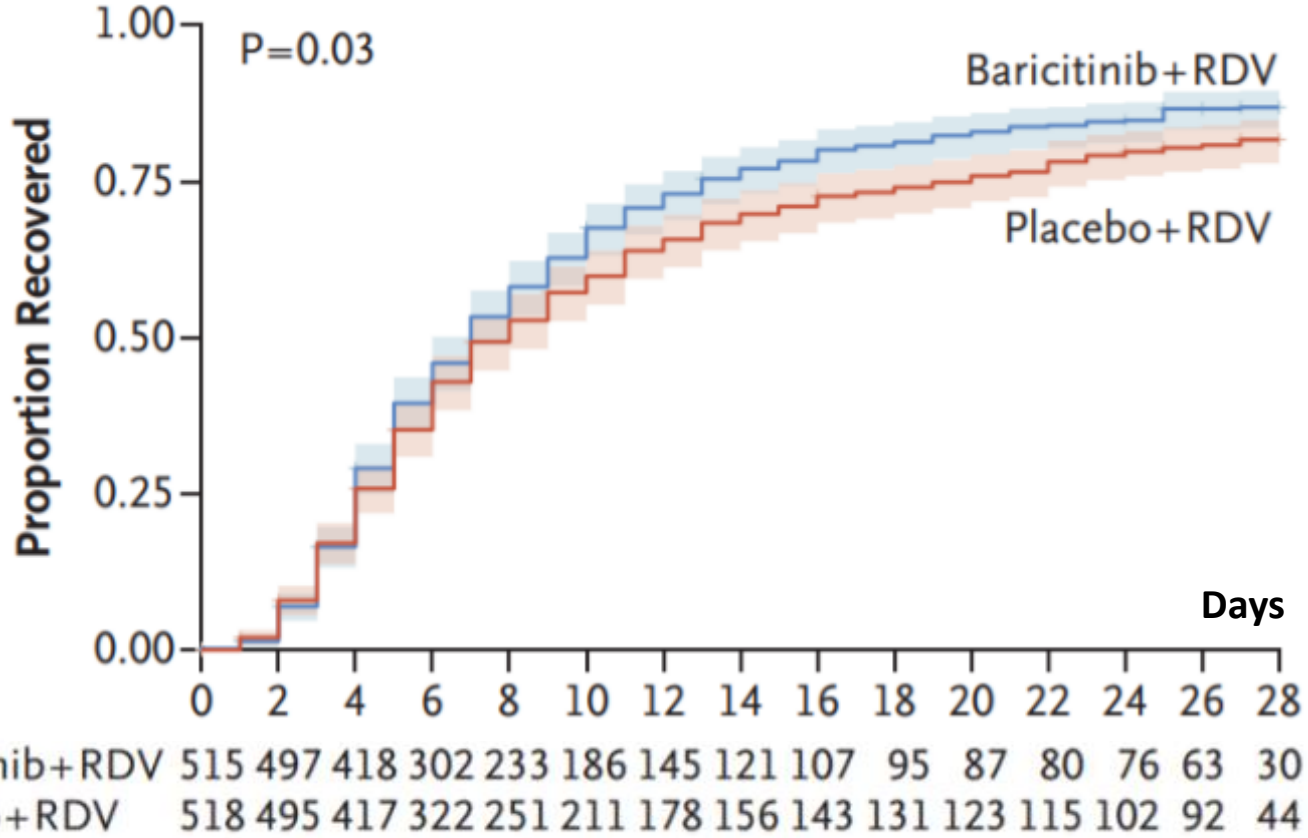
NIV: Non invasive ventilation
MV: mechanical ventilation

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

| 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 $_{95\%}$CI[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 $_{95\%}$CI[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

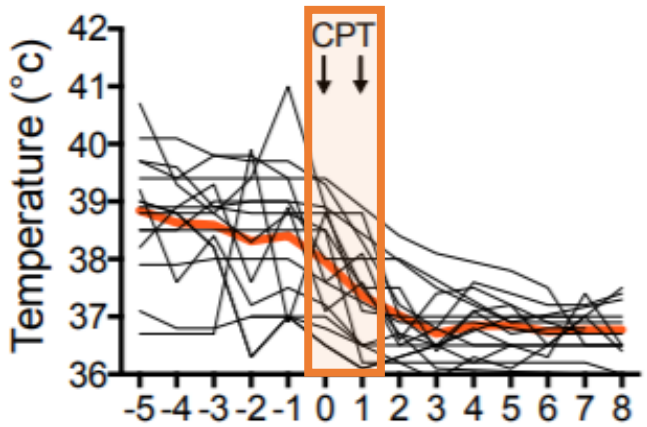
| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| Simonovich | Double-blind, placebo-controlled, multicenter trial, Argentina | CP group *vs.* placebo group | **N= 334** Severe COVID-19 pneumonia ($PaO_2/FiO_2$ <300, or $SpO_2 \leq 93\%$ (room air) or SOFA ≥ 2 points above baseline status | Clinical status 30 days after intervention | ***Death***: CP group: 25/228 (11%) *vs.* placebo group: 12/105 (11,4%)<br><br>***Invasive ventilatory support***: CP group: 19/228 (8,3%) *vs.* placebo group: 10/105 (9,5%)<br><br>***Discharged with full return to baseline physical function***: CP group: 141/228 (61,8%) *vs.* placebo group: 72/105 (68,6%)<br>OR : 0,81 $_{95\%}$CI [0,50-1,31], p = 0,396 |

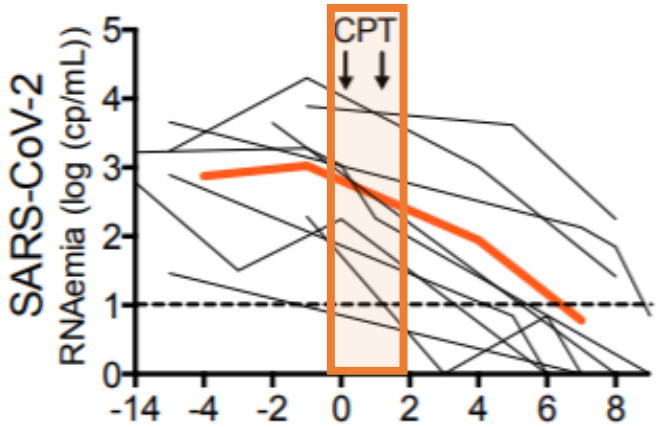
Simonovich V *et al. NEJM* Nov 2020

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



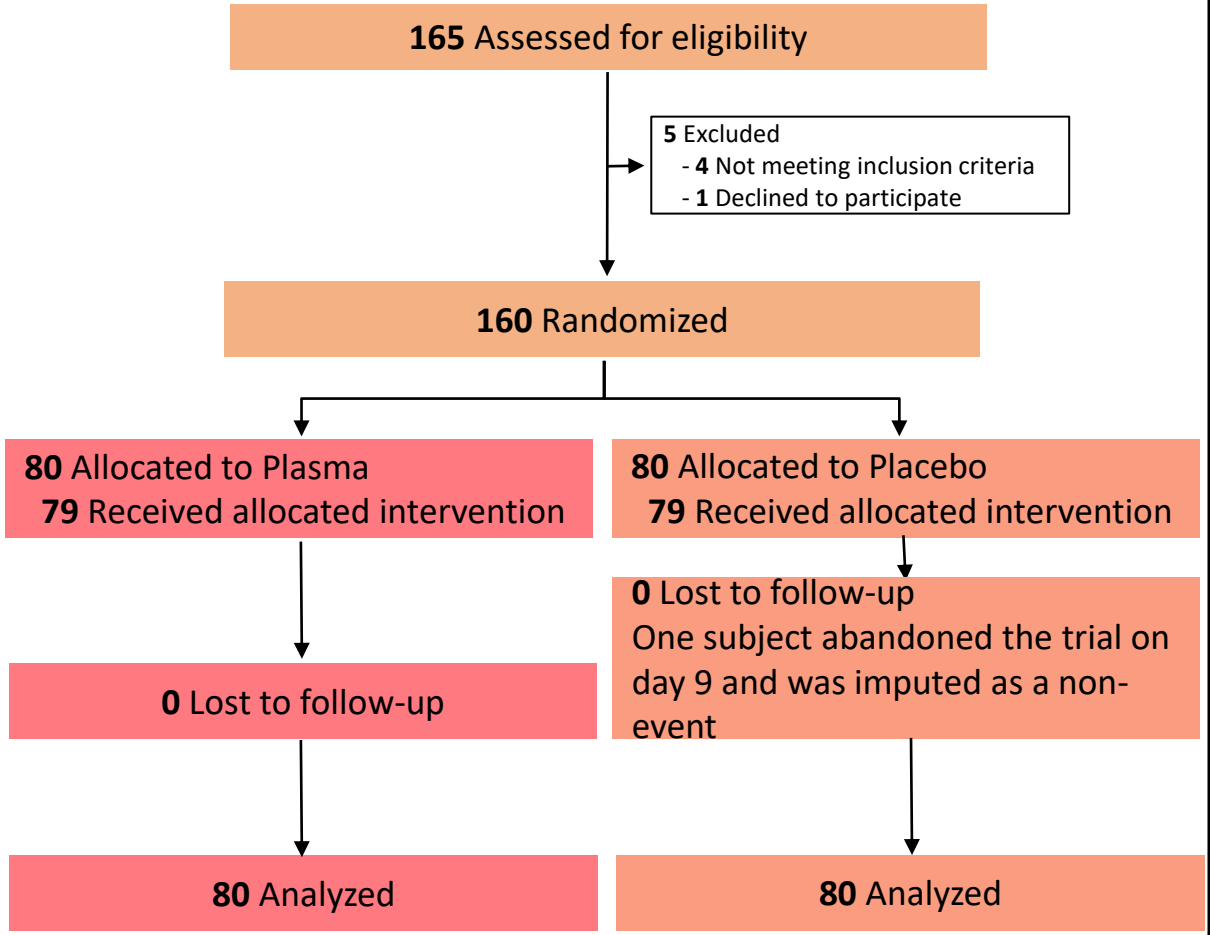

| Characteristics (N=17) | | CP |
|---|---|---|
| Age, median [range] - yr | | 58 [35-77] |
| Male sex – no (%) | | 12 (71) |
| Hematological malignancies | | 15 (88) |
| Non - Hematological malignancies | | 2 (12) |
| COVID -19 severity (WHO score), n (%) | 4 – no (%) | 5 (29) |
| | 5-6 – no (%) | 10 (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

Passive immunity

# Convalescent plasma (CP) - 5

- Randomized, double-blind, placebo-controlled trial, Argentina, high IgG titers against SARS-CoV-2 CP
- **Inclusion criteria**: age ≥ 75 yo, or age between 65 and 74 yo with coexisting condition (HTA, diabetes, obesity, chronic renal failure, cardiovascular disease, COPD), laboratory confirmed COVID-19, at least 2 symptoms within ≤48 h: t° ≥37,5°C or unexplained sweating, or chills; and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, or rhinorrhea
- **Exclusion criteria**: severe respiratory disease
- **Primary outcome**: severe respiratory disease*
- **Secondary outcome** (some of them): life-threatening respiratory disease, noninvasive or invasive ventilation, admission to an intensive care unit
- 160 participants; **80 CP group, 80 placebo group**




*respiratory rate ≥ 30 breaths/min, $SpO_2$ ≤93% (room air)

Libster R *et al. NEJM* Jan 2021

Passive immunity

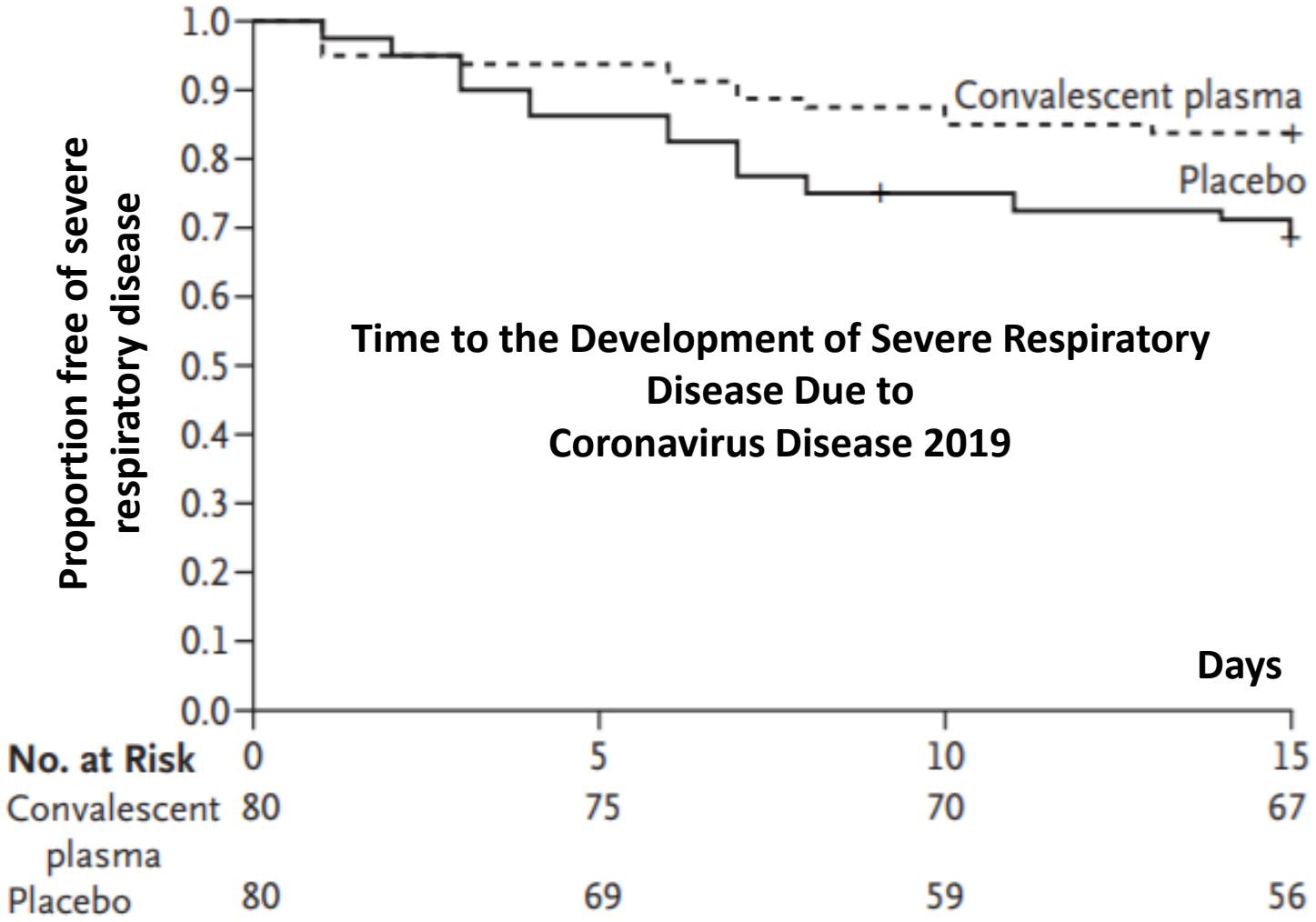
# Convalescent plasma (CP) - 5

| Characteristics | CP (N=80) | Placebo (N=80) |
|---|---|---|
| Age (y) – mean (SD) | 76,4 (8,7) | 77,9 (8,4) |
| Female sex – no (%) | 54 (68) | 46 (58) |
| **Coexisting conditions** | | |
| Hypertension – no (%) | 62 (78) | 52 (65) |
| Treated Diabetes – no (%) | 23 (29) | 13 (16) |
| Obesity – no (%) | 4 (5) | 8 (10) |
| Treated COPD – no (%) | 2 (2) | 5 (6) |
| Cardiovascular disease – no (%) | 14 (18) | 7 (79) |
| Chronic renal failure – no (%) | 1 (1) | 3 (4) |
| **Others** | | |
| Respiratory rate (breaths/min) – mean (SD) | 17 (2,8) | 17,3 (3) |
| $SpO_2$ while breathing ambient air (%) – mean (SD) | 96,1 (1,6) | 96,1 (1,7) |
| Time since onset of symptoms (hr) — no (%) | 39,6 (13,9) | 38,3 (14,3) |

Passive immunity

# Convalescent plasma (CP) - 5

- **Severe respiratory disease**: 13/80 (16%) CP group *vs.* 25/80 (31%) placebo group, RR: 0,52; $_{95\%}$CI [0,29-0,94]
- **Life-threatening respiratory disease:** 4/80 (5%) CP group *vs.* 10/80 (12%) placebo group; RR: 0,40; $_{95\%}$CI [0,13-1,22]
- **Noninvasive ventilation:** 1/80 (1%) CP group *vs.* 6/80 (12%) placebo group; RR: 0,17; $_{95\%}$CI [0,02–1,35]
- **Admission to intensive care unit :** 2/80 (2%) CP group *vs.* 6/80 (8%) placebo group; RR: 0,33; $_{95\%}$CI [0,07–1,60]
- **Limits:** Trial stopped early at 76% of projected sample size because a decrease in Covid-19.

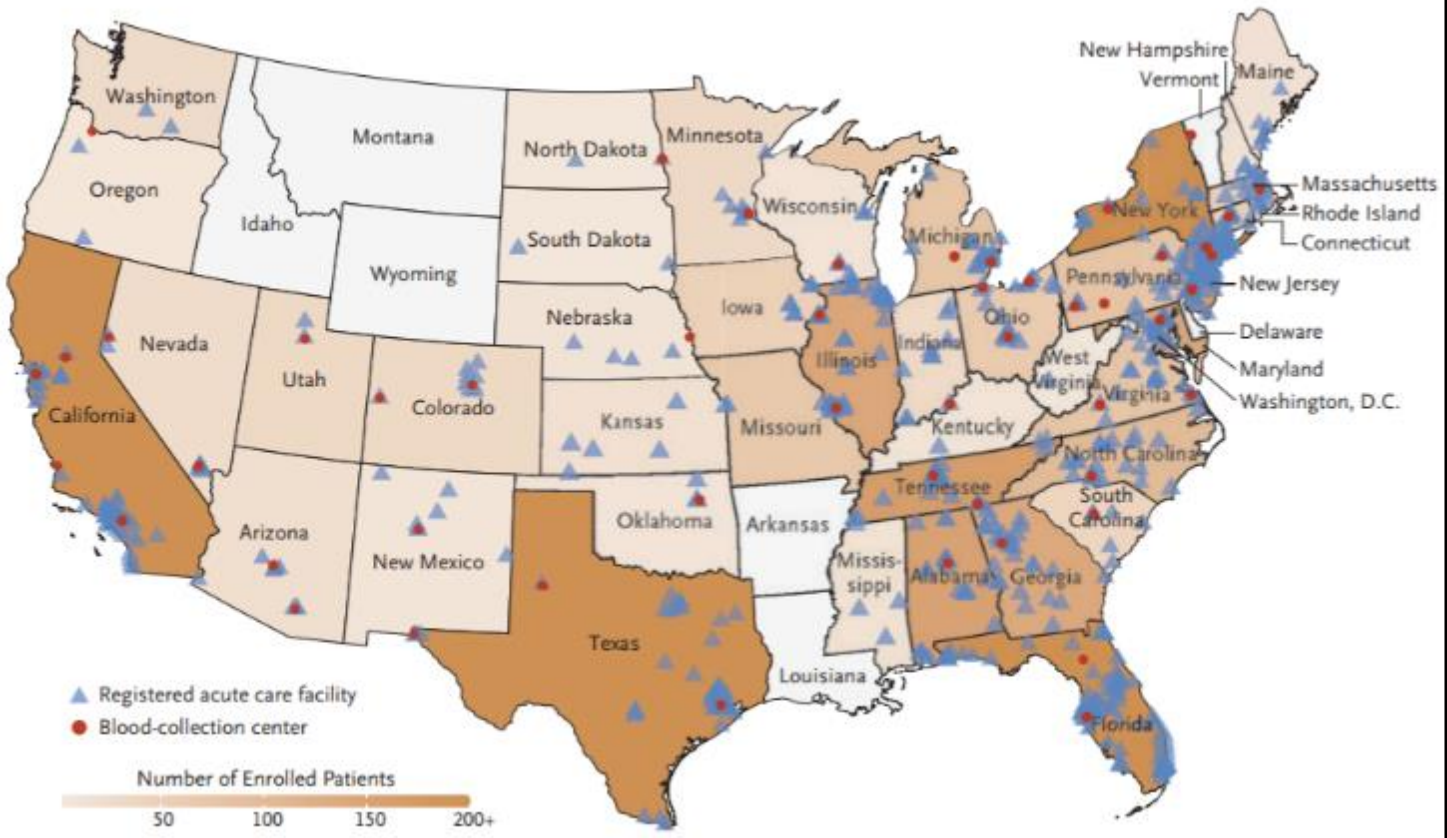



Libster R *et al. NEJM* Jan 2021

Passive immunity

# Convalescent plasma (CP) - 6

- Retrospective study based on a U.S. national registry
- **Inclusion criteria:** hospitalized patients, age ≥ 18yo, positive SARS-CoV-2 RT PCR, patients at high risk for progression to severe or life-threatening COVID-19
- **Main outcome**: mortality at 30 days after the transfusion of convalescent plasma
- Cohort consisted of 3082 patients from 680 acute care facilities across the United States; 561 in **low titer group**, 2006 in **medium titer group** and 515 in **high titer group**.




Joyner MJ *et al. NEJM* Jan 2021

Passive immunity

# Convalescent plasma (CP) - 6

| Characteristics | Low Titer (N=561) | Medium Titer (N=2006) | High Titer (N=515) |
|---|---|---|---|
| Age ≥ 80 – yr | 63/561 (11,2) | 241/2006 (12,0) | 241/2006 (12,0) |
| Female sex – no (%) | 201/559 (36,0) | 774/2002 (38,7) | 221/515 (42,9) |
| **Co existing conditions** | | | |
| Obesity – no (%) | 263/511 (51,5) | 980/1891 (51,8) | 288/490 (58,8) |
| **Clinical status** | | | |
| Severe or life-threatening COVID-19 – no (%) | 382/561 (68,1) | 1286/2006 (64,1) | 341/515 (66,2) |
| ICU care before infusion – no (%) | 344/561 (61,3) | 1226/2006 (61,1) | 298/515 (57,9) |
| Mechanical ventilation before infusion – no (%) | 183/548 (33,4) | 666/1963 (33,9) | 158/510 (31,0) |
| **Risk factors for severe COVID-19 in subgroup of patients with severe or life-threatening COVID-19** | | | |
| Blood oxygen saturation ≤93% | 269/382 (70,4) | 909/1286 (70,7) | 233/341 (68,3) |
| Lung infiltrates >50% within 24 to 48 hr | 194/382 (50,8) | 588/1286 (45,7) | 147/341 (43,1) |
| Respiratory rate ≥30 breaths/min | 177/382 (46,3) | 580/1286 (45,1) | 157/341 (46,0) |
| $PaO_2/FiO_2$<300 | 137/382 (35,9) | 451/1286 (35,1) | 93/341 (27,3) |

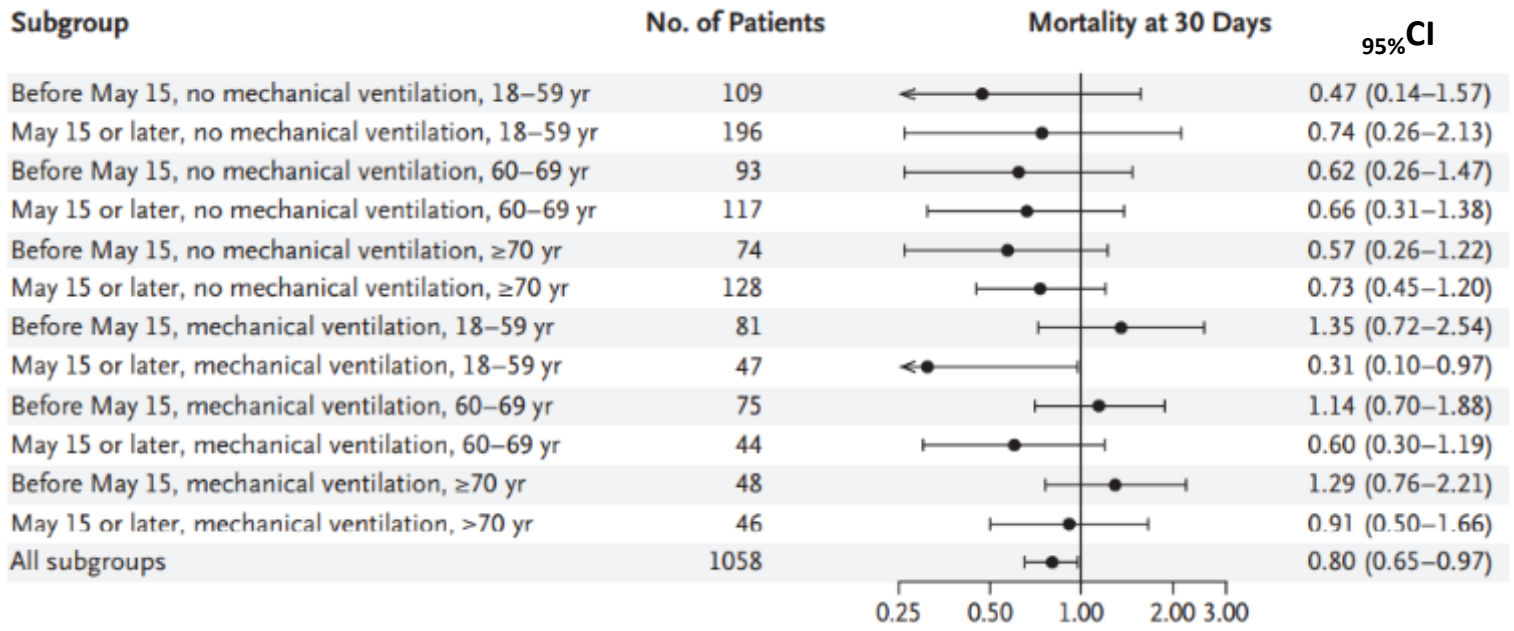
Passive immunity

# Convalescent plasma (CP) - 6

- **Death within 30 days after plasma transfusion:**
  - **Overall population:** 830/3082 (26,9%); $_{95\%}$CI[25,4-28,5]
  - **Low-titer group**: 166/561 (29,6%)
  - **Medium-titer group**: 549/2006 (27,4%); RR: 0,92 $_{95\%}$CI[0,80-1,07]
  - **High-titer group**: 115/515 (22,3%); RR: 0,75 $_{95\%}$CI[0,61-0,93]
- **Limits:** retrospective cohort study, limited availability of data, missing data, lack of precision in details regarding the temporal relationship between concomitant medication use and CP transfusion.

**Relative Risk of Death within 30 Days after Convalescent Plasma Transfusion**

High vs. Low Antibody Levels



| Subgroup | No. of Patients | 95%CI |
|---|---|---|
| Before May 15, no mechanical ventilation, 18–59 yr | 109 | 0.47 (0.14–1.57) |
| May 15 or later, no mechanical ventilation, 18–59 yr | 196 | 0.74 (0.26–2.13) |
| Before May 15, no mechanical ventilation, 60–69 yr | 93 | 0.62 (0.26–1.47) |
| May 15 or later, no mechanical ventilation, 60–69 yr | 117 | 0.66 (0.31–1.38) |
| Before May 15, no mechanical ventilation, ≥70 yr | 74 | 0.57 (0.26–1.22) |
| May 15 or later, no mechanical ventilation, ≥70 yr | 128 | 0.73 (0.45–1.20) |
| Before May 15, mechanical ventilation, 18–59 yr | 81 | 1.35 (0.72–2.54) |
| May 15 or later, mechanical ventilation, 18–59 yr | 47 | 0.31 (0.10–0.97) |
| Before May 15, mechanical ventilation, 60–69 yr | 75 | 1.14 (0.70–1.88) |
| May 15 or later, mechanical ventilation, 60–69 yr | 44 | 0.60 (0.30–1.19) |
| Before May 15, mechanical ventilation, ≥70 yr | 48 | 1.29 (0.76–2.21) |
| May 15 or later, mechanical ventilation, >70 yr | 46 | 0.91 (0.50–1.66) |
| All subgroups | 1058 | 0.80 (0.65–0.97) |



Joyner MJ *et al. NEJM* Jan 2021

# THERAPEUTIC (February 18th 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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