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MedRxiv (October 15) version

Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

*A complete list of SOLIDARITY Trial investigators is provided in the Supplementary Appendix.

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Background

- Beigel JH, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med 2020

  doi:10.1056/NEJMc2022236

  - Shortening time to recovery with Remdesivir vs. Placebo, most notably in those with need of oxygen (1000 patients)

- Wang Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020, doi.org/10.1016/S0140-6736(20)31022-9

  - Among patients with symptom onset <10d, faster time of recovery (statistically non significant), (237 patients)

- Spinner CD, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020, doi:10.1001/jama.2020.16349

  - 5 versus 10 days Remdesivir (600 patients), no significant difference in clinical status on day 11

Aim of the study

- Evaluation of treatments in large randomized trials
- WHO expert groups identified 4 re-purposed drug that might have at least moderate effect on mortality

- Primary Endpoint
  - Effect on in-hospital mortality in all COVID-19 patients
    - with moderate COVID-19/with severe COVID-19

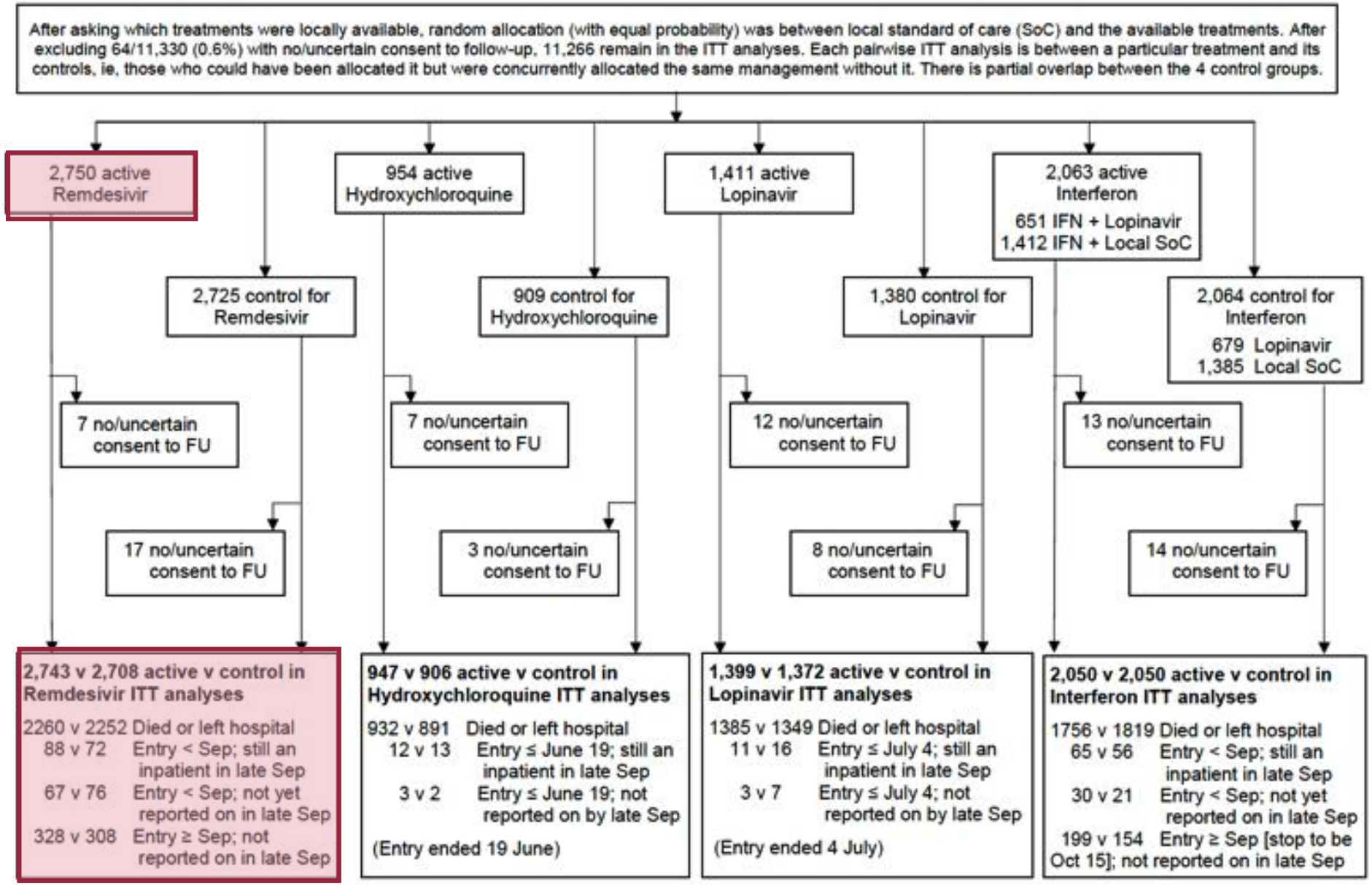
- Secondary Endpoints
  - Initiation of ventilation
  - Length of hospital stay

Methods

- Methods:
  - Multi-country, open-label randomized trial among hospitalized patients
  - Adaptive trial (unpromising drugs could be dropped out, others added)
  - Online randomization
  - Online reporting of death in hospital or discharge alive and use of study drug
  - Equal randomization between control and wichever other study drug locally available
    - Remdesivir iv: 200mg day 0; days 1-9 100mg
  - All treatments stopped at discharge
  - No follow up after discharge

- Inclusion
  - Patients > 18y, hospitalized with diagnosis of COVID-19, without contraindication to any study drug

Figure 1. WHO Solidarity Trial – information to October 4, 2020 on entry, follow-up (FU) and intent-to-treat (ITT) analyses



Allocation

- total of 11’330 patients
  - 64 excluded
- 405 hospitals
- 30 countrys

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Table 1. Entry characteristics by random allocation, and compliance with that allocation

Excludes 64 without clear consent to follow-up. Comparisons are of each study drug vs concurrent allocation to the same treatment without it. As the control groups overlap, the total number (11,266) is less than the sum of the numbers in the pairwise comparisons.

	All in any intent-to-treat analysis				Remdesivir vs its control		Hydroxychloroquine vs its control		Lopinavir vs its control		Interferon vs its control*	
	Entered No.	%	No. died	28-d KM%	Active	Control	Active	Control	Active	Control	Active	Control
All participants	11266	100	1253	11.8	2743	2708	947	906	1399	1372	2050	2050
Entry characteristics												
Age (years)												
<50	3995	35	237	6.2	961	952	335	317	511	501	720	697
50-69	5125	45	618	12.8	1282	1287	410	396	597	596	934	973
70+	2146	19	398	20.4	500	469	202	193	291	275	396	380
Respiratory support												
No oxygen at entry	3204	28	78	2.5	661	664	345	341	528	539	482	490
On oxygen at entry	7146	63	844	12.8	1828	1811	517	483	759	719	1429	1430
Already ventilated	916	8	331	39.0	254	233	85	82	112	114	139	130
Bilateral lung lesions												
No	1266	11	49	3.7	287	259	154	170	235	256	162	155
Yes	8832	78	1043	12.7	2175	2153	656	618	985	945	1723	1718
Not imaged at entry	1168	10	161	14.9	281	296	137	118	179	171	165	177
Prior days in hospital												
0	3289	29	319	9.8	724	712	296	281	423	403	678	677
1	3713	33	384	10.8	917	938	317	312	442	445	681	662
2+	4264	38	550	14.6	1102	1058	334	313	534	524	691	711
Geographic location												
Europe** or Canada	2488	22	188	7.8	715	698	286	267	349	350	254	244
Latin America§	1941	17	400	22.7	470	514	97	96	145	148	474	478
Asia and Africa†	6837	61	665	10.3	1558	1496	564	543	905	874	1322	1328
Other characteristics												
Male	6985	62	852	13.0	1706	1725	574	535	851	802	1303	1278
Current smoking	830	7	93	11.8	178	161	92	82	141	124	136	138
History of – Diabetes	2768	25	379	14.7	707	666	199	205	341	324	489	537
- Heart disease	2337	21	319	14.7	571	567	193	194	289	290	427	456
- Chronic lung disease	635	6	102	17.2	151	145	62	66	95	87	114	109
- Asthma	529	5	56	11.5	139	139	41	46	65	56	75	97
- Chronic liver disease	135	1	21	17.2	36	41	15	14	15	23	11	22
Compliance with allocated treatment												
% who were taking the study drug midway through its scheduled duration‡					95.8	1.6	94.6	5.6	93.6	2.0	93.7	1.9
% of those reported as discharged who were still in hospital on: Day 7					69	59	64	54	68	59	55	51
Day 14					22	19	23	20	31	22	19	18
Day 21					9	8	11	10	12	11	8	7

Results

11‘266 participants

- > 80% age < 70y
- 8% ventilated at randomization
- 62% male
- 25% with diabetes
- 62% randomized between day 0-1
- Characteristics balanced by unstratified 50/50 randomization

Compliance:

- 98.5 began treatment with Remdesivir, midway through 96% were still taking it

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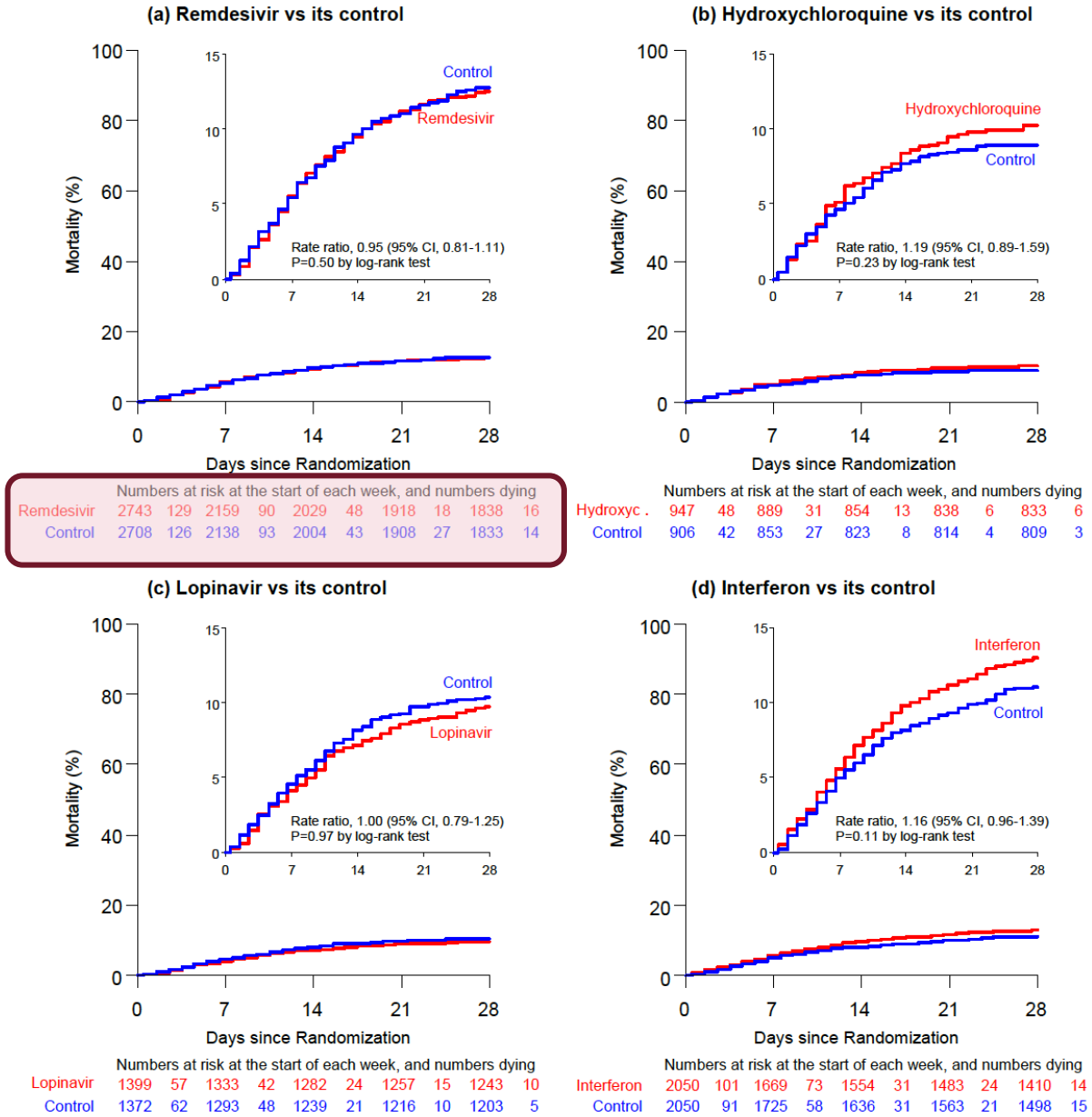
Fig 2. Effects of (a) Remdisivir, (b) Hydroxychloroquine, (c) Lopinavir, (d) Interferon on 28-day mortality



Kaplan-Meier estimates of 28-day in-hospital mortality

- No effect on mortality for all patients
- Hydroxychloroquine and Lopinavir-Ritonavir discontinued June 18 and July 4
- Interferon ceased Oct 16

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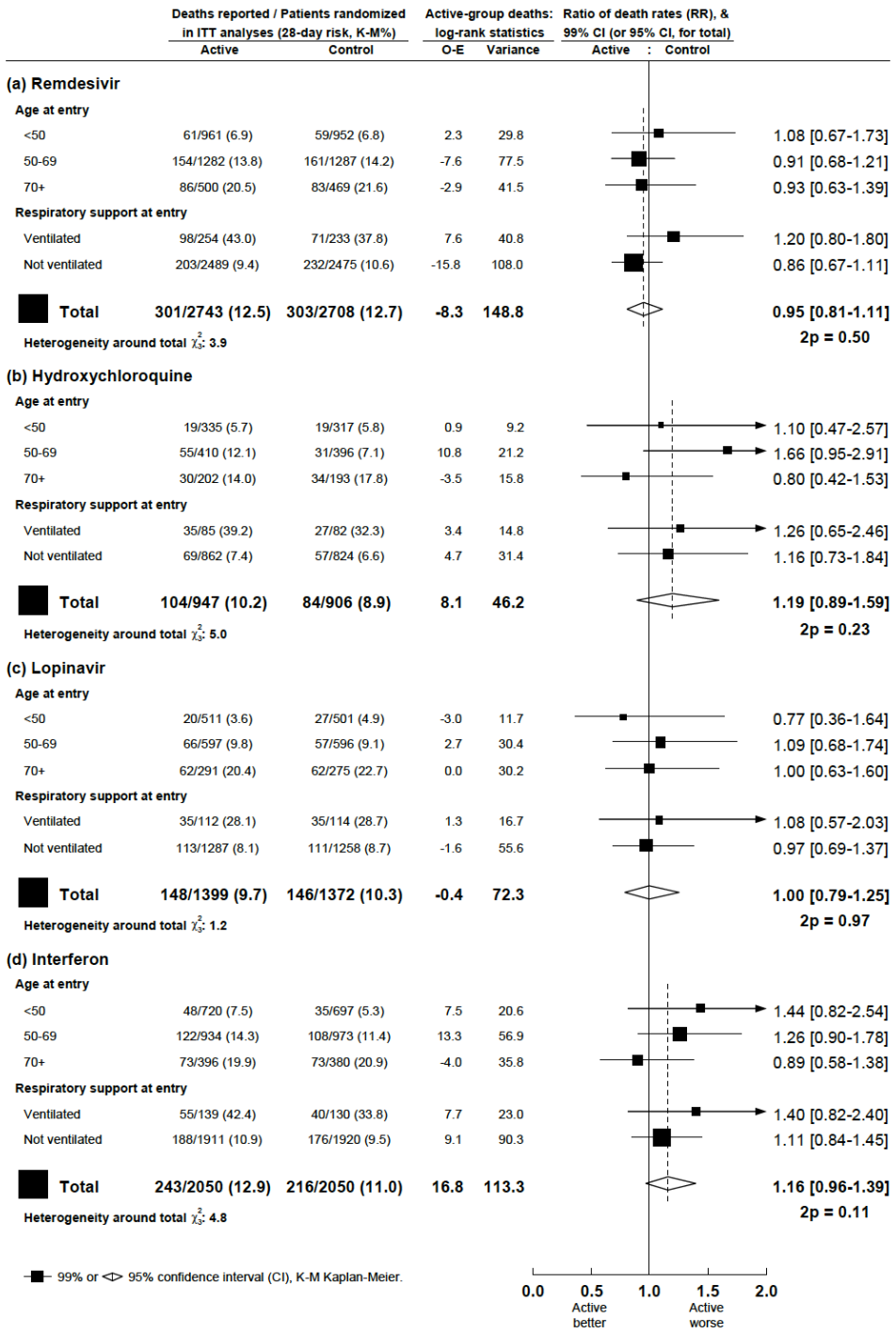

- No significant effect on mortality of any study drug
- Total 1‘253 death, 28-d Mortality 11.8%
  - overall 20% when age > 70y
  - 39% when ventilated
- Death: median at day 8 (IQR 4-14)
- Hospital discharge: median at day 8 (IQR 5-13)

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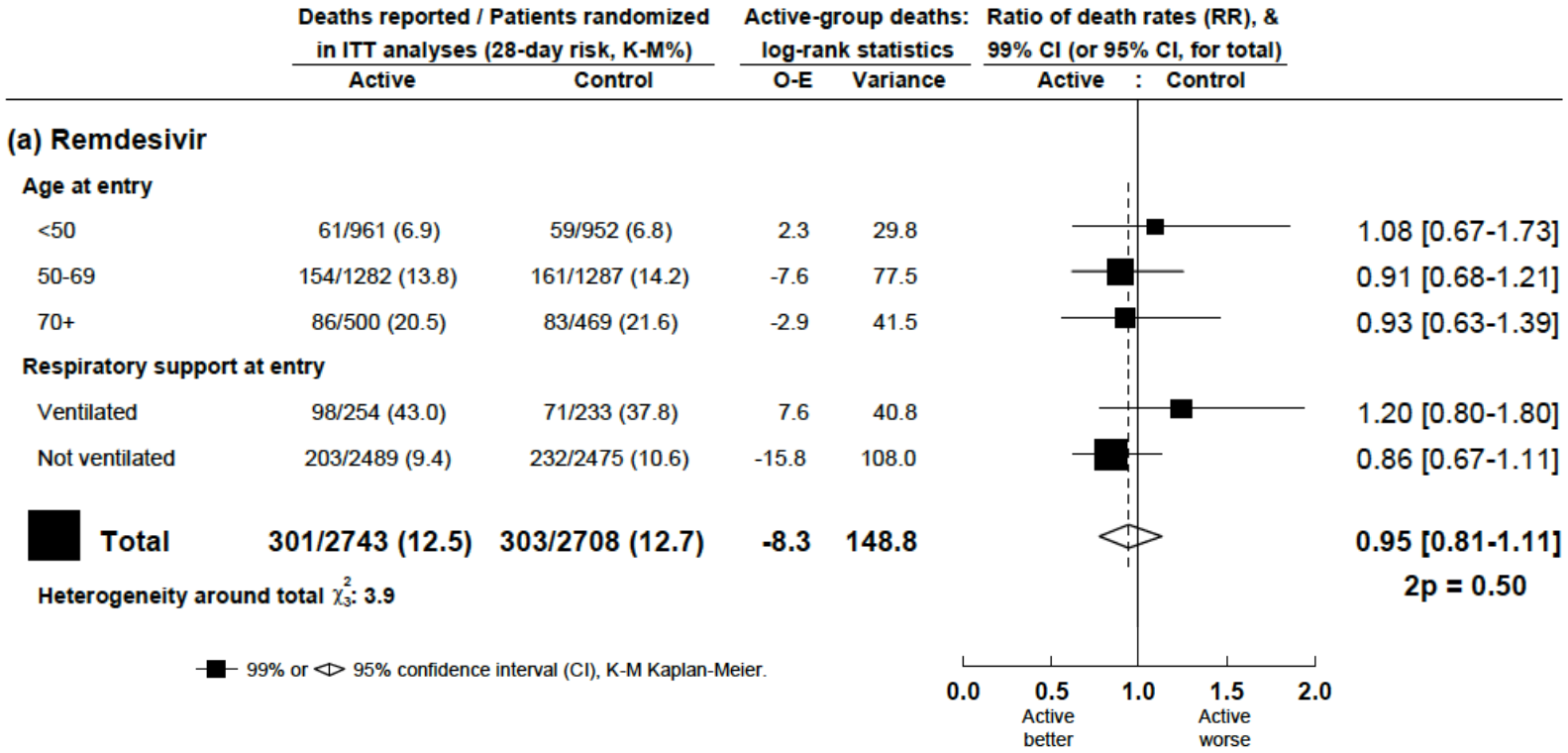
Fig 3. Rate ratios of any death, stratified by age and respiratory support at entry



- Remdesivir
  - Death rate ratio (RR) 0.95 (CI 0.81-1-11) overall
  - no significant effect in stratified subgroup analysis (age and respiratory support)

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Table S1. Treatment allocation vs initiation of ventilation in those not already being ventilated at the time of randomization

Ventilation includes invasive or non-invasive mechanical ventilation or extra-corporeal membrane oxygenation.

	Remdesivir vs its control		Hydroxychloroquine vs its control		Lopinavir vs its control		Interferon vs its control*	
	Active	Control	Active	Control	Active	Control	Active	Control
Not ventilated at entry	2489	2475	**862**	**824**	**1287**	**1258**	**1911**	**1920**
Ventilated later; died	117	108	29	19	50	44	108	91
Ventilated later; discharged	139	146	42	44	67	68	81	98
Ventilated later; pending*	39	30	4	3	7	7	20	21
Total ventilated (number, and %)†	295 11.9	284 11.5	**75 8.7**	**66 8.0**	**124 9.6**	**119 9.5**	**209 10.9**	**210 10.9**

- No significant effect on initiation of ventilation

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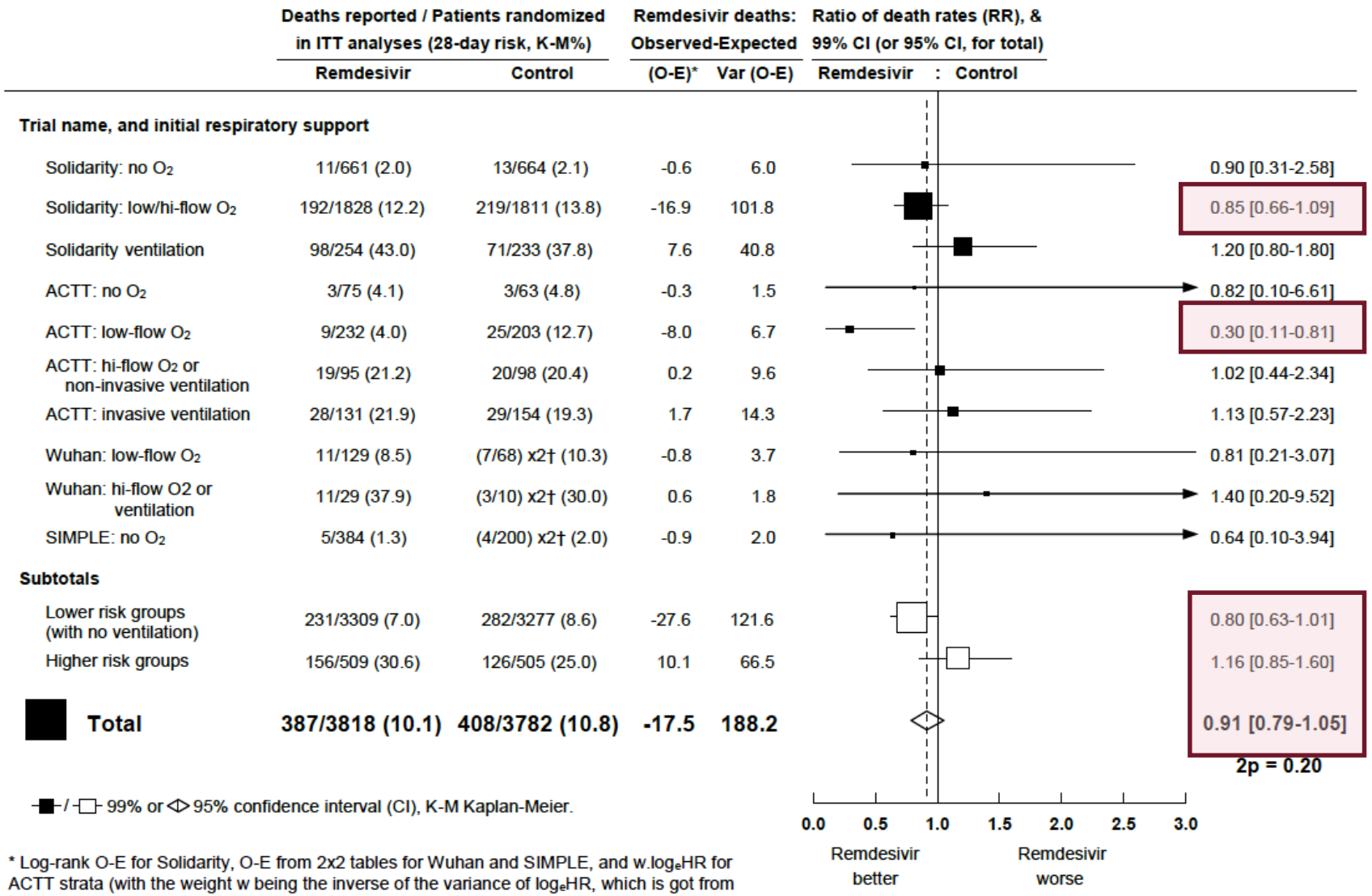
Fig. 4 Remdesivir vs control – Meta-analysis of mortality in trials with random allocation



* 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.

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Conclusion/Limitations/Questions

- No effect on main outcome mortality
- No effect on initiation of ventilation and duration of hospitalization
  - ➢ Increased percentage of remaining in the hospital > 7d when treatment duration longer than > 7d?
- No effect when combined analysis with other trials

– Large confidence intervals in subgroup analysis
  - ➢ Trend toward better Outcome with intervention in subgroup with moderate COVID-19?
– Differences between geographic regions? USA not represented
– Standard of care Protocol?
– No follow up/little clinical information
✚ Large studypopulation (still recruiting 2’000 patients per month)
✚Adaptive studydesign able to assess further treatments

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Vielen Dank für die Aufmerksamkeit