Therapies for COVID-19: remdesivir and steroids

David L. Wyles, MD

Chief, Division of Infectious Diseases

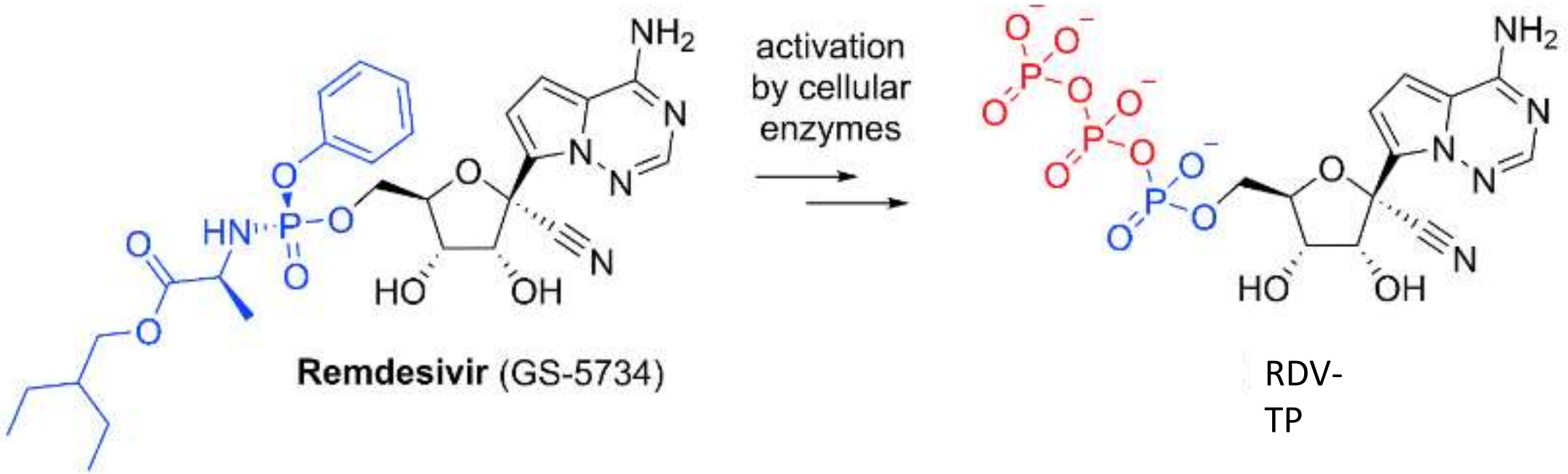
Denver Health

Disclaimer

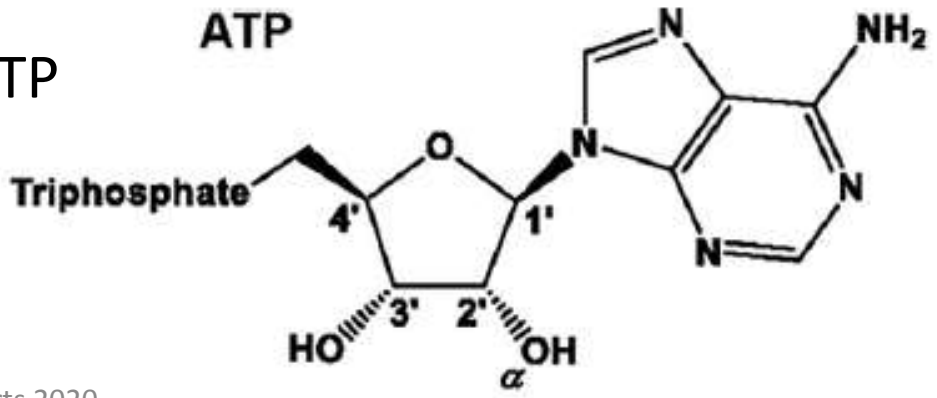
Treatments for COVID-19 have evolved rapidly

- Current treatment guidance looks nothing like initial recommendations circa March 2020
- Large clinical trials of multiple therapies, many in combination, are ongoing and being conducted with unprecedented speed
- Two therapies have emerged as the mainstays of current COVID-19 treatment
  - Antiviral- remdesivir
  - Anti-inflammatory/anti-fibrotic- corticosteroids

Remdesivir: in vitro MOA and activity

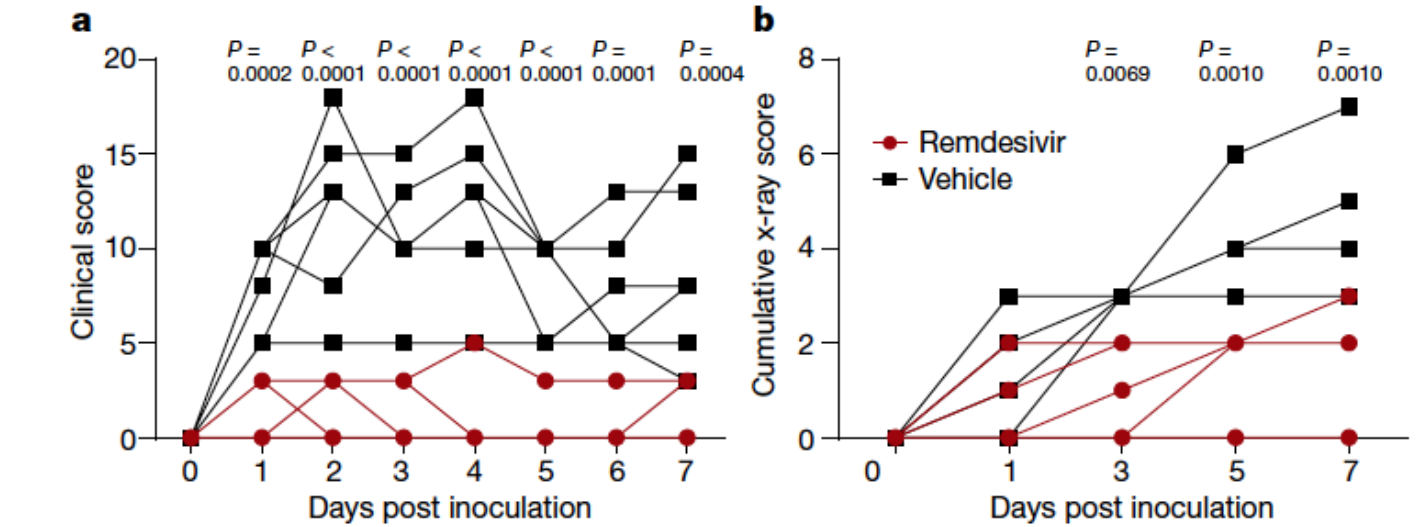


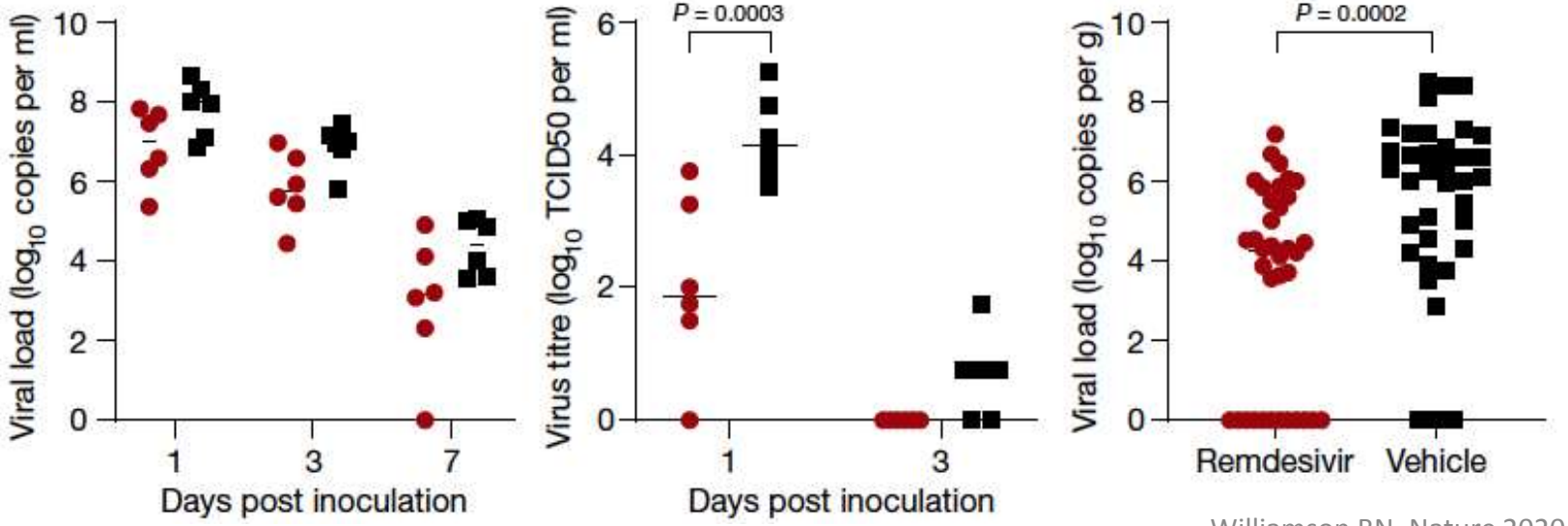
- More efficiently incorporated by SARS-CoV2 RdRp than ATP
- Non-obligate chain terminator (i+3)
- Low μM to low nM potency
  - HAE cells EC_{50}= 10nM

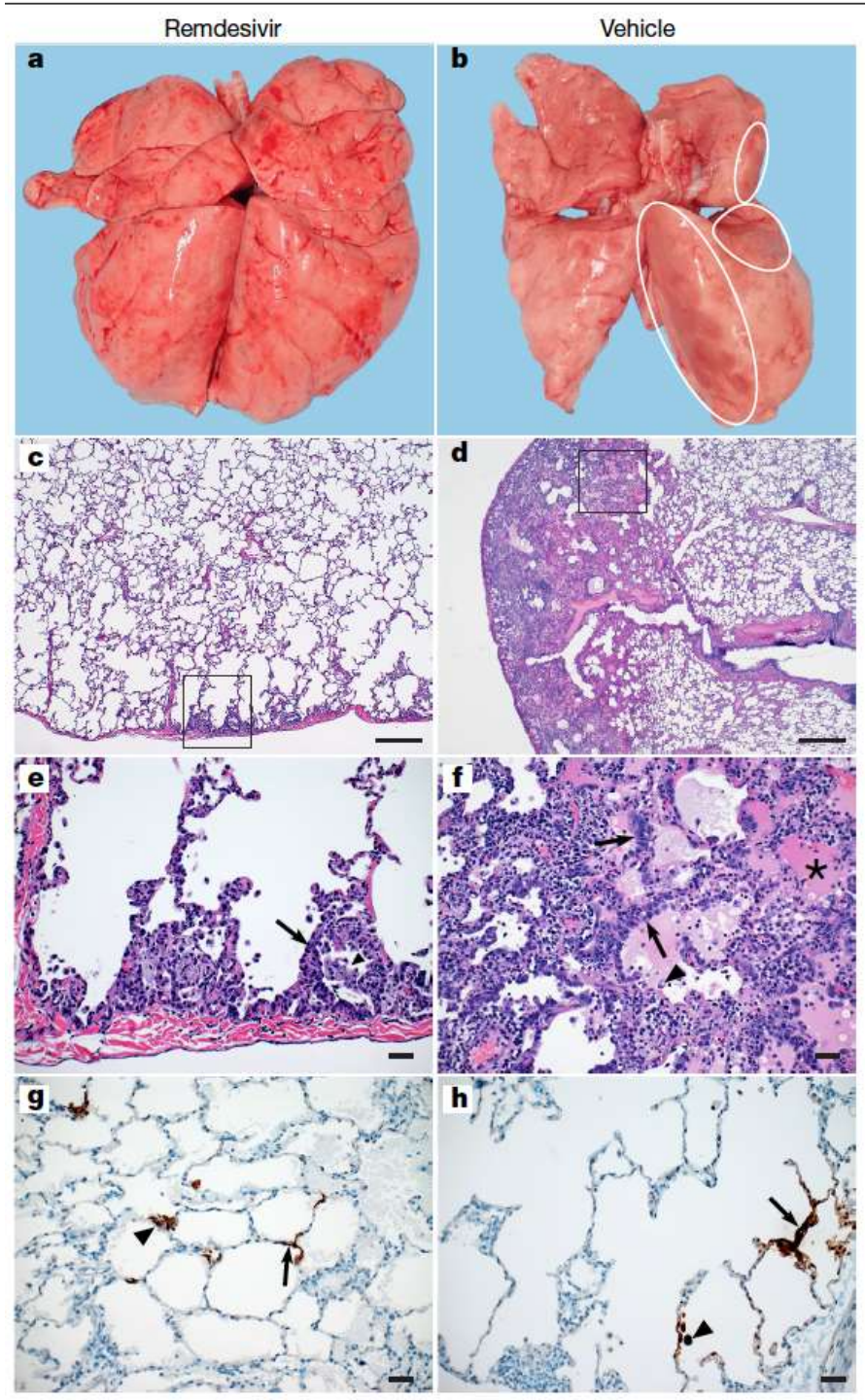


Konkolova E Antiviral Res 2020. Gordon CJ. JBC 2020. Pruijssers AJ. Cell Reports 2020

Remdesivir in macaque model







Williamson BN. Nature 2020.

Key clinical questions with remdesivir

- What to make of “conflicting” data?
- Timing
  - Earlier presumed better
- Usefulness based on disease severity
  - Mild disease (no hypoxia)
  - Intubated/ECMO
- What is the optimal duration?
  - 5 vs 10 days
- Safety
- Limitations/can it be improved?
  - Complicated cellular activation
  - IV administration

First RCT of RDV in Wuhan

RCT, blinded, placebo controlled

2:1 RDV to Pbo; stratified

COVID with signs of LRTI

Older (66), 71% with comorbidity

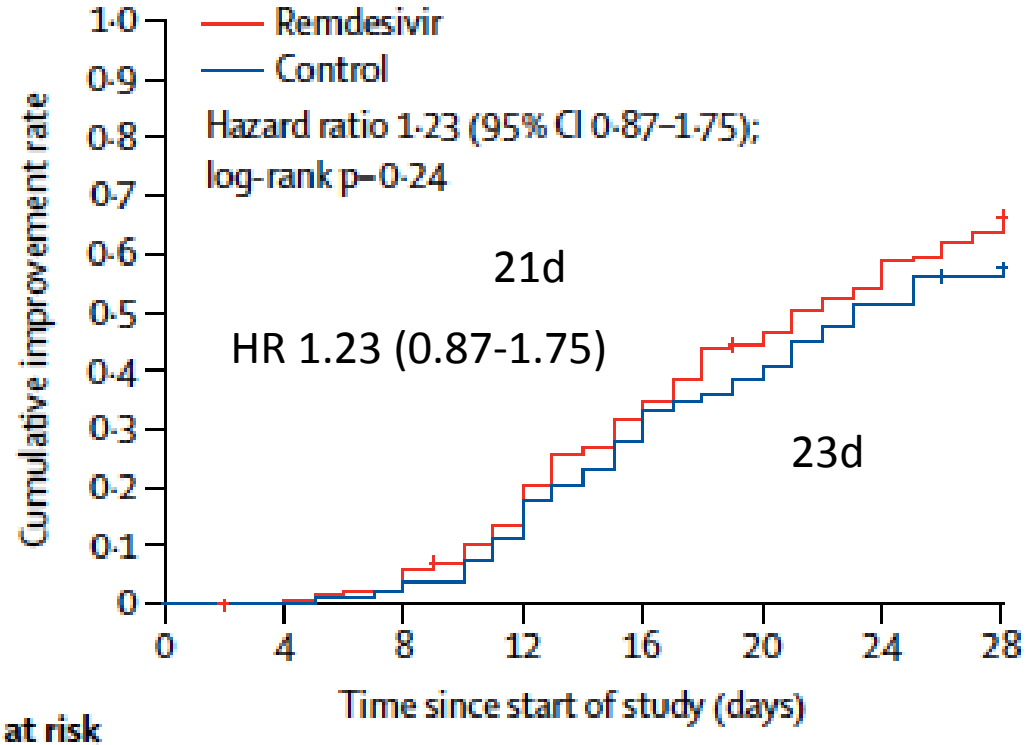
<1% mechanical vent/ECMO

~40% steroids prior to enrollment

66% steroids during admission

Primary endpoint: 2 point improvement

- 6 point scale



Number at risk (number censored)								
Remdesivir	158	155	147	123	101	82	63	25
	(0)	(2)	(0)	(1)	(0)	(1)	(0)	(26*)
Control	78	78	75	64	52	46	38	17
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(16*)

RDV/Pbo @<10d: 18 vs 23d; HR 1.52 (0.95-2.43)

Wang et al. Lancet 2020.

ACT

Prospe

- RDV
- Hosp

Prima

- Impr

Secon

- Impr
- Mort

Characteristic	All (N=1063)	Remdesivir (N=541)	Placebo (N=522)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.3)	352 (65.1)	332 (63.6)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	134 (12.6)	77 (14.2)	57 (10.9)
Black or African American	219 (20.6)	108 (20.0)	111 (21.3)
White	565 (53.2)	279 (51.6)	286 (54.8)
Hispanic or Latino — no. (%)	249 (23.4)	132 (24.4)	117 (22.4)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	193/920 (21.0)	91/467 (19.5)	102/453 (22.5)
One	248/920 (27.0)	131/467 (28.1)	117/453 (25.8)
Two or more	479/920 (52.1)	245/467 (52.5)	234/453 (51.7)
Coexisting conditions — no./total no. (%)			
Hypertension	460/928 (49.6)	231/469 (49.3)	229/459 (49.9)
Obesity	342/925 (37.0)	177/469 (37.7)	165/456 (36.2)
Type 2 diabetes	275/927 (29.7)	144/470 (30.6)	131/457 (28.7)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

ACTT1 Preliminary results

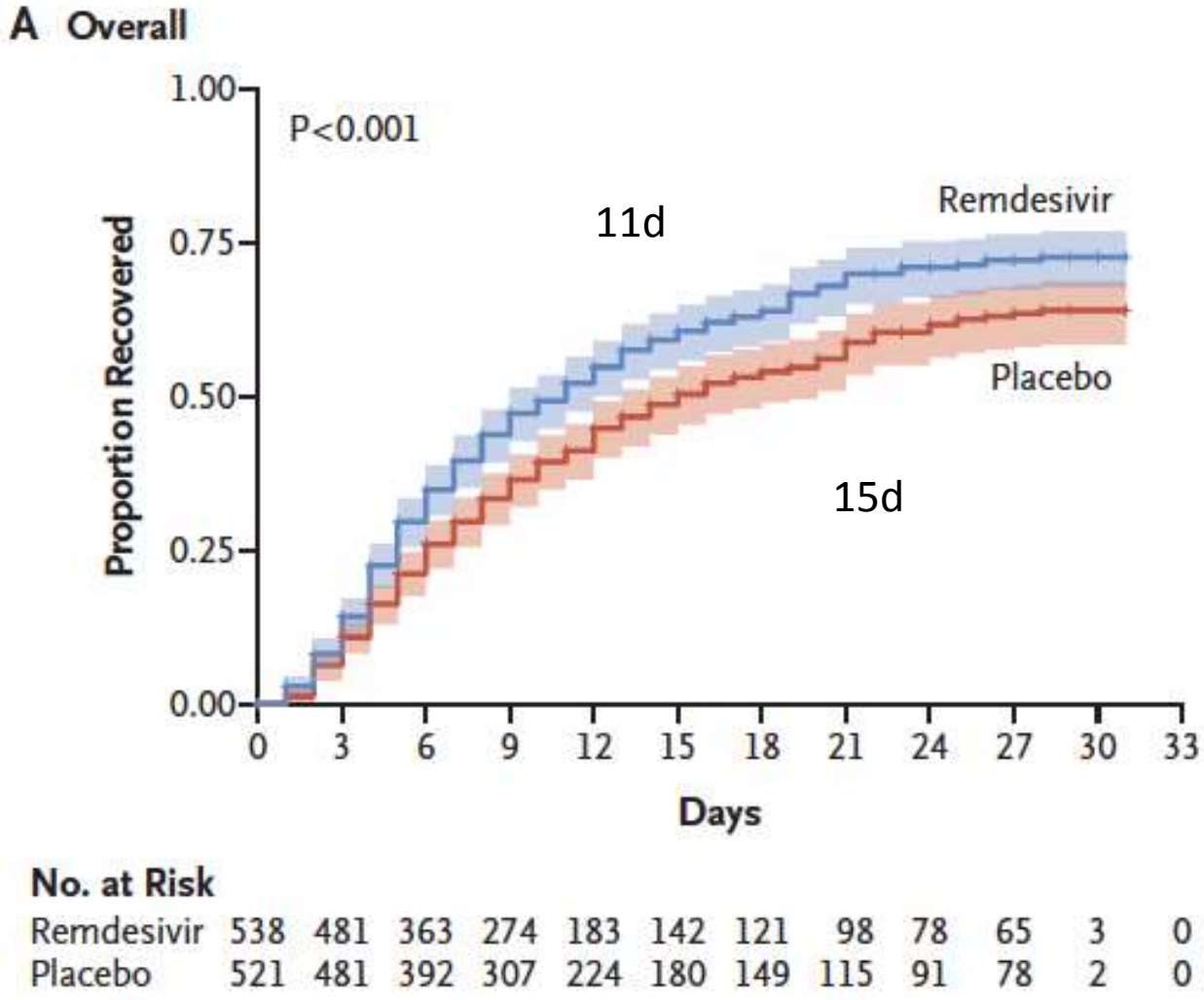
<u>Recovery RR</u>

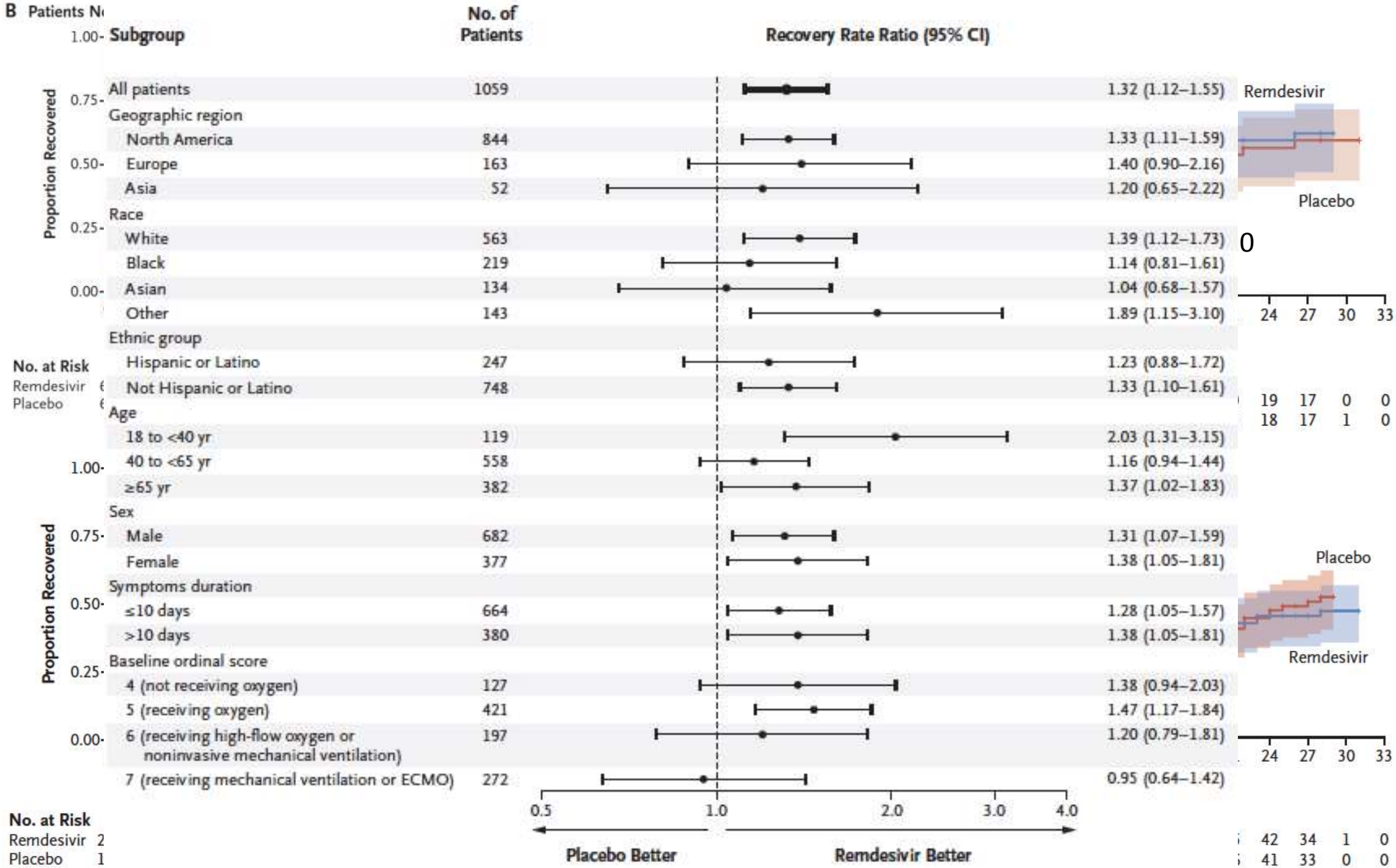
1.32 (1.12- 1.55, p<0.001)

<u>Mortality at 14d</u>

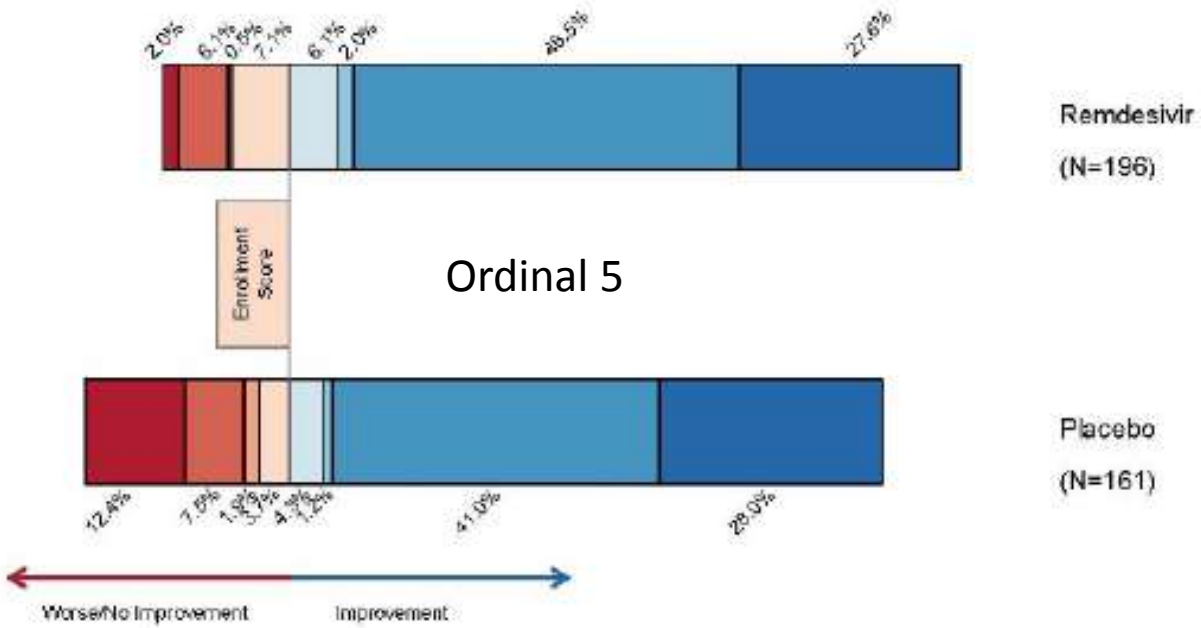
RDV 7.1% vs Pbo 11.9%

HR 0.75 (0.47-1.09)

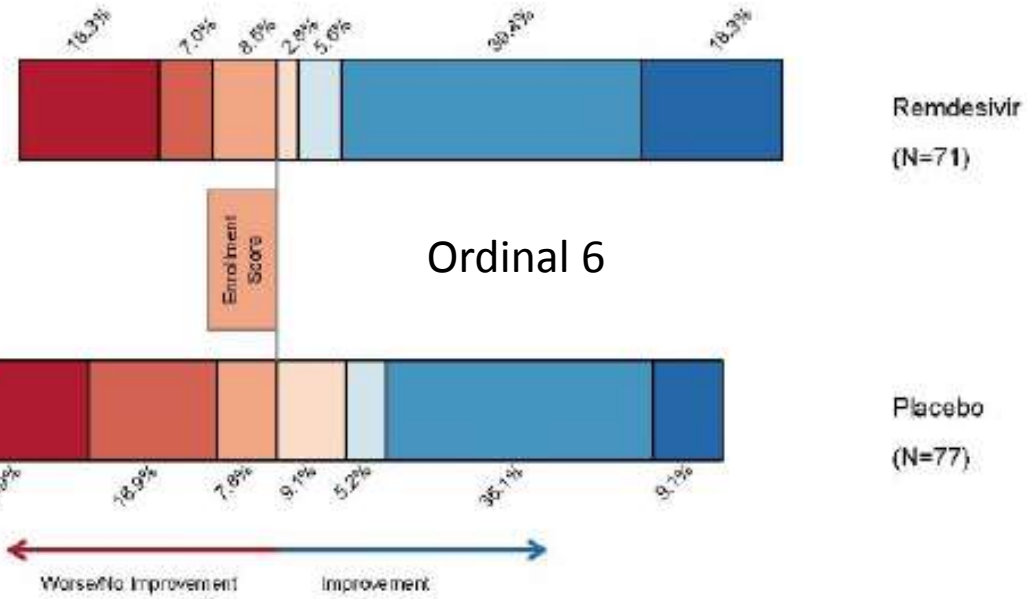



B Patients N
Subgroup
No. of Patients
Recovery Rate Ratio (95% CI)
All patients 1059 1.32 (1.12–1.55)
Geographic region
North America 844 1.33 (1.11–1.59)
Europe 163 1.40 (0.90–2.16)
Asia 52 1.20 (0.65–2.22)
Race
White 563 1.39 (1.12–1.73)
Black 219 1.14 (0.81–1.61)
Asian 134 1.04 (0.68–1.57)
Other 143 1.89 (1.15–3.10)
Ethnic group
Hispanic or Latino 247 1.23 (0.88–1.72)
Not Hispanic or Latino 748 1.33 (1.10–1.61)
Age
18 to <40 yr 119 2.03 (1.31–3.15)
40 to <65 yr 558 1.16 (0.94–1.44)
≥65 yr 382 1.37 (1.02–1.83)
Sex
Male 682 1.31 (1.07–1.59)
Female 377 1.38 (1.05–1.81)
Symptoms duration
≤10 days 664 1.28 (1.05–1.57)
>10 days 380 1.38 (1.05–1.81)
Baseline ordinal score
4 (not receiving oxygen) 127 1.38 (0.94–2.03)
5 (receiving oxygen) 421 1.47 (1.17–1.84)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation) 197 1.20 (0.79–1.81)
7 (receiving mechanical ventilation or ECMO) 272 0.95 (0.64–1.42)
0.5
1.0
2.0
3.0
4.0
Placebo Better
Remdesivir Better
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
No. at Risk
Remdesivir 6
Placebo 6
19 17 0 0
18 17 1 0
24 27 30 33
Remdesivir
Placebo
0
No. at Risk
Remdesivir 2
Placebo 1
42 34 1 0
41 33 0 0

Day 15 status

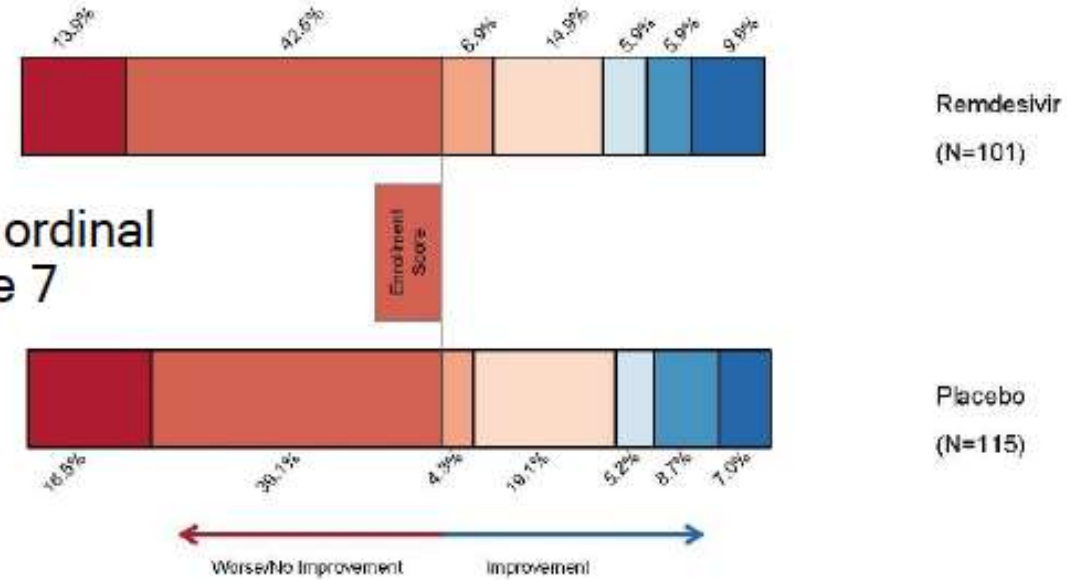


Ordinal 5



Ordinal 6

Baseline ordinal score 7

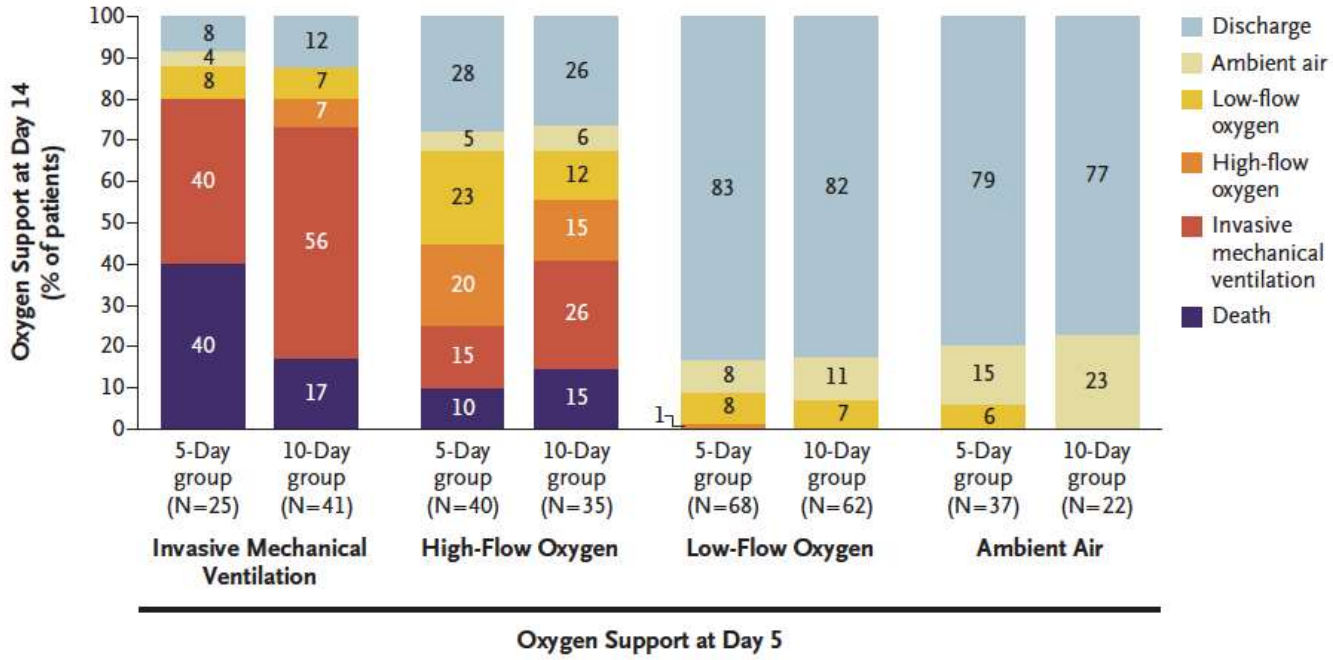


Compare and contrast: Wuhan study vs ACTT1

- Population
  - Older in China study
  - More HTN, DM in ACTT. Likely much more obesity.
  - More severe disease in ACTT1
  - High rate of steroid use in China
- Primary outcomes
  - Wang et al- time to 2-point decrease in scale or discharge
  - ACTT1- time to recovery (ordinal 1-3)
- Size
  - Wang et al study stopped early and underpowered

What is the optimal duration of RDV?

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)
Median age (IQR) — yr	61 (50–69)	62 (50–71)
Male sex — no. (%)	120 (60)	133 (68)
Race — no./total no. (%)†		
White	142/200 (71)	134/192 (70)
Black	21/200 (10)	23/192 (12)
Asian	20/200 (10)	25/192 (13)
Other	17/200 (8)	10/192 (5)
Median body-mass index (IQR)‡	29 (25–34)	29 (25–33)
Coexisting conditions of interest — no. (%)		
Diabetes	47 (24)	43 (22)
Hyperlipidemia	40 (20)	49 (25)
Hypertension	100 (50)	98 (50)
Asthma	27 (14)	22 (11)
Clinical status on the 7-point ordinal scale — no. (%)§		
2: Receiving invasive mechanical ventilation or ECMO	4 (2)	9 (5)
3: Receiving noninvasive ventilation or high-flow oxygen	49 (24)	60 (30)
4: Receiving low-flow supplemental oxygen	113 (56)	107 (54)
5: Not receiving supplemental oxygen but requiring medical care	34 (17)	21 (11)
Median duration of hospitalization before first dose of remdesivir (IQR) — days	2 (1–3)	2 (1–3)
Median duration of symptoms before first dose of remdesivir (IQR) — days	8 (5–11)	9 (6–12)



Goldman JD. NEJM 2020

RDV in critically ill patients

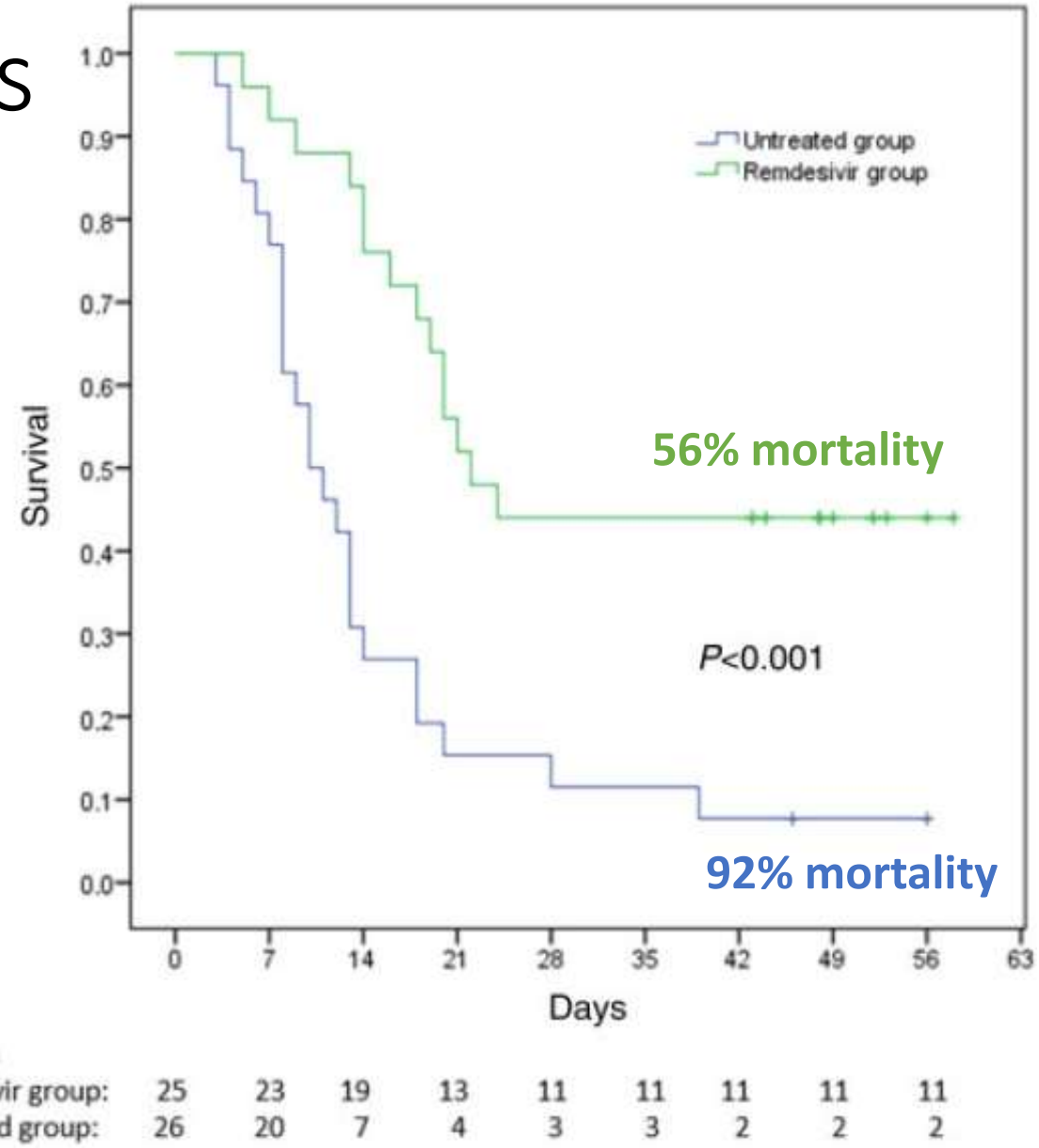
- Compassionate use experience in ICU
  - RDV IV for 10d
- Consecutive ICU admission over 3 weeks screened within 48hrs
- All on mechanical ventilation
  - Excluded ALT>5x and CrCl <30
- Could continue HCQ
  - LPV/r stopped
- Trend toward more tociluzimab use in RDV group
- No steroid use/not mentioned

Characteristics	Remdesivir group (*N* = 25)	No remdesivir group (*N* = 26)
Male sex, *n* (%)	23 (92)	24 (92.3)
Median (IQR) age (years)	64 (57–75)	70 (63.3–76)
Interval between symptom onset and ICU admission, median (IQR) (days)	11 (8–13)	9 (8–11)
Comorbidities, *n* (%)		
ischaemic heart disease	3 (12)	4 (15.4)
congestive heart failure	0 (0)	4 (15.4)
COPD	0 (0)	3 (11.5)
diabetes mellitus	3 (12)	4 (15.4)
chronic kidney disease	2 (8)	2 (7.7)
hypertension	14 (56)	14 (53.8)
Median (IQR) Charlson Comorbidity Index	2 (1–3)	3 (3–4)
Laboratory values		
mean ± SD WBC/mm^3	9172 ± 3203	9318 ± 3826
mean ± SD neutrophils/mm^3	7902 ± 3224	8173 ± 3511
median (IQR) lymphocytes/mm^3	600 (500–830)	550 (300–900)
median (IQR) platelets × 10^3/mm^3	192 (162–242)	184 (145–247)
median (IQR) creatinine (mg/dL)	0.97 (0.89–1.24)	1.11 (0.85–1.57)
median (IQR) ALT (U/L)	45 (26–67)	45 (37.3–61.8)
median (IQR) AST (U/L)	34 (23–55)	33.5 (27.5–43.8)
median (IQR) total bilirubin (mg/dL)	0.9 (0.7–1.2)	0.8 (0.6–1.28)
median (IQR) LDH (U/L)	450 (342–510)	542 (416–559)
mean ± SD CRP (mg/dL)	20.9 ± 13.8	20.2 ± 9.7
Median (IQR) SOFA score at admission	4 (3–5)	5 (4–6)
CRRT, *n* (%)	10 (40)	15 (57.7)
Concomitant therapies, *n* (%)		
hydroxychloroquine	17 (68)	16 (61.5)
lopinavir/ritonavir	15 (60)	14 (53.8)
tocilizumab	7 (28)	2 (7.7)

Pasquini Z. JAC 2020.

RDV in critically ill patients

- MV analysis
  - Mortality associated with Charlson Index
    - OR 1.18 (1.03-1.37)
  - Survival benefit of RDV
    - OR 3.51 (1.77-6.95)



RDV and sulfobutyl-ether cyclodextrin (SBECD)

- Animal toxicity at 50-100x the exposure of 5-10d RDV
  - Hepatic necrosis
  - Renal tubular damage
- Human recommended safety threshold: 250mg/kg per day of SBECD
- Effectively cleared by CRRT or hemodialysis
- SBECD in RDV
  - 100mg lyophilized powder 3gm SBECD
  - 100mg concentrated solution 6gm SBECD

Current recommendations for use and EUA

RDV 200mg IV x1, then 100mg IV QD for 5-10d total

IDSA

1. Recommends RDV use for hospitalized patients with sats <94% and on supplemental O2
2. 5d is recommended for those not on mechanical ventilation or ECMO

Criteria for EUA use:

Discussion with patient and provide fact sheet

Daily LFTs; not recommend if ALT>5x ULN

Not recommended for CrCl <30 *unless* potential benefit outweighs risk

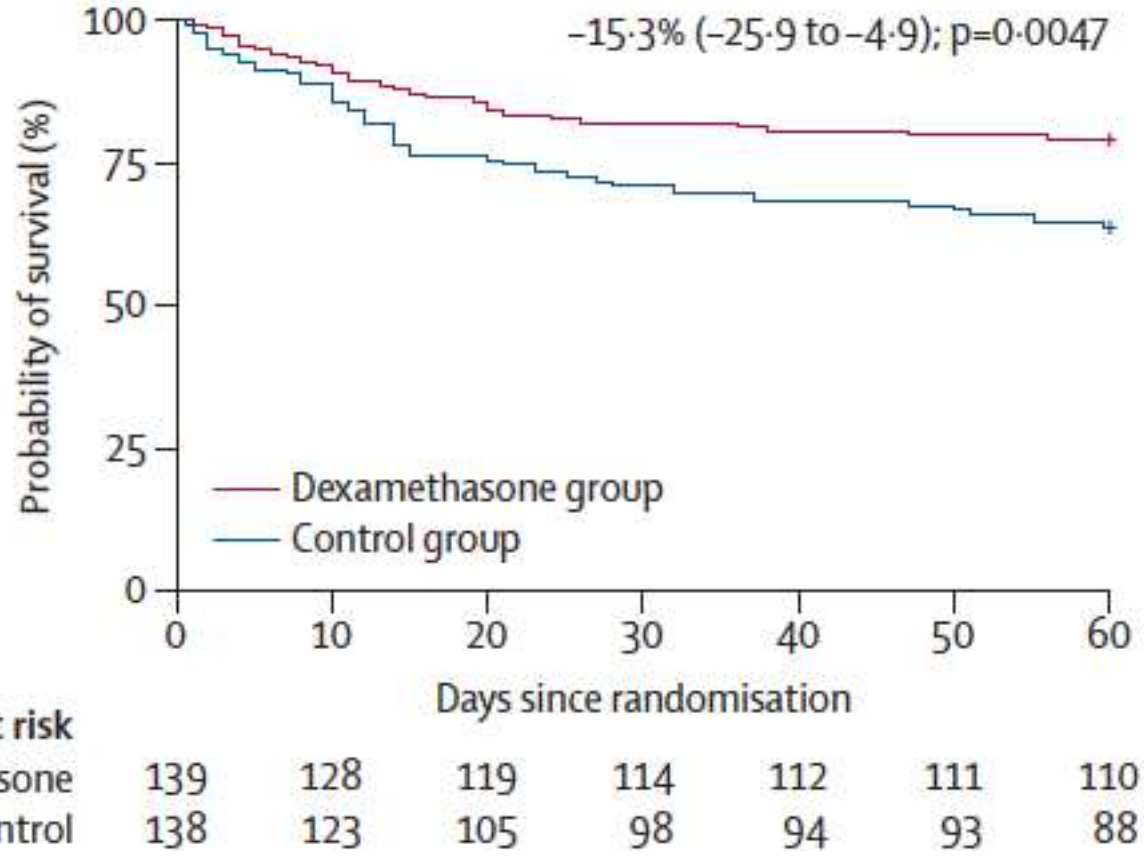
https://www.fda.gov/media/137566/download

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

*Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luís A Conesa, Carmen Martín-Rodríguez, Francisco J Díaz-Domínguez, Pablo Serna-Grande, Rosana Rivas, José Ferreres, Javier Belda, Lucía Capilla, Alec Tallet, José M Añón, Rosa L Fernández, Jesús M González-Martín for the dexamethasone in ARDS network**

Lancet Respir Med 2020; 8: 267–76

- Randomized, open label study
- Dex 20mg IV x5d, then 10mg IV x5d
- Within 30hr of ARDS onset
- Majority with pneumonia/sepsis (78%)
- Primary endpoint ventilator free days
  - 12.3 dex vs 7.5 control, p<0.0001



RECOVERY trial

Prospective, randomized study across UK

- 2:1 SOC vs dex (6mg QD up to 10d)
- Only exclusion investigator opinion

Primary outcome: 28d mortality

- Subgroups: age, sex, baseline respiratory status and days since onset

Key secondary:

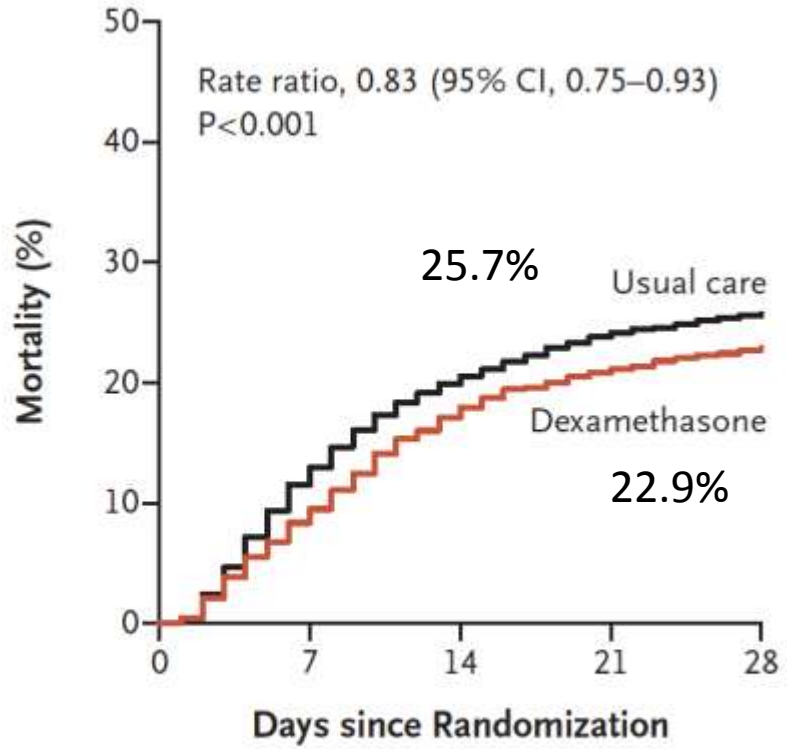
- Time to discharge
- Progression to mechanical ventilation

Characteristic	Treatment Assignment	
	Dexamethasone (N=2104)	Usual Care (N=4321)
Age†		
Mean — yr	66.9±15.4	65.8±15.8
Distribution — no. (%)		
<70 yr	1141 (54)	2504 (58)
70 to 79 yr	469 (22)	859 (20)
≥80 yr	494 (23)	958 (22)
Sex — no. (%)		
Male	1338 (64)	2749 (64)
Female‡	766 (36)	1572 (36)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)
Respiratory support received — no. (%)		
No oxygen	501 (24)	1034 (24)
Oxygen only	1279 (61)	2604 (60)
Invasive mechanical ventilation	324 (15)	683 (16)
SARS-CoV-2 test result		
Positive	1850 (88)	3848 (89)
Negative	247 (12)	453 (10)
Test result not yet known	7 (<1)	20 (<1)

56% in both groups with comorbid conditions
8% in SOC group got dex

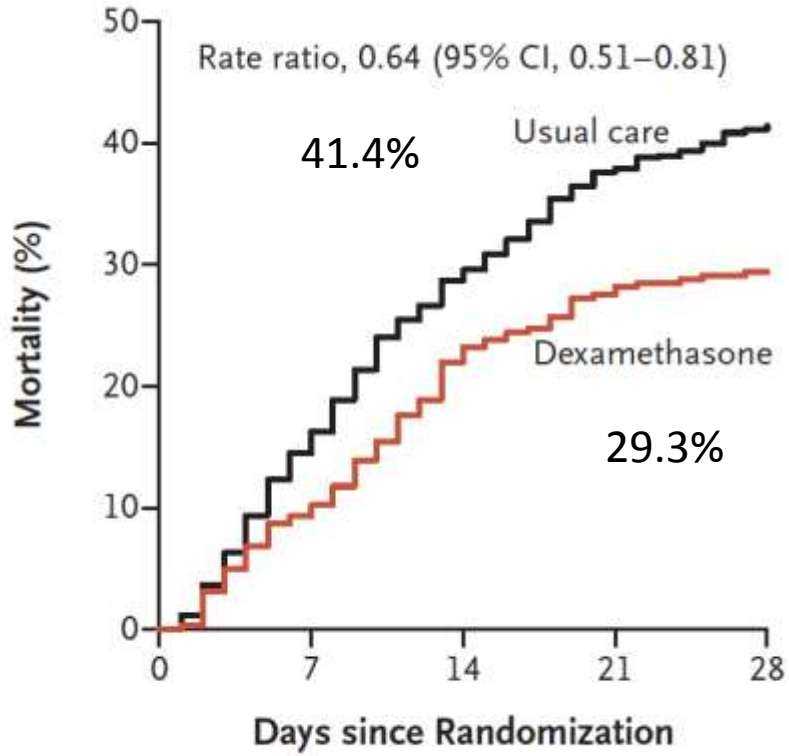
The RECOVERY Collaborative Group. NEJM 2020.

A All Participants (N=6425)



No. at Risk					
Usual care	4321	3754	3427	3271	3205
Dexamethasone	2104	1903	1725	1659	1621

B Invasive Mechanical Ventilation (N=1007)

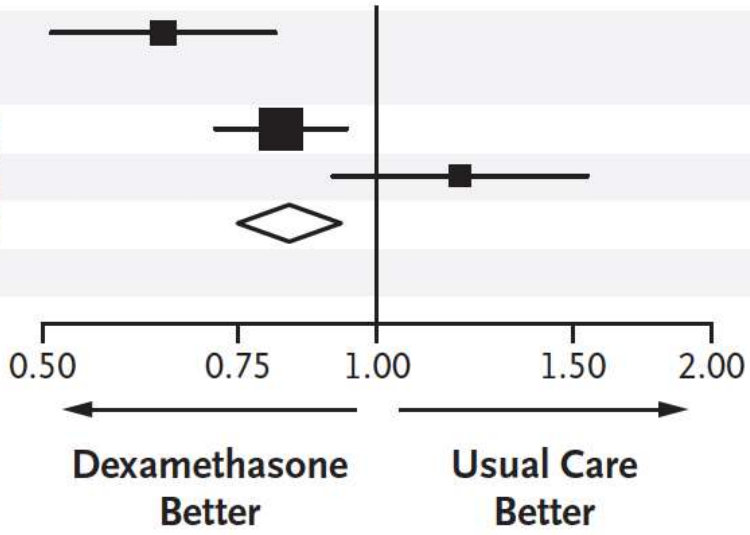


No. at Risk					
Usual care	683	572	481	424	400
Dexamethasone	324	290	248	232	228

Additional results

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
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)**
			P<0.001

Chi-square trend across three categories: 11.5



Decreased risk of progression to MV/ECMO in dex group
HR 0.77 (0.62-0.95)

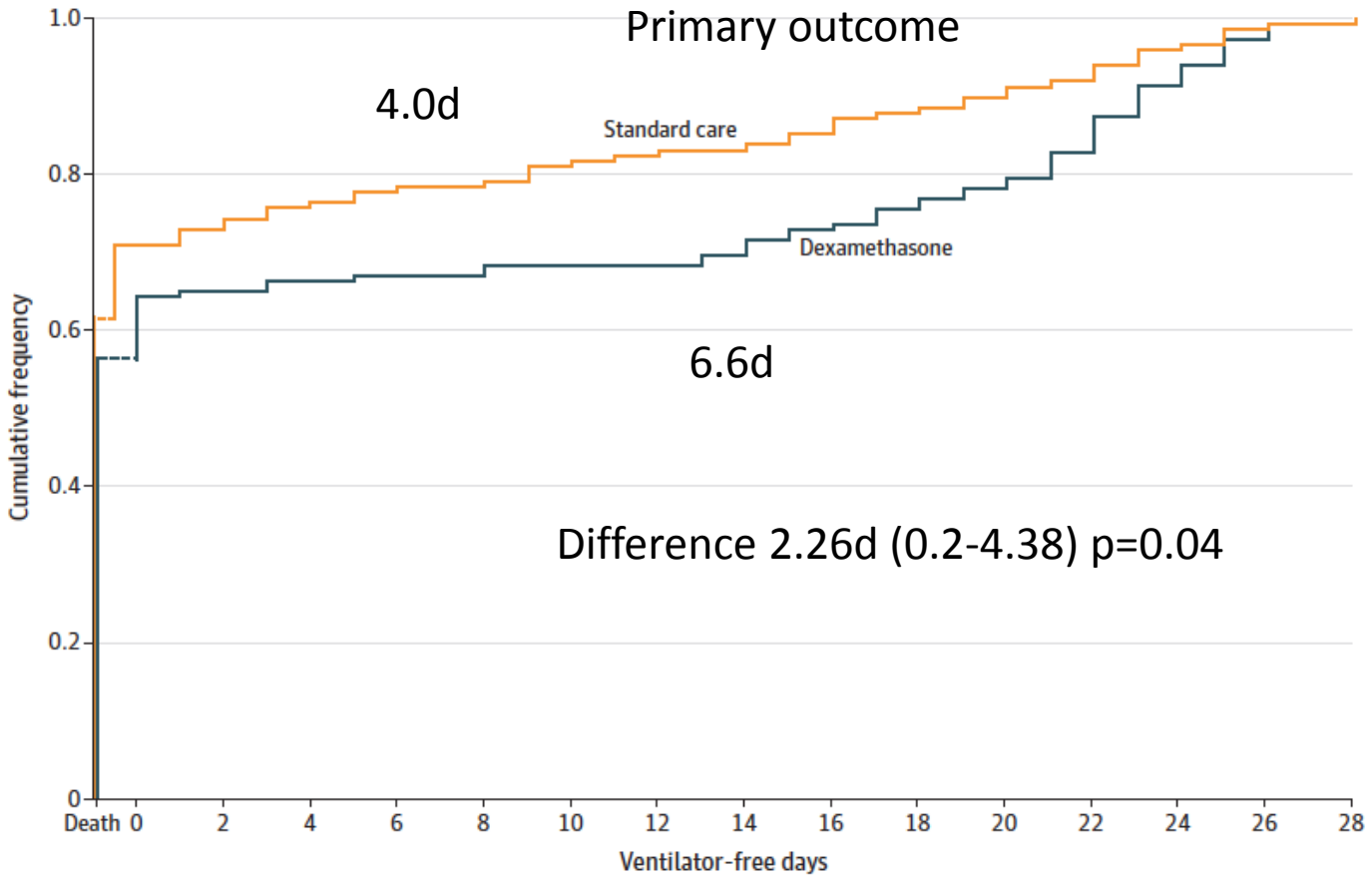
CoDEX Study

- Randomized, open label study
  - Dex 20mg x5d, 10mg x5d
  - Within 48hr of ARDS (Pa02/Fi02 <200)
- Exclusions
  - Expected death in 24hr
  - Steroids in last 15d or >1d in hospital
- Steroids and other COVID treatments allowed after randomization

Characteristic	No. (%) Dexamethasone (n = 151)	Control (n = 148)
Age, mean (SD), y	60.1 (15.8)	62.7 (13.1)
Sex		
Women	61 (40.4)	51 (34.5)
Men	90 (59.6)	97 (65.6)
SAPS III[b]	69.4 (12.6)	71.1 (12.6)
SOFA, median (IQR)[c]	9 (7-10.5)	8 (7-11)
Time since symptom onset, median (IQR), d	9 (7-11)	10 (6-12)
Mechanical ventilation prior to randomization, median (IQR), d	1 (0-2)	1 (0-1)
COVID-19 status[d]		
Positive	144 (95.4)	142 (95.9)
Probable	7 (4.6)	5 (3.4)
Negative	0	1 (0.7)
Comorbidities and risk factors		
Hypertension	91 (60.3)	107 (72.3)
Diabetes	57 (37.8)	69 (46.6)
Obesity	46 (30.5)	35 (23.7)
Heart failure	11 (7.3)	12 (8.1)
Chronic kidney failure	7 (4.6)	9 (6.1)
Current smoker	6 (4.0)	7 (4.7)
Corticosteroids before randomization	7 (4.6)	3 (2)
Moderate or severe ARDS prior to randomization, h		
≤24	136 (90.1)	138 (93.9)
>24-≤48	15 (9.9)	9 (6.1)
Vasopressor use	99 (65.6)	101 (68.2)
Prone position	33 (21.8)	33 (22)
Additional medication		
Hydroxychloroquine	36 (23.8)	28 (18.9)
Azithromycin	104 (68.9)	109 (73.6)
Other antibiotics	133 (88.1)	128 (86.5)
Oseltamivir	44 (29.1)	52 (35.1)

Tomazini BM. JAMA 2020

Increased ventilator free-days with dex



Recommendation for steroid use

Dose: dexamethasone 6mg IV/PO QD x 10d (or until discharge)

IDSA

1. Steroids recommended in those with severe COVID-19
   - Hypoxemia (<94%) and requiring supplemental 02
2. Steroids NOT recommended for those with COVID-19 without hypoxemia requiring supplemental 02

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-8

Summary

- Accumulating data support both remdesivir and dexamethasone in severe COVID-19
  - Most hospitalized patients should be treated with both agents
  - Shortened time to recovery, decreased mortality in select populations
- 5 days of RDV appear adequate for most patients
- Both appear safe