TEHRAN UNIVERSITY OF MEDICAL SCIENCES

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

WHO Solidarity trial consortium

Introduction

- A WHO COVID-19 research forum in February 2020 recommended evaluation of treatments in large randomized trials

  Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon-β1a

- In March 2020, WHO began a large, simple, multi-country, open-label randomized trial among hospital inpatients of the effects of these 4 drugs on in-hospital mortality.

- The trial was adaptive; Hydroxychloroquine and Lopinavir were eventually dropped, but others, such as monoclonal antibodies, will be added.

- Interim mortality results for the original 4 drugs are reported.

METHODS

- Protocol:
  - Involve hundreds of potentially over-stressed hospitals in dozens of countries
  - No form-filling was required
  - Online randomization of consented patients
  - Online reporting of death in hospital or discharge alive
  - No other reporting was required unless doctors suspected an unexpected serious adverse reaction (SUSAR)

METHODS

- Eligible patients:
  - were age ≥18 years
  - hospitalized with a diagnosis of COVID-19
  - without anticipated transfer elsewhere within 72 hours
  - with no contra-indication to any study drug
  - Participants were randomized in control and study drugs.

METHODS

- Drugs:
  - Placebos were not used
  - Remdesivir, Hydroxychloroquine, Lopinavir-Ritonavir and Interferon (given with Lopinavir, until July 4)
  - Hydroxychloroquine and Lopinavir were discontinued for futility on June 18 and July 4, 2020, respectively
  - Interferon is ceasing on October 16
  - Daily doses were those already used for other diseases
  - All treatments were stopped at discharge

METHODS

- Dosages:
  - Hydroxychloroquine dosage >>>> to maximize any efficacy without undue cardiac risk >>>> based on that for amoebic liver abscess, rather than for malaria
  - **Remdesivir (intravenous):** Day 0, 200mg; days 1-9 100mg
  - **Hydroxychloroquine (oral):** Hour 0, four tablets; Hour 6, four tablets; Hour 12, begin two tablets twice daily for 10 days. Each tablet contained 200mg
  - **Lopinavir (oral):** Two tablets twice daily for 14 days. Each tablet contained 200mg Lopinavir (plus 50mg Ritonavir, to slow hepatic clearance of Lopinavir).
  - **Interferon (mainly subcutaneous):** Three doses over six days of 44µg subcutaneous Interferon-ß1a; patients on high-flow oxygen, ventilators or ECMO were instead to be given 10µg intravenously once daily for six days.

METHODS

- Endpoints:
  - Primary objective: assess effects on in-hospital mortality in moderate COVID and in those with severe COVID.
  - Secondary outcomes: initiation of ventilation and hospitalization duration
- Sample size:
  - The larger the number entered the more accurate the results will be
  - But numbers entered will depend on how the epidemic develops
  - But realistic, appropriate sample sizes could not be estimated at the start of the trial

METHODS

STATISTICAL ANALYSES:

- The four main sets of analyses involve the evenly randomized pairwise comparisons of each study drug vs its controls.
- The controls were those patients who could have been allocated that drug (at that moment, in that hospital), but instead got allocated standard of care.
- If, for a particular study entrant, more than one study drug was available, allocation to standard of care would put that patient into the control group for each of them.
- All analyses relate mortality to allocated treatment (ie, they are intent-to-treat analyses)

METHODS

- STATISTICAL ANALYSES:
  - Unstratified Kaplan-Meier methods plot 28-day risk
  - Death rate ratios (RRs) and p-values are from log-rank analyses
  - Forest plots (with 95% CIs only for overall results, otherwise 99% CIs) and chi-squared statistics >>>> help interpret any apparent heterogeneity of treatment RRs between subgroups
  - Analyses used SASv9.4 and Rv4.02

RESULTS

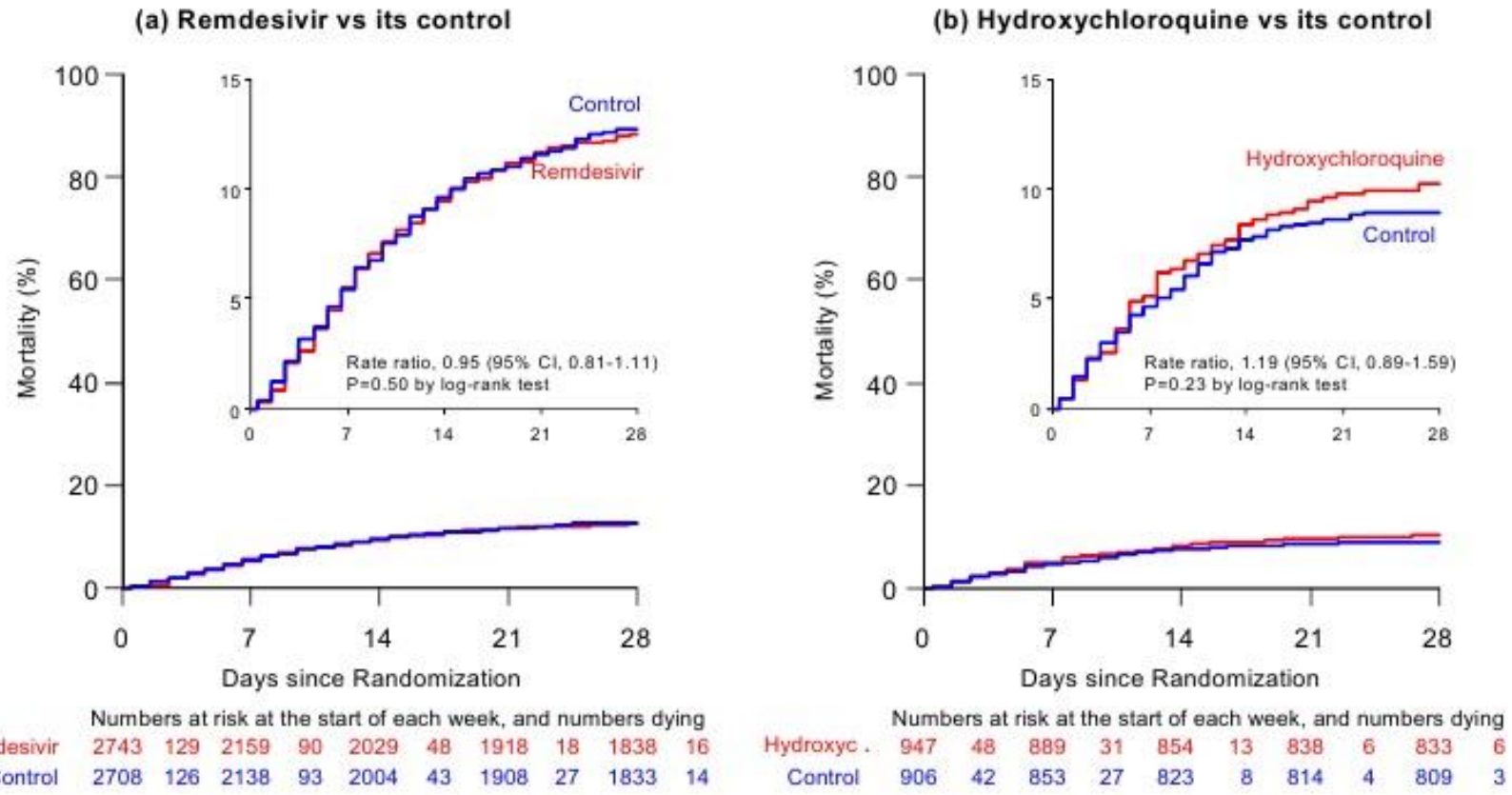
- From March 22 to October 4, 2020:
- 11,330 patients were entered from 405 hospitals in 30 countries in all 6 WHO region
- 64 (0.6%) had no consent to follow-up, leaving 11,266 for intent-to-treat analyses:
- 2750 allocated Remdesivir
- 954 Hydroxychloroquine
- 1411 only Lopinavir-ritonavir
- 2063 Interferon, and 4088 no study drug

	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

Table1.Entry characteristics by random allocation, and compliance with that allocation

Effects of (a) Remdesivir and (b) Hydroxychloroquine on 28-day mortality

Kaplan-Meier graphs of in-hospital mortality. The inset shows the same data on an expanded y-axis.



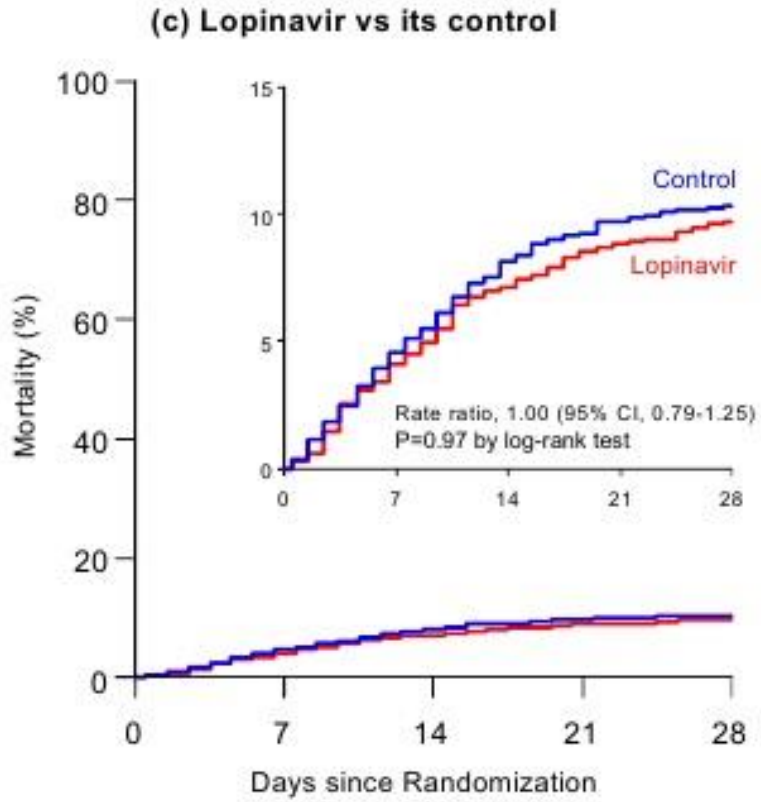
Numbers at risk at the start of each week, and numbers dying

Remdesivir	2743	129	2159	90	2029	48	1918	18	1838	16
Control	2708	126	2138	93	2004	43	1908	27	1833	14

Numbers at risk at the start of each week, and numbers dying

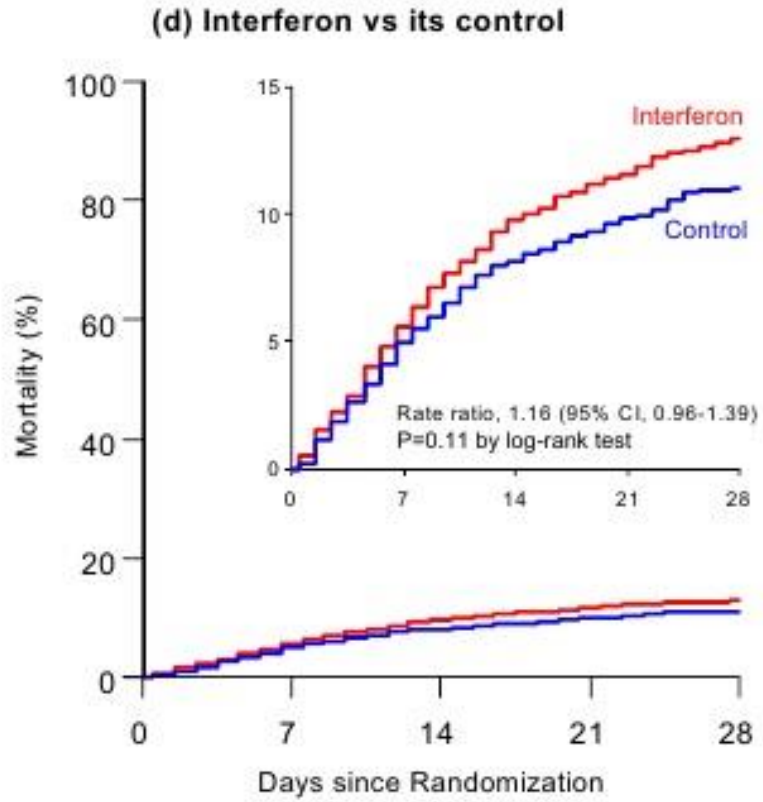
Hydroxyc .	947	48	889	31	854	13	838	6	833	6
Control	906	42	853	27	823	8	814	4	809	3

Effects of (c) Lopinavir and (d) interferon on 28-day mortality



Numbers at risk at the start of each week, and numbers dying

Lopinavir	1399	57	1333	42	1282	24	1257	15	1243	10
Control	1372	62	1293	48	1239	21	1216	10	1203	5



Numbers at risk at the start of each week, and numbers dying

Interferon	2050	101	1669	73	1554	31	1483	24	1410	14
Control	2050	91	1725	58	1636	31	1563	21	1498	15

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DISCUSSION

- The main outcomes of mortality, initiation of ventilation and hospitalization duration were not clearly reduced by any study drug.

- The chief aim was to help determine whether any of 4 re-purposed antivirals could at least moderately affect in-hospital mortality, and whether any effects differed between moderate and severe disease.

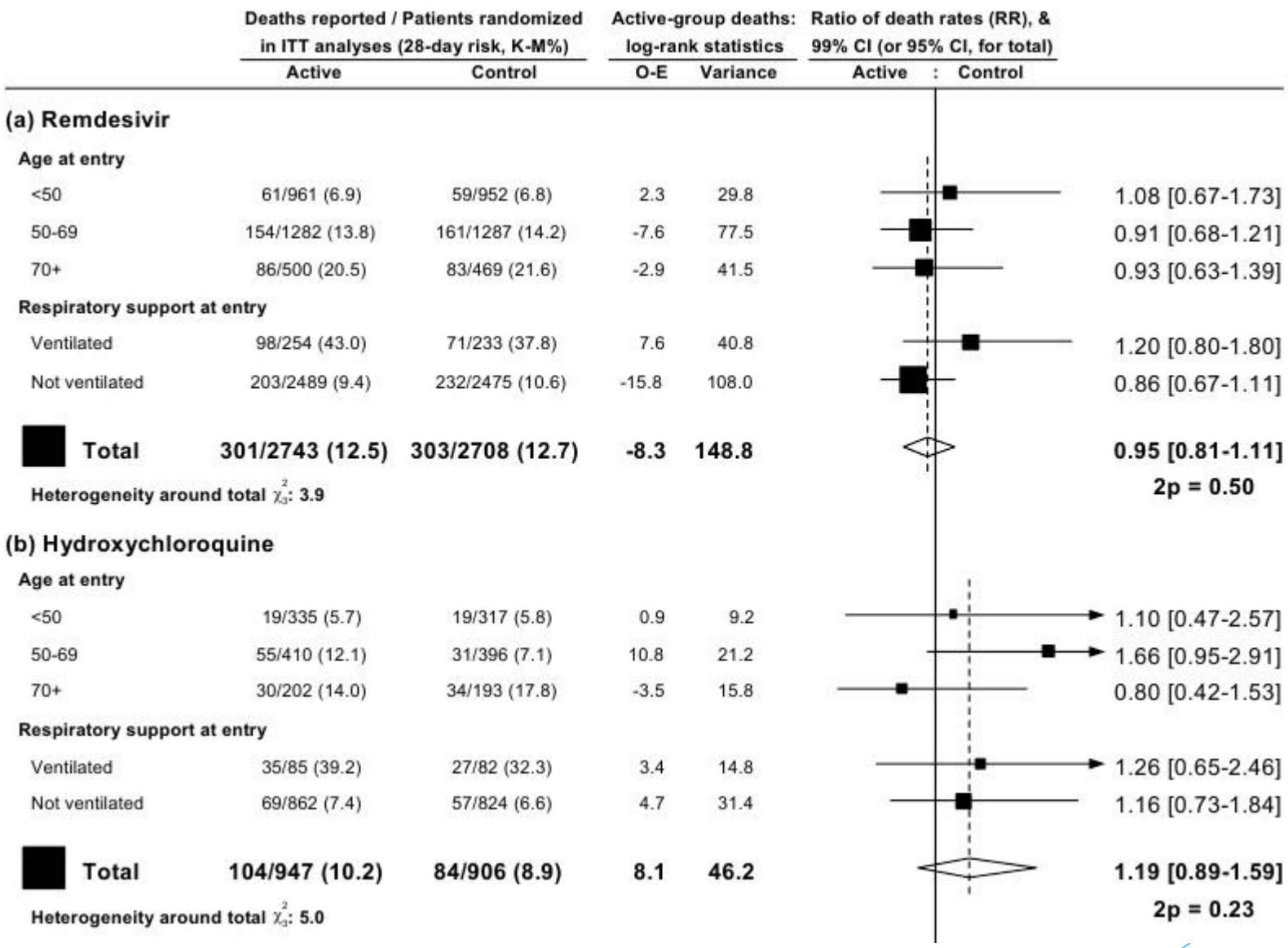
DISCUSSION

- **Remdesivir:**
  - There are 4 trials of Remdesivir vs the same management without it:
  - Solidarity (604 deaths in about 5000 randomized), ACTT-1 (136 deaths in about 1000) and two smaller trials (41 deaths)
  - Combining data appropriately from all 4 trials,8 the Remdesivir vs control death rate ratio (RR) is 0.91 (95% CI 0.79-1.05).
  - The confidence interval is comfortably compatible with prevention of a small fraction of all deaths, but is also comfortably compatible with prevention of no deaths

DISCUSSION

- **Hydroxychloroquine and Lopinavir:**
  - Solidarity found no definite evidence of benefit or of hazard in any subgroup.
  - The only other substantial trial of these two drugs is Recovery
  - For Hydroxychloroquine, the joint mortality RR (combining 2 trials) was 1.11, 95% CI 0.99-1.24, with no apparent benefit whether ventilated or not.
  - A recent meta-analysis identified 27 small randomized Hydroxychloroquine trials (total 167 deaths, RR=1.00, 0.71-1.42);12 combining all 29 trials, RR=1.10, 0.99-1.22, again excluding any material benefit.
  - For Lopinavir (always co-administered with Ritonavir), the joint mortality RR (combining Solidarity, Recovery and the only informative smaller trial13) was 1.02, 95% CI 0.91-1.14.

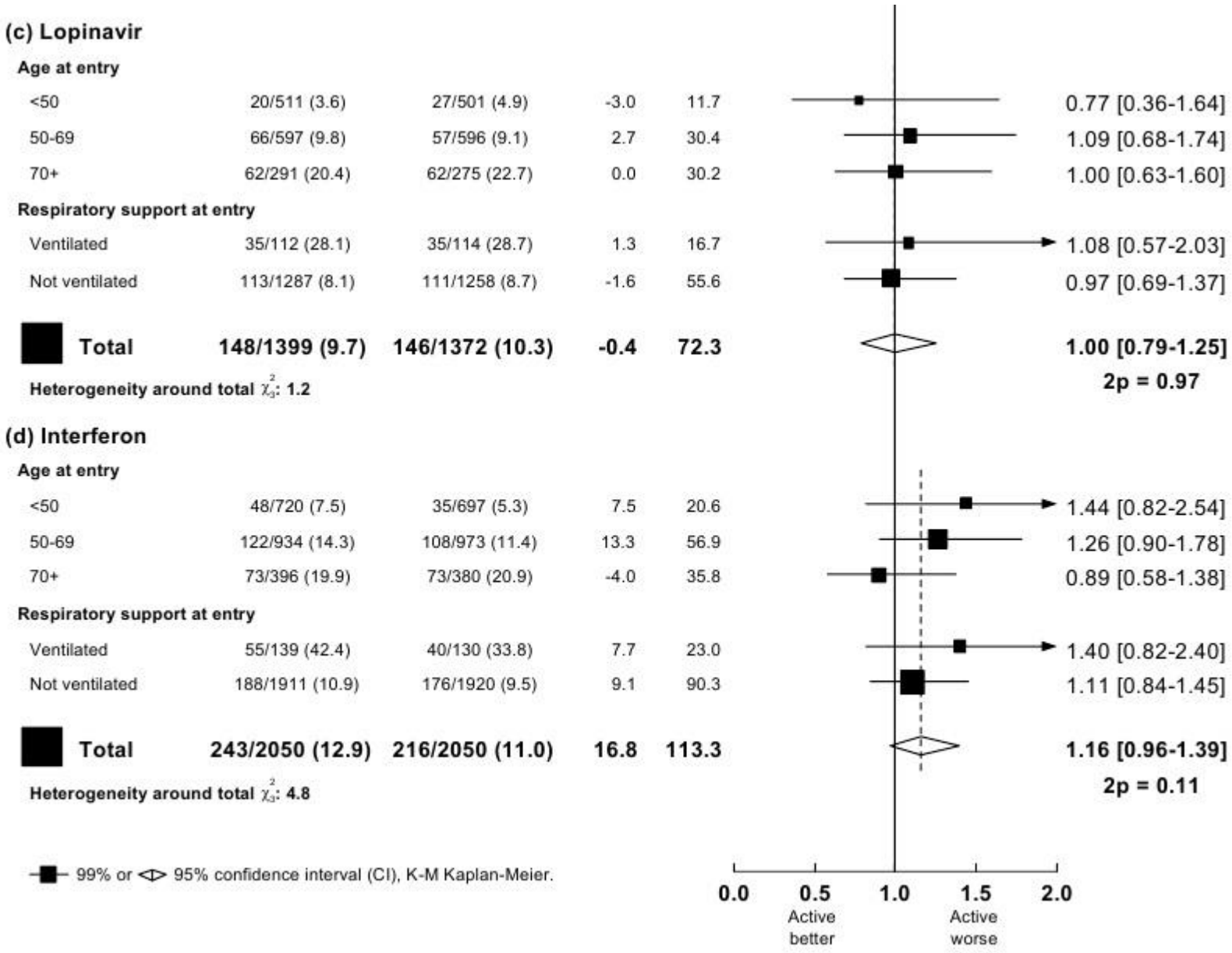
Rate ratios of any death



DISCUSSION

- **Interferon-β1a:**
  - no large mortality trials have been reported
  - the mortality RR in Solidarity was 1.16, 0.96-1.39; p=0.11
  - About half the interferon-allocated patients (and half their controls) received corticosteroids,16 but the interferon vs control mortality RR seemed unaffected by corticosteroids.

Rate ratios of any death



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Thanks for your attention