COVID-19
ONLINE EDUCATIONAL PROGRAM

Remdesivir - What do the Clinical Trials Tell us?

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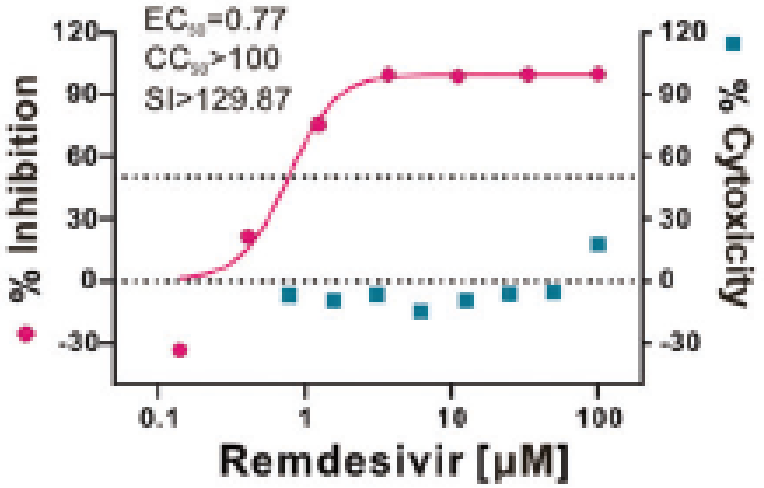
academic medical education

Disclosures

- **The speaker is a consultant to and has received honoraria and/or research support from the following companies:**
  - Atea
  - Decoy
  - Gilead
  - GlaxoSmithKline
  - Merck
  - Novartis
  - Rigel
  - ViiV

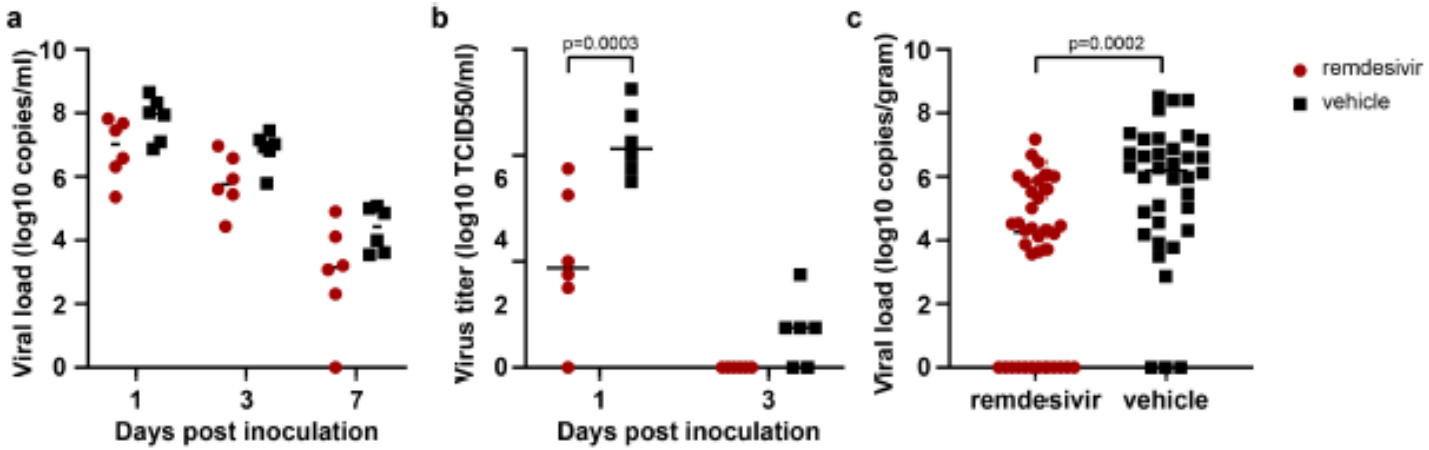
Remdesivir

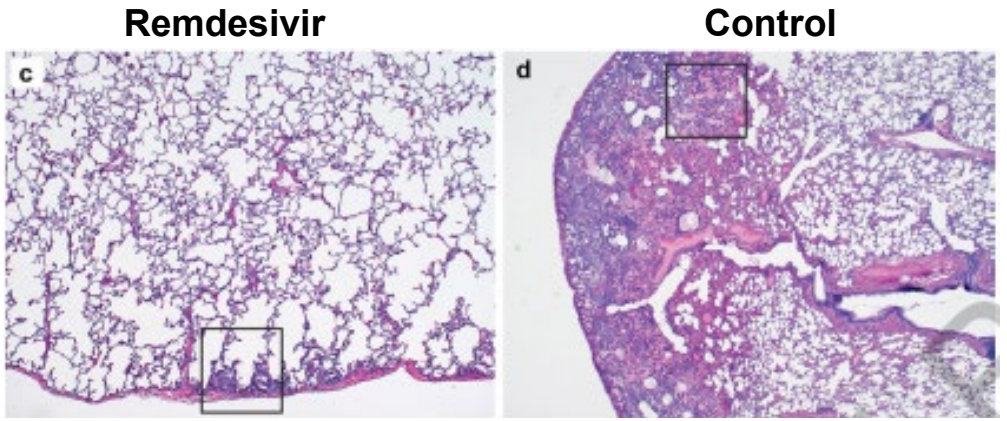
- RNA-dependent RNA polymerase inhibitor with in vitro activity against Ebola, SARS, MERS and SARS-CoV-2[1,2]
- Inferior to bNAbs against Ebola[3]
- Effective against MERS in murine and NHP models[1,4]
- Effective against SARS-CoV-2 in NHP[5]



1. Sheahan TP et al Nat Commun 2020
2. Wang M et al Cell Res 2020
3. Mulangu S et al N Engl J Med 2019
4. de Witt E et al Proc Nat Acad Sci USA 2020
5. Williamson BN et al Nature 2020

Remdesivir in NHP model of SARS-CoV-2

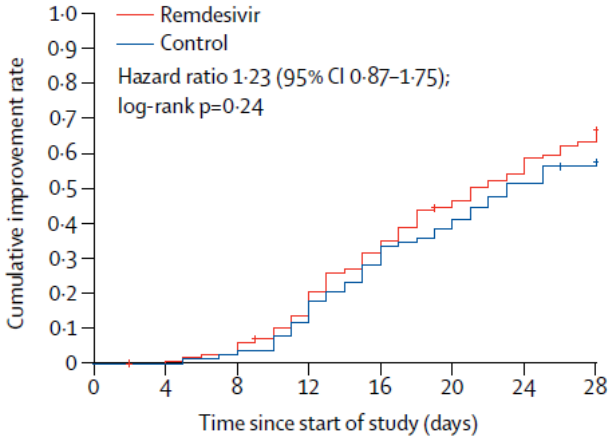


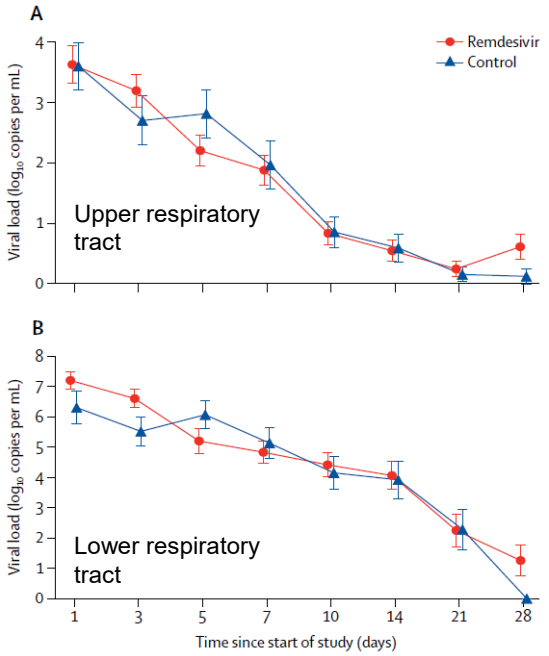


Williamson BN et al Nature 2020

Remdesivir in patients with severe COVID-19

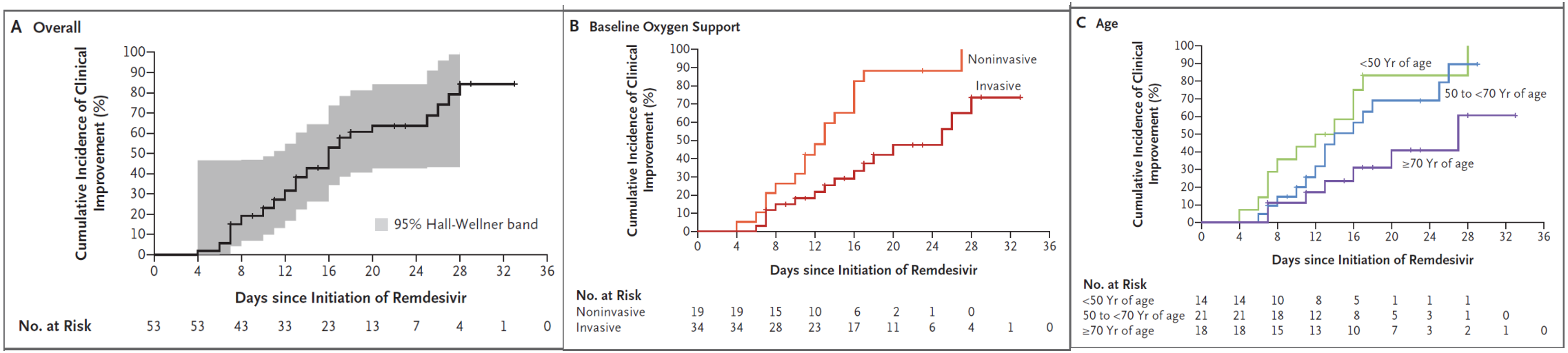
- **Double-blind, placebo-controlled RCT**
- **Randomized 2:1 remdesivir vs placebo**
- **Primary outcome: time to clinical improvement by day 28**
- **Enrollment halted due to control of COVID-19 in Wuhan**
  - Only 237 of planned 453 enrolled
  - Power reduced from 80% to 58%





Wang Y et al Lancet 2020

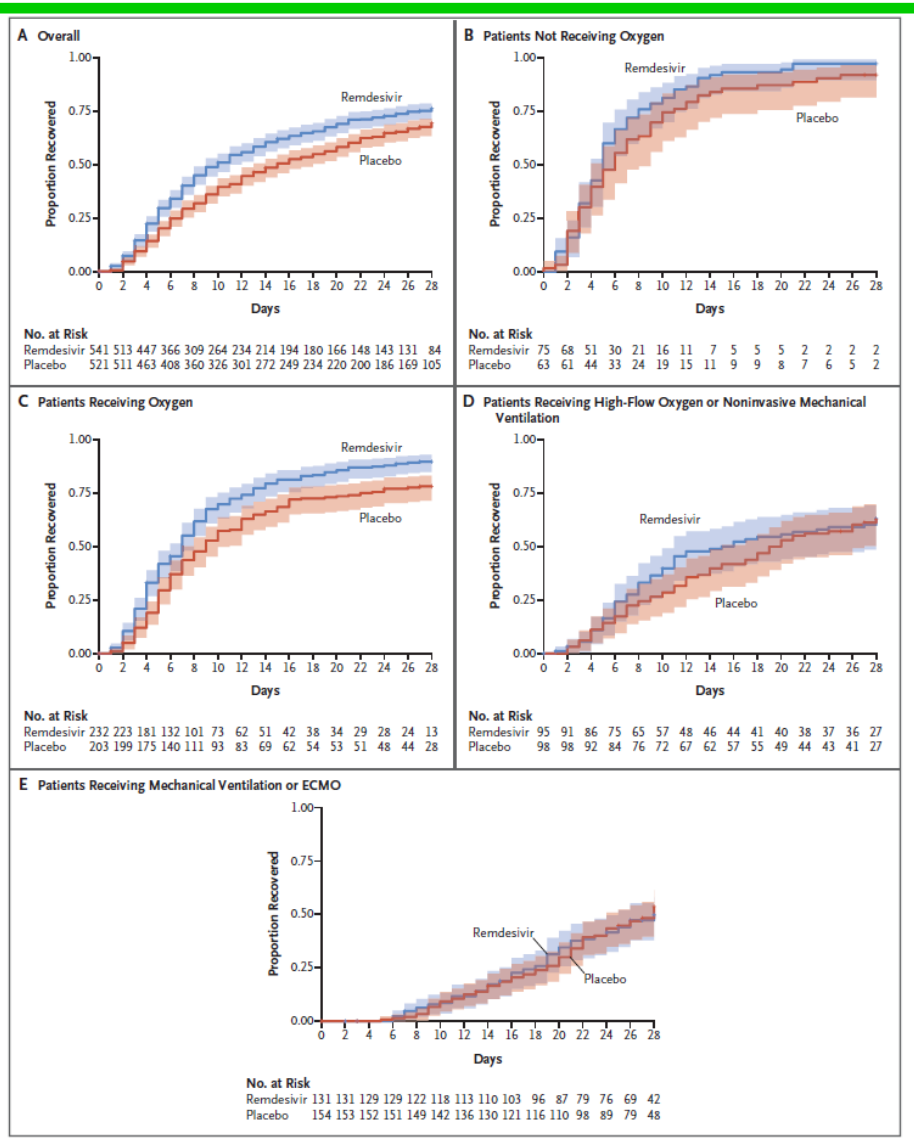
Open-label experience with compassionate-use remdesivir in patients with severe COVID-19



Grein J et al N Engl J Med 2020

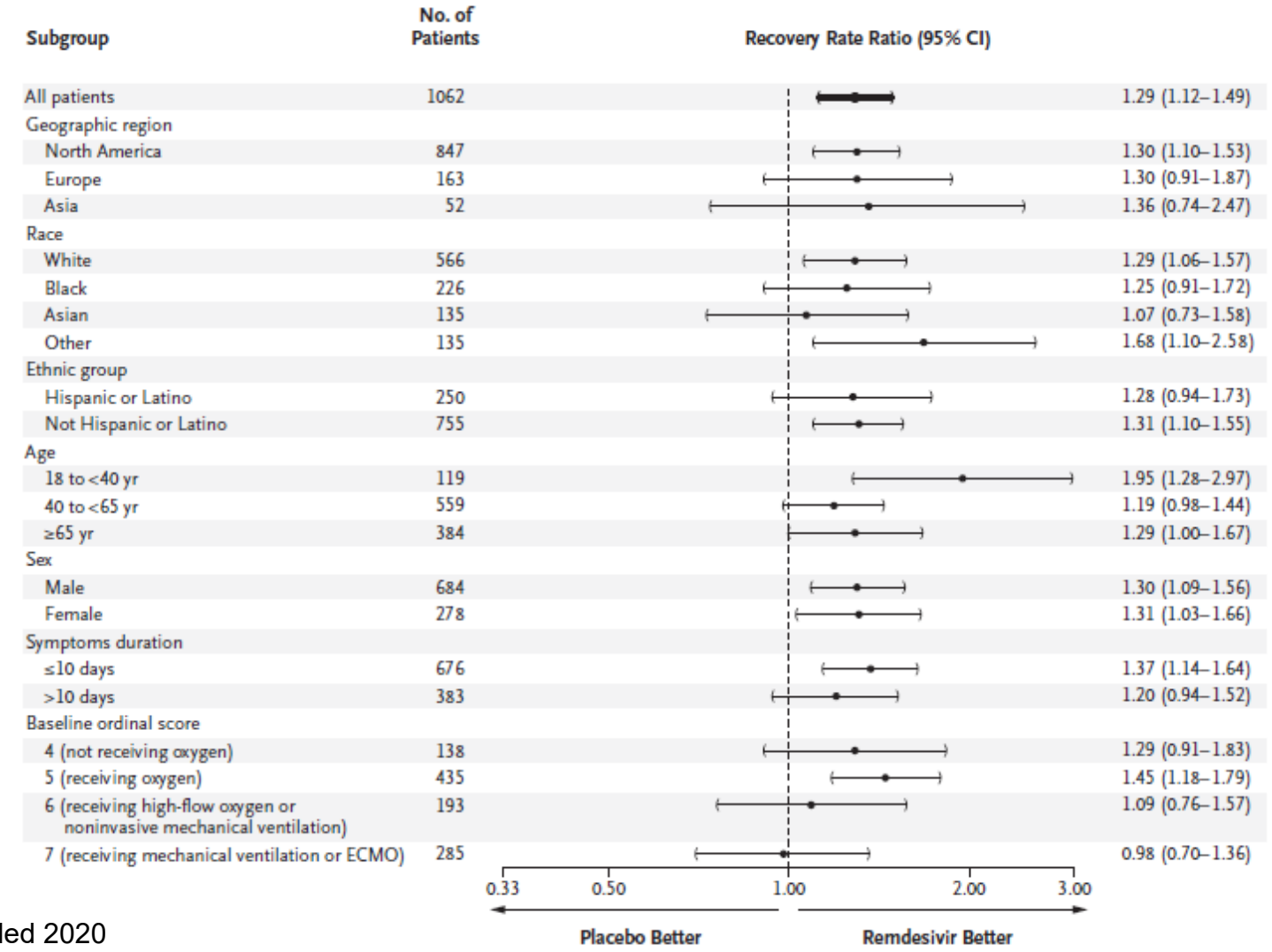
ACTT-1 Study

- **Placebo-controlled, double-blind RCT in hospitalized adults with COVID-19 pneumonia**
- **Participants randomized 1:1 to RDV or placebo**
- **Primary endpoint: time to recovery within 28 days**
  - Preliminary analysis conducted after 606 recoveries were attained
- **Baseline characteristics:**
  - ~80% with ≥1 other conditions
  - ~27% intubated or ECMO at entry



Beigel JH et al N Engl J Med 2020

ACTT-1: subgroup analysis



Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
All patients	1062	1.29 (1.12–1.49)
Geographic region		
North America	847	1.30 (1.10–1.53)
Europe	163	1.30 (0.91–1.87)
Asia	52	1.36 (0.74–2.47)
Race		
White	566	1.29 (1.06–1.57)
Black	226	1.25 (0.91–1.72)
Asian	135	1.07 (0.73–1.58)
Other	135	1.68 (1.10–2.58)
Ethnic group		
Hispanic or Latino	250	1.28 (0.94–1.73)
Not Hispanic or Latino	755	1.31 (1.10–1.55)
Age		
18 to <40 yr	119	1.95 (1.28–2.97)
40 to <65 yr	559	1.19 (0.98–1.44)
≥65 yr	384	1.29 (1.00–1.67)
Sex		
Male	684	1.30 (1.09–1.56)
Female	278	1.31 (1.03–1.66)
Symptoms duration		
≤10 days	676	1.37 (1.14–1.64)
>10 days	383	1.20 (0.94–1.52)
Baseline ordinal score		
4 (not receiving oxygen)	138	1.29 (0.91–1.83)
5 (receiving oxygen)	435	1.45 (1.18–1.79)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	193	1.09 (0.76–1.57)
7 (receiving mechanical ventilation or ECMO)	285	0.98 (0.70–1.36)

Beigel JH et al N Engl J Med 2020

Incidence of Grade 3 or 4 AEs and SAEs in ACTT-1

	Remdesivir (N=532)			Placebo (N=516)			
Safety Event Outcome	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**P-value**
Grade 3 or 4 AE	273	51	47.0, 55.6	295	57	52.8, 61.5	0.058
SAE	130	24	20.9, 28.3	163	32	27.7, 35.7	0.010

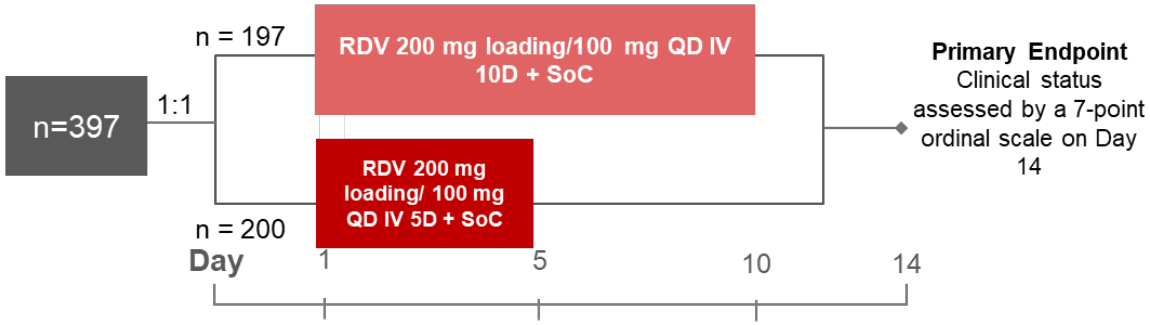
N = Number of participants in the Treated Population.
n = Number of participants in a given treatment group who experienced the specified safety event outcome.
95% CI calculated using C-P/Blaker method.
P-value calculated using Two-Sided Barnard's Exact Test.

Beigel JH et al NEJM 2020 (supplemental information)

Remdesevir SIMPLE trial: severe disease

Study GS- US 540-5774

Randomized, open-label, multicenter trial



Clinical improvement was defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital.

Major eligibility criteria

- SARS-CoV-2 by PCR
- Pulmonary infiltrate
- SpO_2 ≤94%
- Not receiving mechanical ventilation or ECMO

Source: Gilead Sciences; Goldman JD et al N Engl J Med 2020.

SIMPLE severe disease trial: baseline characteristics

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)
Median AST level (IQR) — U/liter¶	41 (29–58)	46 (34–67)
Median ALT level (IQR) — U/liter	32 (22–50)	36 (23–58)
Median creatinine clearance by Cockcroft–Gault (IQR) — ml/min	106 (80–142)	103 (80–140)

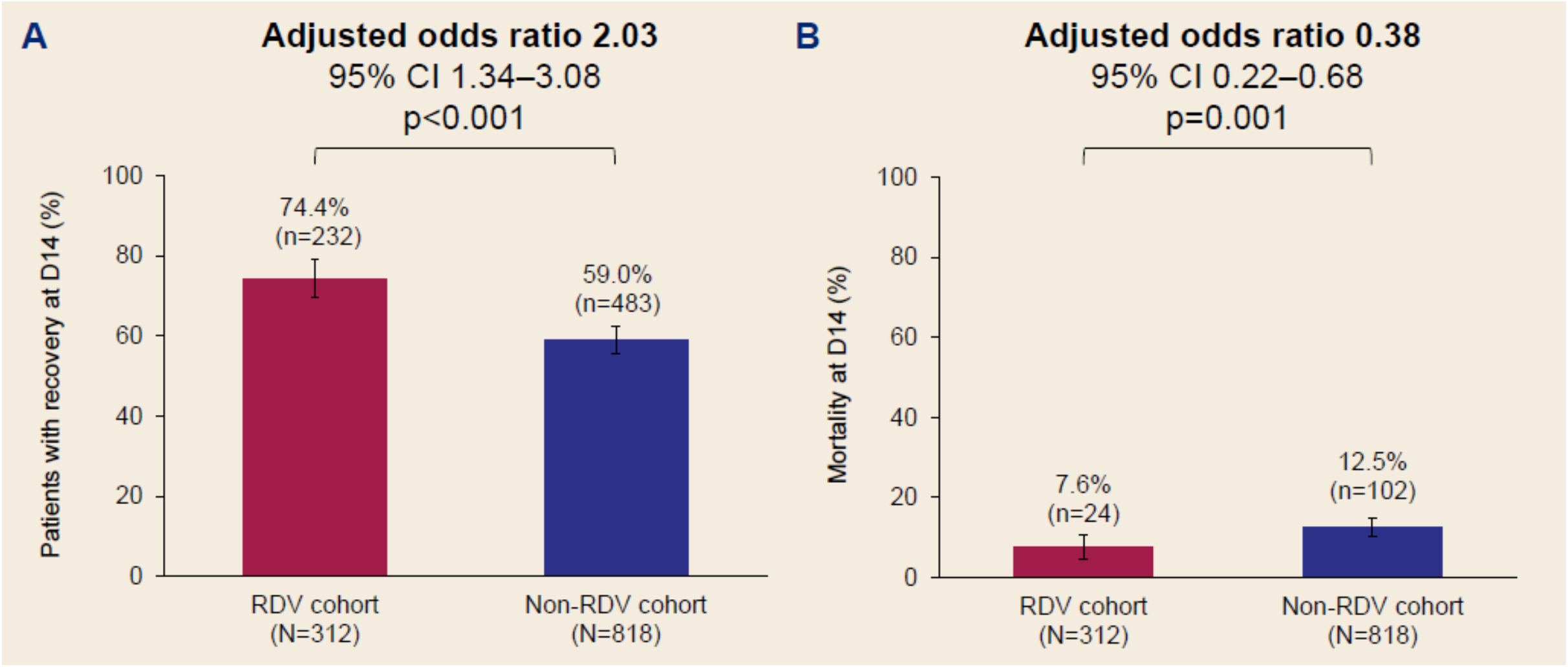
Goldman JD et al N Engl J Med 2020.

SIMPLE severe: primary and secondary endpoints

Characteristic	5-Day group (N=200)	10-Day group (N=197)	Baseline-adjusted difference (95% CI)
Clinical status at Day 14 (7-point ordinal scale)			P=0.14
Death—no. of participants (%)	16 (8)	21 (11)	
Time to clinical improvement (median day)	10	11	0.79 (0.61-1.101)
Clinical improvement at Day 14—no. of participants (%)	129 (64)	107 (54)	-6.5% (-15.7-2.8)
Time to recovery (median day)	10	11	0.81 (0.64-1.04)
Clinical recovery at Day 14—no. of participants (%)	129 (64)	106 (54)	-6.3 (-15.4-2.8)

Modified from Goldman JD et al N Engl J Med 2020.

Remdesivir for Severe COVID-19 Versus a Standard of Care Cohort: 14-day Outcomes



Remdesivir SIMPLE trial: moderate disease

- **3-arm, double-blind, placebo-controlled RCT**
  - 5 d vs 10 d vs SOC
- **Entry criteria:**
  - SARS-CoV-2+ PCR
  - SpO2 >94%
- **N=600**
- **Primary endpoint: clinical status at day 11**
- **5-day arm showed greater clinical improvement vs SOC**
  - OR 1.65 [95% CI 1.09-2.48]; p=0.017

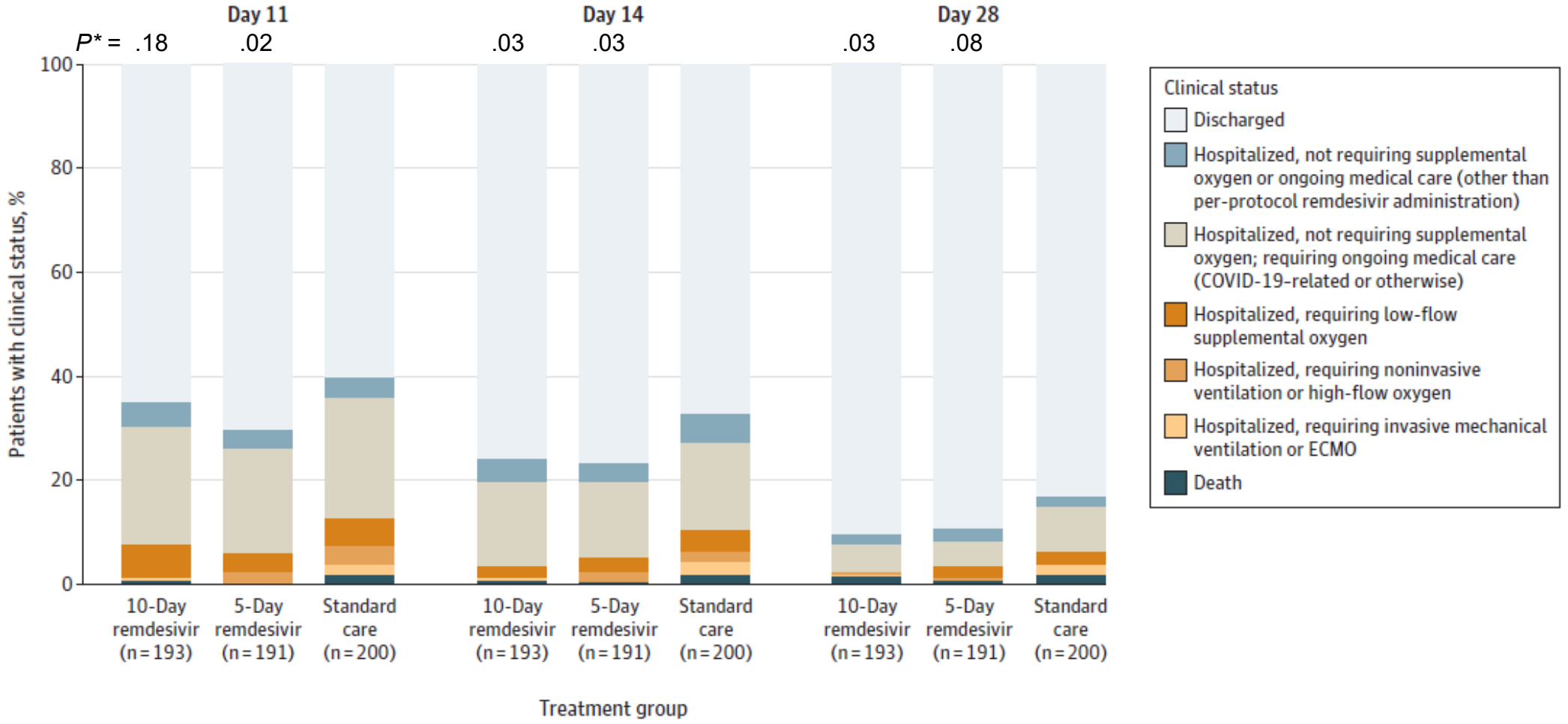
Spinner CD et al JAMA 2020

SIMPLE moderate disease trial: baseline characteristics

Characteristics	10-Day remdesivir (n = 193)	5-Day remdesivir (n = 191)	Standard care (n = 200)
Age, median (IQR), y	56 (45-66)	58 (48-66)	57 (45-66)
Sex, No. (%)			
Male	118 (61)	114 (60)	125 (63)
Female	75 (39)	77 (40)	75 (38)
Race, No./total (%)			
White	107/188 (57)	109/186 (59)	112/193 (58)
Black	37/188 (20)	35/186 (19)	27/193 (14)
Asian	31/188 (16)	34/186 (18)	37/193 (19)
Other[a]	13/188 (7)	8/186 (4)	17/193 (9)
Hispanic or Latino ethnicity, No./total (%)[b]	42/186 (23)	25/187 (13)	34/186 (18)
Body mass index, median (IQR)[c]	28 (25-32)	27 (24-30)	27 (24-31)
Day 1 clinical status on 7-point scale, No. (%)			
3: Hospitalized, requiring noninvasive ventilation or high-flow oxygen	1 (1)	2 (1)	2 (1)
4: Hospitalized, requiring low-flow supplemental oxygen	23 (12)	29 (15)	36 (18)
5: Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care	163 (84)	160 (84)	160 (80)
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care[d]	6 (3)	0	2 (1)
Coexisting conditions, No. (%)			
Cardiovascular disease	111 (58)	111 (58)	107 (54)
Hypertension	85 (44)	82 (43)	81 (41)
Diabetes	85 (44)	71 (37)	76 (38)
Asthma	31 (16)	22 (12)	28 (14)
Duration of hospitalization before first dose of remdesivir, median (IQR), d	2 (1-3)	2 (1-3)	2 (1-3)
Duration of symptoms before first dose of remdesivir, median (IQR), d	8 (5-11)	8 (5-11)	9 (6-11)

Spinner CD et al JAMA 2020

Remdesivir SIMPLE trial: moderate disease results



**P values for comparison of 10- and 5-day remdesivir arms, respectively, vs standard of care*

Spinner CD et al JAMA 2020

Remdesivir adverse event summary

Adverse events	No./total (%)		
	10-Day remdesivir (n = 193)	5-Day remdesivir (n = 191)	Standard care (n = 200)
Any adverse event	113 (59)	98 (51)	93 (47)
Any grade ≥3 adverse event	24 (12)	20 (10)	24 (12)
Any serious adverse event	10 (5)	9 (5)	18 (9)
Discontinuation of treatment because of adverse event	8 (4)	4 (2)	NA
Death[b]	3 (2)	2 (1)	4 (2)
Adverse events occurring in >5% of participants in any treatment group			
Nausea	18 (9)	19 (10)	6 (3)
Diarrhea	10 (5)	12 (6)	14 (7)
Hypokalemia	13 (7)	10 (5)	4 (2)
Headache	10 (5)	10 (5)	5 (3)
Laboratory abnormalities			
Any grade	128/179 (72)	131/180 (73)	136/186 (73)
Grade 3	25/179 (14)	18/180 (10)	25/186 (13)
Grade 4	4/179 (2)	5/180 (3)	9/186 (5)
Alanine aminotransferase increase			
Any grade	57/177 (32)	61/179 (34)	71/182 (39)
Grade 3 (>5 to 10 times ULN)	6/177 (3)	4/179 (2)	11/182 (6)
Grade 4 (>10 times ULN)	0	0	3 (2)
Aspartate aminotransferase increase			
Any grade	56/175 (32)	56/177 (32)	60/182 (33)
Grade 3 (>5 to 10 times ULN)	2/175 (1)	3/177 (2)	6/182 (3)
Grade 4 (>10 times ULN)	0	1/177 (1)	5/182 (3)
Creatinine clearance decrease			
Any grade	45/176 (26)	26/178 (15)	55/183 (30)
Grade 3 (30 to <60 mL/min or 30% to <50% decrease from baseline)	7/176 (4)	4/178 (2)	9/183 (5)
Grade 4 (<30 mL/min, ≥50% decrease from baseline, or dialysis needed)	2/176 (1)	0	5/183 (3)

Spinner CD et al JAMA 2020

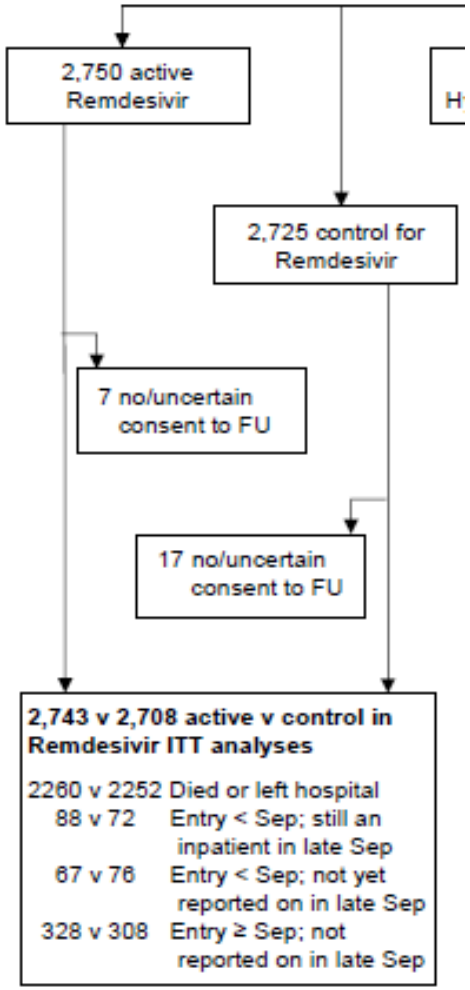
SOLIDARITY study (remdesivir arms)

Eligibility criteria
- Hospitalized adults with COVID-19
- Not having received study drug

Primary endpoint
- In-hospital mortality

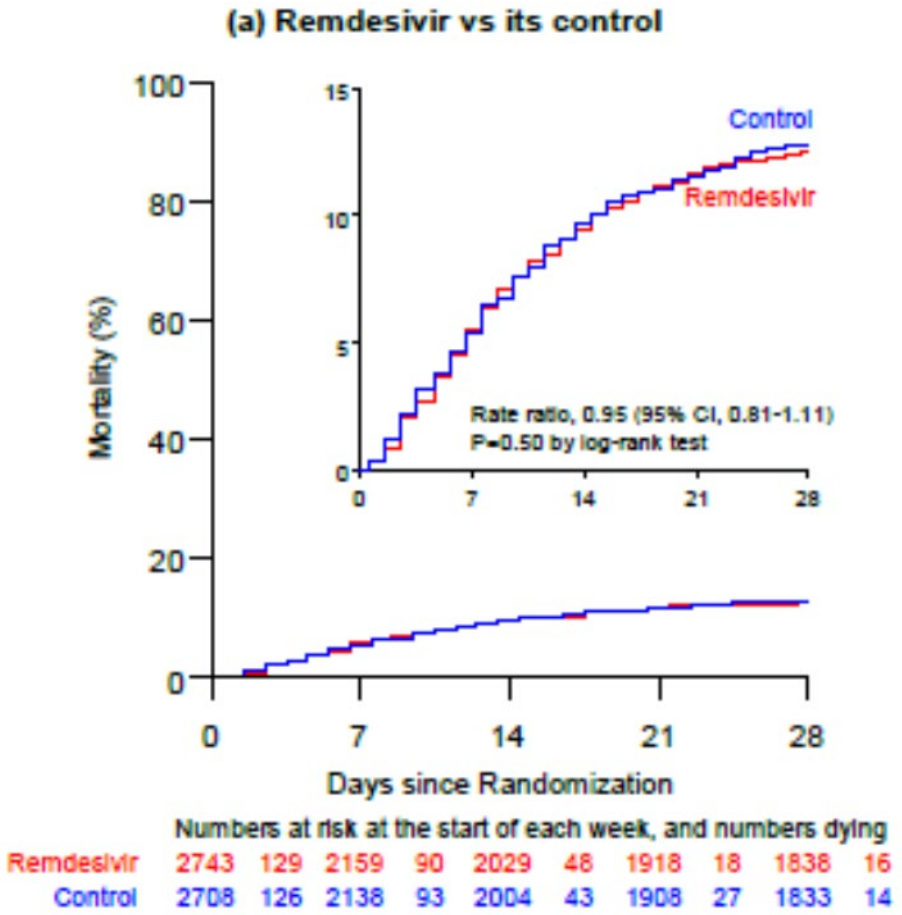
Secondary endpoints
- initiation of mechanical ventilation; duration of hospitalization

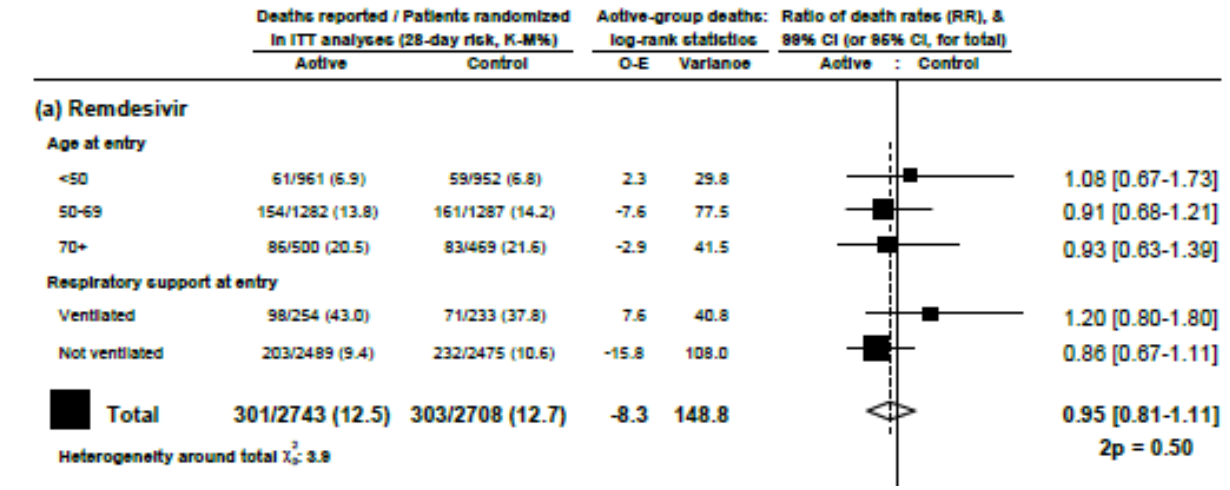
Entry characteristics	Remdesivir (N=2743)	Control (N=2708)
Age (years)		
<50	961 (35%)	952 (35%)
50-69	1282 (47%)	1287 (48%)
70+	500 (18%)	469 (27%)
Respiratory support		
No oxygen at entry	661 (24%)	664 (25%)
On oxygen at entry	1828 (67%)	1811 (67%)
Already ventilated	254 (9%)	233 (9%)



WHO Solidarity Trial Consortium medRxiv 2020

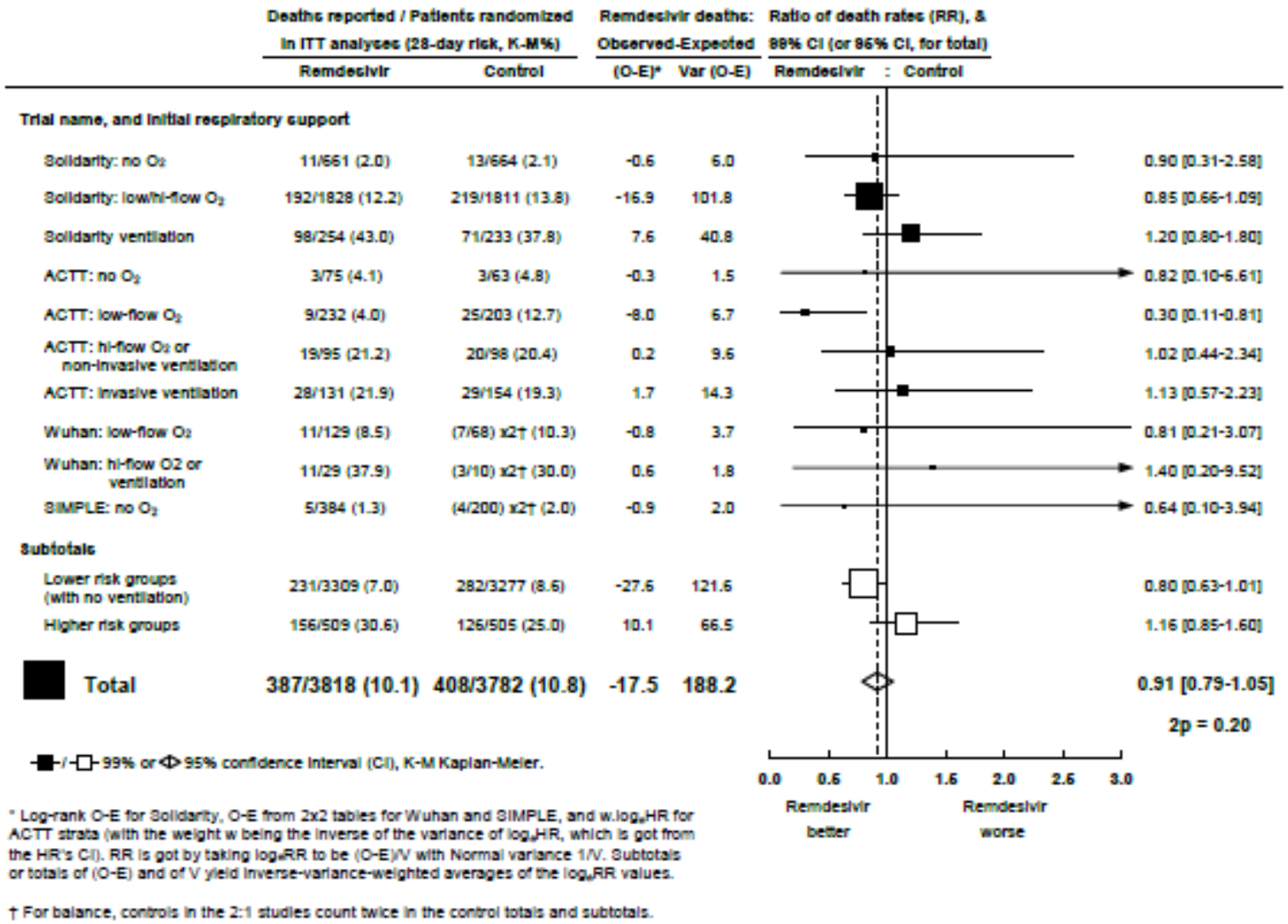
SOLIDARITY remdesivir arms in-hospital mortality





WHO Solidarity Trial Consortium medRxiv 2020

SOLIDARITY: metanalysis of remdesivir trials



* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log$_e$HR for ACTT strata (with the weight w being the inverse of the variance of log$_e$HR, which is got from the HR's CI). RR is got by taking log$_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log$_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

DHHS recommendations for remdesivir

- **For Patients With Mild or Moderate COVID-19**
  - There are insufficient data for the Panel to recommend either for or against the use of remdesivir in patients with mild or moderate COVID-19.
- **For Patients With COVID-19 Who Require (low flow) Supplemental Oxygen**
  - The Panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first (AI).
- **For Patients Who Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO**
  - Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

DHHS Covd-19 Treatment Guidelines: available at https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/ accessed 2 November 2020

Conclusions

- RCTs demonstrate clinical benefit (improved clinical status; reduced time to recovery) in hospitalized patients with moderate and severe disease in some, but not all, trials
- No survival benefit in trials conducted to date
- DHHS guidelines currently recommend use of remdesivir in hospitalized patients requiring low-flow supplemental O_2
- Trials of remdesivir in earlier disease (patients not requiring hospitalization) are ongoing.