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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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RR calculations include in-hospital deaths after day 28, but percentages cited in forest plots (except for meta-analyses) are from K-M analyses that exclude deaths after day 28.

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India: the Indian Council of Medical Research under RFC No ECD/NTF-1-20-21; HETEROLABS Limited Hyderabad donated Remdesivir;

Iran: funding from the Iran Ministry of Health and Medical Education;

Ireland: The Department of Health, Republic of Ireland, in collaboration with the Health Research Board;

Italy: funding and in kind support from the Azienda OspedalieraIntegrata of Verona and the Servizio di Farmacia, Azienda Ospedaliera Integrata, Verona;

Malaysia: funding support from the Ministry of Health NIH Research Grant;

Norway: funding support from the Clinical Therapy Research in the Specialist Health Services (KLINBEFORSK);

Philippines: the Department of Science and Technology, Philippine Council for Health Research and Development; Department of Health

Portugal: Agency for Clinical Research and Biomedical Innovation (AICIB); the Ministry of Health

South Africa: the South African Medical Research Council with funds received from the Department of Science and Innovation;

Spain: the Spanish Clinical Research Network (SCReN, Institute of Health Carlos III, through PT17/0017/0018 - integrated in the State Plan I+D+I 2013-2016 and co-financed by FEDER), Research Project COV20/00612 (CTE-COVID-19, ISCIII), and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); Hospital Universitario Virgen Macarena, Sevilla, Spain, has received funding support from the Instituto de Salud Carlos III, Spanish Network for Research in Infectious Diseases (REIPI; RD16/0016/0001), co-financed by European Development Regional Fund "A way to achieve Europe", Operative program IntelligentGrowth 2014-2020;

Switzerland: the Swiss National Science Foundation (NSF) in collaboration with the Federal Office of Public Health (FOPH).

WHO: supported through its COVID-19 Strategic Preparedness and Response Plan, including funding from the United Kingdom's Department for International Development (DFID, now replaced by the Foreign, Commonwealth & Development Office (FCDO); the German Federal Ministry of Health (BMG); the Ministry of Foreign Affairs of Denmark; the Kingdom of Saudi Arabia (the King Salman Humanitarian Aid and Relief Center); and the Government of the State of Kuwait.

Table S1. Treatment allocation vs death and/or initiation of ventilation

Ventilation includes invasive or non-invasive mechanical ventilation, or extra-corporeal membrane oxygenation (ECMO). Follow-up for mortality ceased at (first) discharge from hospital.

	Remdesivir vs its control		Hydroxy-chloroquine vs its control		Lopinavir vs its control		Interferon vs its control	
	Active	**Control**	**Active**	**Control**	**Active**	**Control**	**Active**	**Control**
Not ventilated at entry	n=3787	n=3782	n=864	n=818	n=1292	n=1253	n=2000	n=2011
Ventilation initiated after entry; died	242	251	29	19	52	46	142	113
Ventilation initiated after entry; lived	293	342	46	46	72	76	114	132
Ventilation initiated after entry	**535**	**593**	**75**	**65**	**124**	**122**	**256**	**245**
	14.1%	**15.7%**	**8.7%**	**7.9%**	**9.6%**	**9.7%**	**12.8%**	**12.2%**
P-value (from figure S5)	**p=0.04**		**p=0.65**		**p=0.76**		**p=0.53**	
Never ventilated; died	209	258	40	42	65	71	105	102
Died, or ventilation initiated after entry	**744**	**851**	**115**	**107**	**189**	**193**	**361**	**347**
	19.6%	**22.5%**	**13.3%**	**13.1%**	**14.6%**	**15.4%**	**18.0%**	**17.3%**
P-value (from figure S7 analyses)	**p=0.001**		**p=0.98**		**p=0.34**		**p=0.77**	
Already ventilated at entry	n=359	n=347	n=84	n=82	n=112	n=115	n=144	n=136
Died	151	134	35	28	34	36	69	51
	42.1%	38.6%	41.7%	34.1%	30.4%	31.3%	47.9%	37.5%
P-value (from figure S7 analyses)	p=0.32		p=0.38		p=0.88		p=0.07	
All patients	n=4146	n=4129	n=948	n=900	n=1404	n=1368	n=2144	n=2147
Died, or ventilation initiated after entry	**895**	**985**	**150**	**135**	**223**	**229**	**430**	**398**
	21.6%	**23.9%**	**15.8%**	**15.0%**	**15.9%**	**16.7%**	**20.1%**	**18.5%**
P-value (from figure S7)	**p=0.009**		**p=0.66**		**p=0.42**		**p=0.16**	

All p-values are stratified for age and, where relevant, for respiratory support at entry

Table S2. Numbers (and percentages) using selected non-study drugs

	Remdesivir vs its control		Hydroxychloroquine vs its control		Lopinavir vs its control		Interferon vs its control	
	Active N=4146	**Control N=4129**	**Active N=948**	**Control N=900**	**Active N=1404**	**Control N=1368**	**Active N=2144**	**Control N=2147**
Corticosteroids	2782 67.1	2820 68.3	190 20.0	197 21.9	367 26.1	387 28.3	1232 57.5	1286 59.9
Convalescent plasma	125 3.0	151 3.7	7 0.7	3 0.3	23 1.6	15 1.1	54 2.5	51 2.4
Anti-IL-6 medication	174 4.2	199 4.8	21 2.2	18 2.0	42 3.0	42 3.1	66 3.1	88 4.1
Non-trial interferon	5 0.1	30 0.7	1 0.2	1 0.1	4 0.3	0 0.0	2 0.1	31 1.4
Non-trial antiviral	115 2.8	262 6.4	76 8.0	73 8.1	111 7.9	111 8.1	122 5.7	179 8.3

Table S3. Multivariate analysis simultaneously estimating all 4 effects

The pre-planned primary analyses in the main text involved 4 pairwise comparisons (using log-rank methods), one between each treatment group and its controls, as indicated in the flowchart (Figure 1). These 4 primary analyses were stratified by age and by whether the patient was already ventilated at the time of randomisation, and found no definitely favorable or definitely unfavorable effect of any of the 4 study drugs on all-cause in-hospital mortality (Table 1, Figure S1). The RRs in these 4 pre-planned pairwise comparisons were:

Remdesivir vs its control (by pre-planned log-rank analysis) RR=0.91 (95% CI 0.82-1.02),

Hydroxychloroquine vs its control (by pre-planned log-rank analysis) RR=1.12 (0.84-1.48),

Lopinavir vs its control (by pre-planned log-rank analysis) RR=0.94 (0.75-1.18), and

Interferon vs its control (by pre-planned log-rank analysis) RR=1.21 (1.03-1.42, p=0.02).

As there was some overlap between the 4 control groups, an exploratory sensitivity analysis used multivariate Cox regression to fit all 4 treatment effects simultaneously, assuming the independence of any effects of lopinavir and of interferon. This multivariate analysis was stratified by the set of study drugs that was locally available at randomisation (13 occupied strata). Hence, no reduction of the dataset was needed to ensure that comparisons were only between concurrently randomised treatments, and that they were not subject to any selective biases. It was adjusted for several of the prognostic factors listed in Table 1: age (<40, 40-49, 50-59, 60-69, 70-79, 80+ years), sex, diabetes, bilateral lung lesions at entry (no, yes, not imaged at entry), and respiratory support at entry (no oxygen, oxygen but no ventilation, ventilation). This multivariate sensitivity analysis had not been pre-planned as a primary or a secondary analysis. For each of the 4 study drugs the multivariate analysis yielded RRs for active treatment vs local standard of care (SoC) that were similar to those in the pre-planned primary pairwise comparisons (except that the conventionall adverse effect of interferon ceased to be conventionally significant, again finding no definitely favorable or unfavorable effect of any of the 4 study drugs:

Remdesivir vs local SoC (by multivariate analysis) RR=0.93 (95% CI 0.84-1.04),

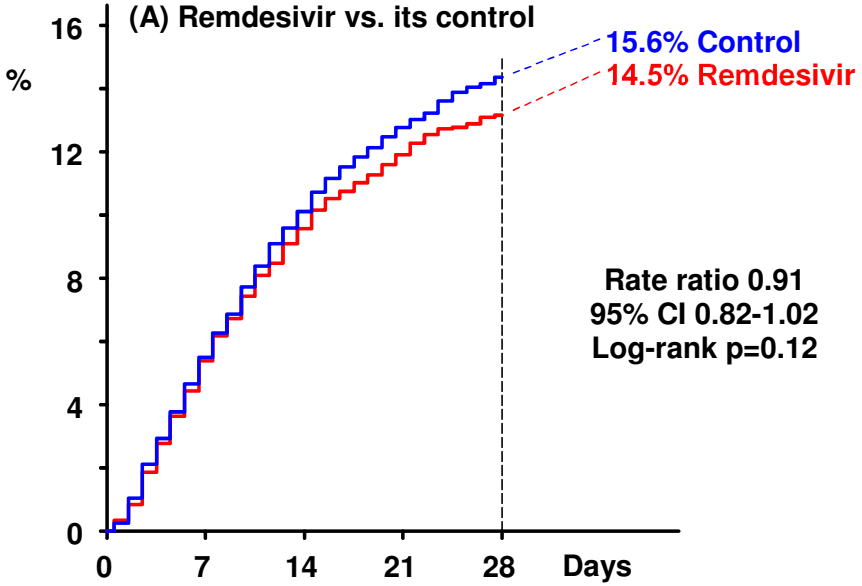
Hydroxychloroquine vs local SoC (by multivariate analysis) RR=1.09 (0.86-1.40),

Lopinavir vs local SoC (by multivariate analysis) RR=0.93 (0.76-1.14), and

Interferon vs local SoC (by multivariate analysis) RR=1.15 (0.99-1.34, p=0.06).

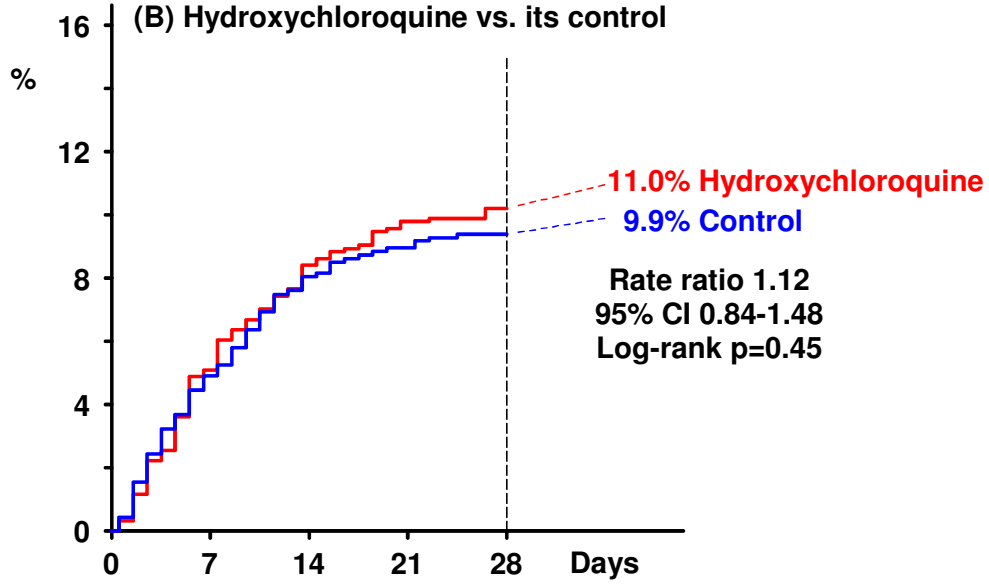
Figure S1A-S1D. Effects on in-hospital mortality of (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, and (D) interferon

Kaplan-Meier graphs, not standardised. Rate ratios (RR, 95% CI) include later in-hospital deaths, and standardise for age and ventilation at entry.



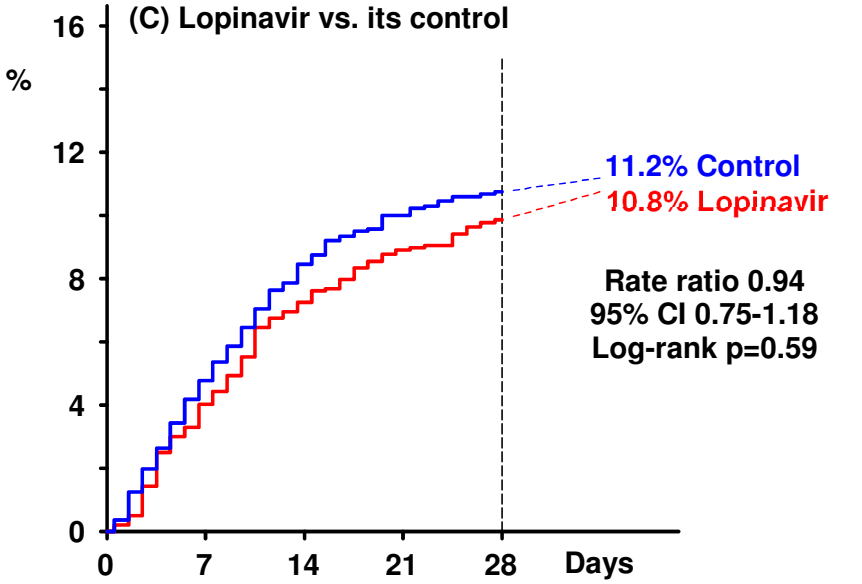
Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Remdesivir	4146	222	3878	171	3703	96	3606	51	3554	62
Control	4129	225	3861	189	3665	108	3557	65	3490	56



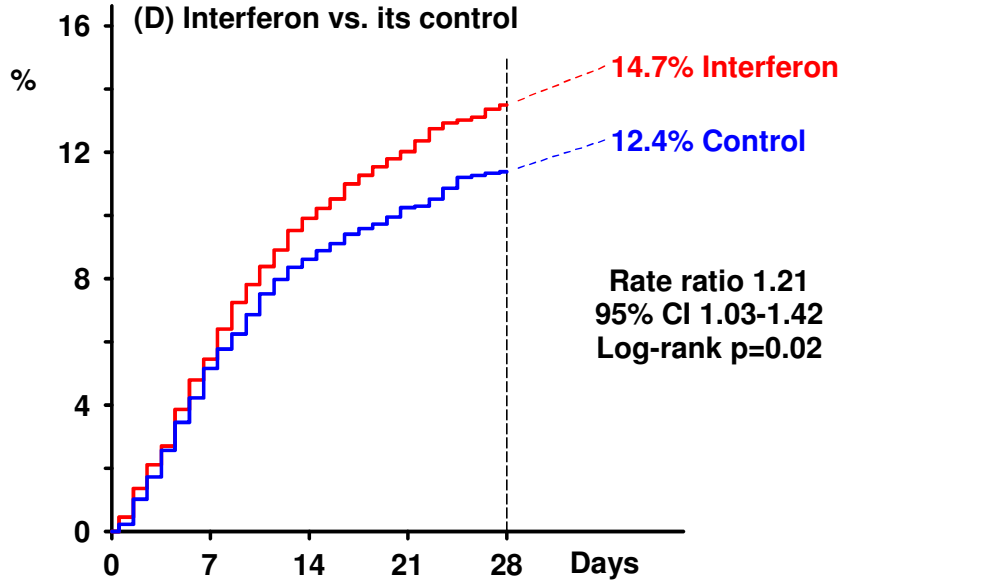
Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Hydroxychlor.	948	48	890	31	858	13	845	4	841	8
Control	900	44	848	28	820	8	812	4	808	5



Weekly denominators (all not yet dead/lost), and numbers dying in hospital

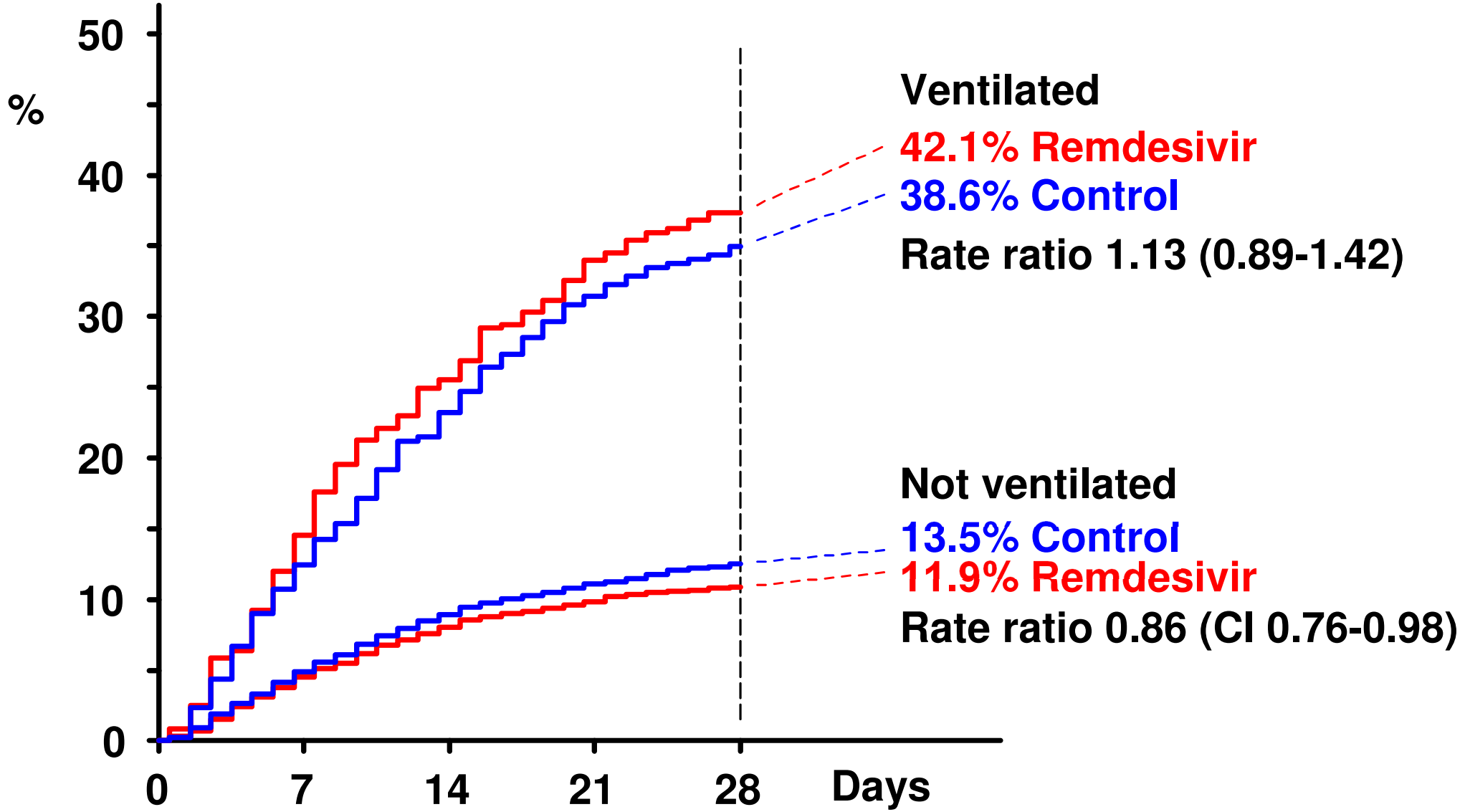
Lopinavir	1404	56	1334	45	1286	23	1263	13	1250	14
Control	1368	65	1292	50	1242	21	1220	10	1208	7



Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Interferon	2144	116	1999	94	1904	45	1859	31	1828	30
Control	2147	110	2015	73	1939	35	1904	24	1880	24

Figure S2A. Subdivision by ventilation at randomisation of the apparent effects of remdesivir on the probability of death in hospital from any cause



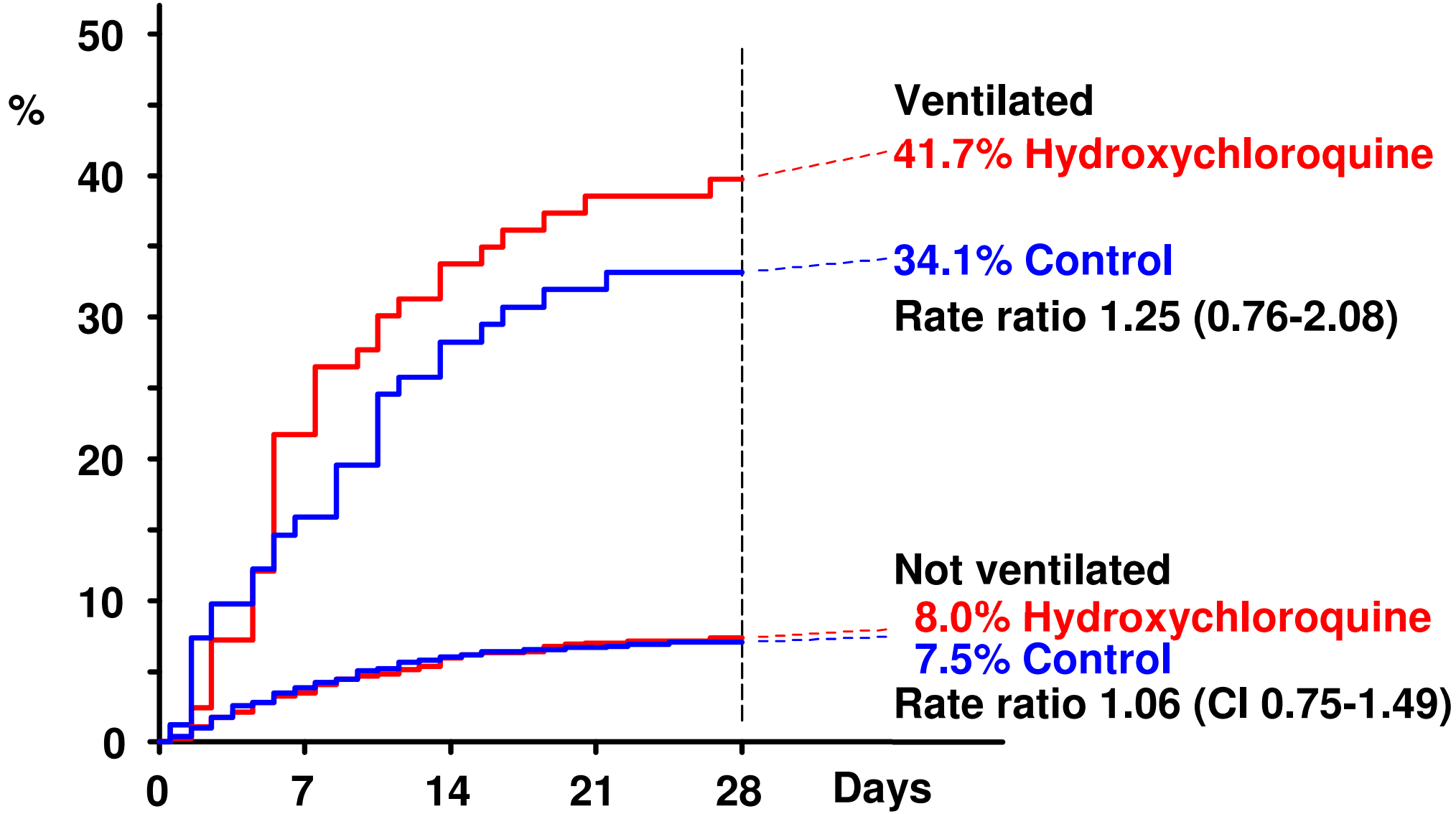
Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Remdesivir	359	52	305	39	264	30	234	12	222	18
Control	347	43	301	37	263	28	235	12	222	14
Remdesivir	3787	170	3573	132	3439	66	3372	39	3332	44
Control	3782	182	3560	152	3402	80	3322	53	3268	42

Ventilated

Not ventilated

Figure S2B. Subdivision by ventilation at randomisation of the apparent effects of hydroxychloroquine on the probability of death in hospital from any cause



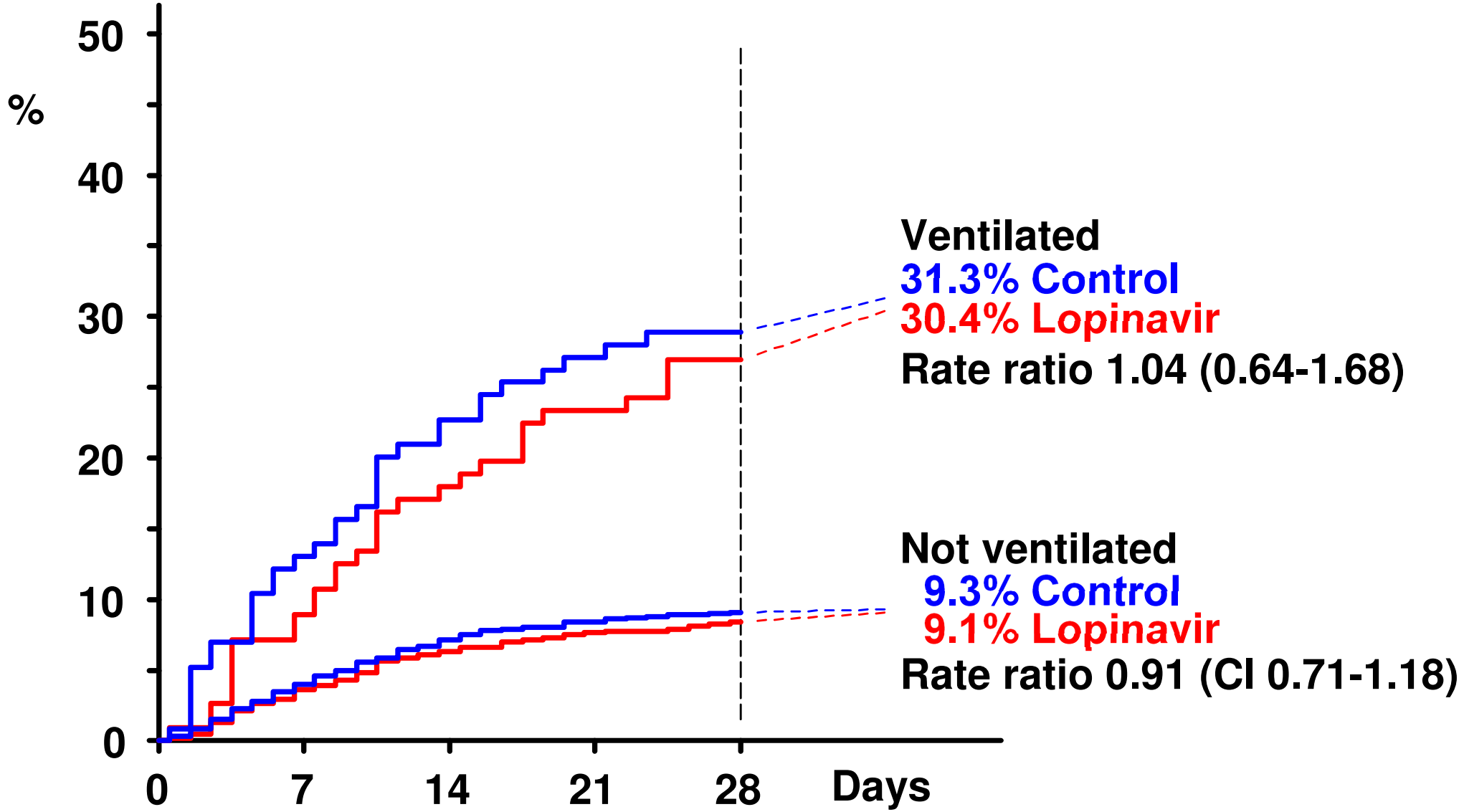
Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Hydroxychlor.	84	18	65	10	55	4	51	1	50	2
Control	82	13	68	10	58	3	55	1	54	1
Hydroxychlor.	864	30	825	21	803	9	794	3	791	6
Control	818	31	780	18	762	5	757	3	754	4

Ventilated

Not ventilated

Figure S2C. Subdivision by ventilation at randomisation of the apparent effects of lopinavir on the probability of death in hospital from any cause



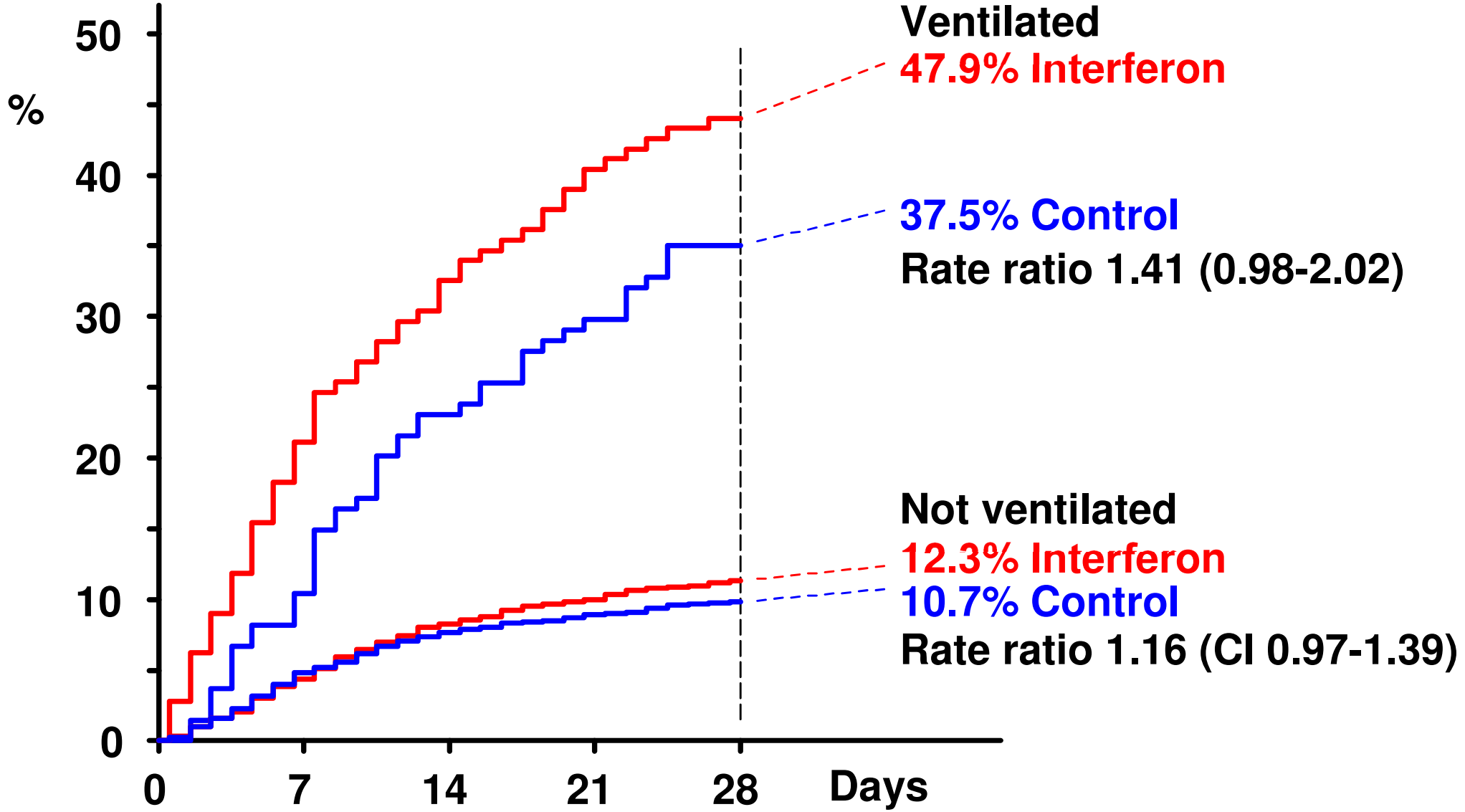
Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Lopinavir	112	10	101	10	91	6	85	4	81	4
Control	115	15	99	11	88	5	83	2	80	3
Lopinavir	1292	46	1233	35	1195	17	1178	9	1169	10
Control	1253	50	1193	39	1154	16	1137	8	1128	4

Ventilated

Not ventilated

Figure S2D. Subdivision by ventilation at randomisation of the apparent effects of interferon on the probability of death in hospital from any cause



Weekly denominators (all not yet dead/lost), and numbers dying in hospital

Interferon	144	30	111	16	94	11	83	5	78	7
Control	136	14	120	17	103	9	94	7	87	4
Interferon	2000	86	1888	78	1810	34	1776	26	1750	23
Control	2011	96	1895	56	1836	26	1810	17	1793	20

Ventilated

Not ventilated

Figure S3A-S3D. Death rate ratios, stratified by age and respiratory support at entry, for (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon, each vs its control

Analyses in subgroups of age are stratified by ventilation, and vice-versa, so each total is stratified for both factors.

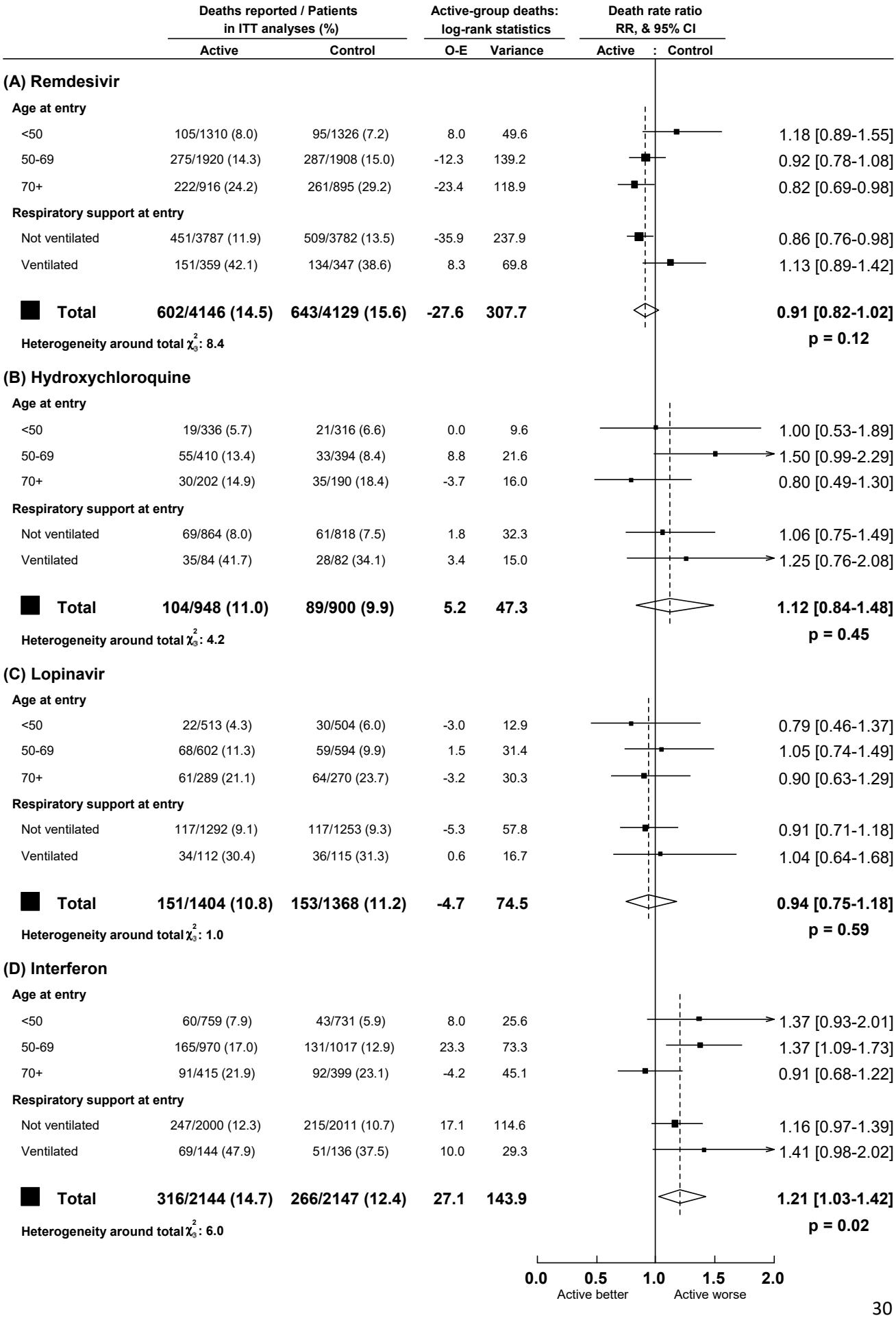
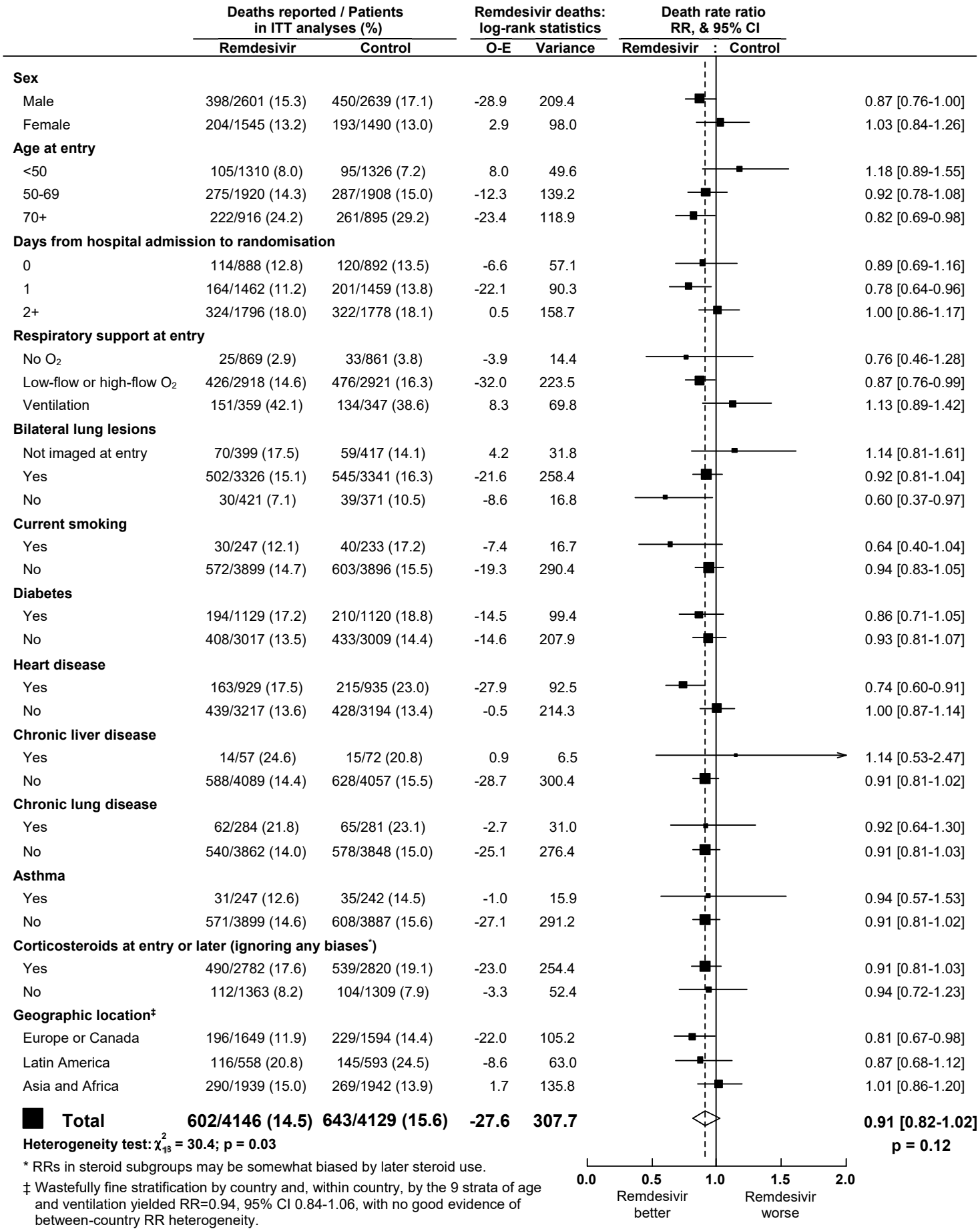


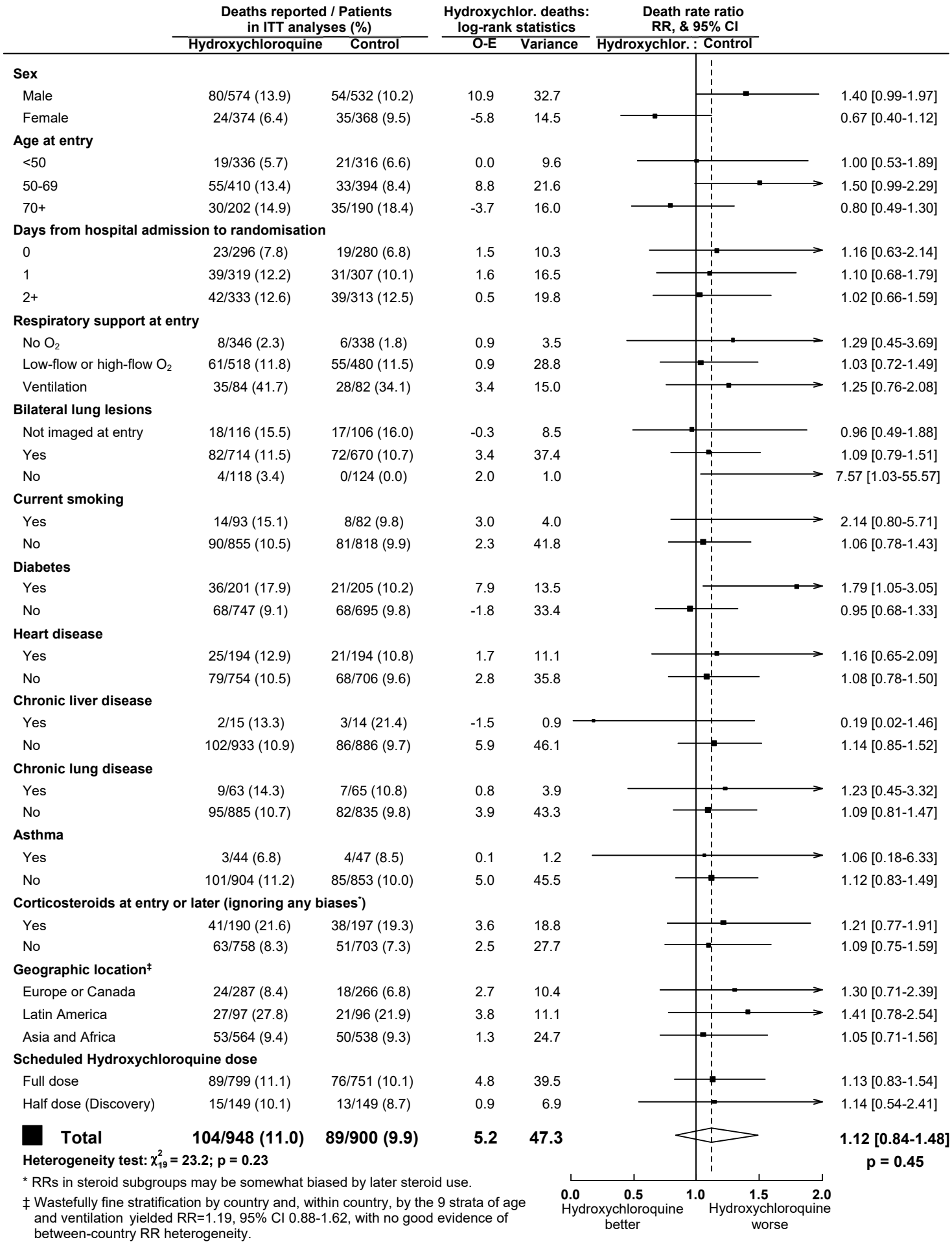
Figure S4A. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=0.94, 95% CI 0.84-1.06, with no good evidence of between-country RR heterogeneity.

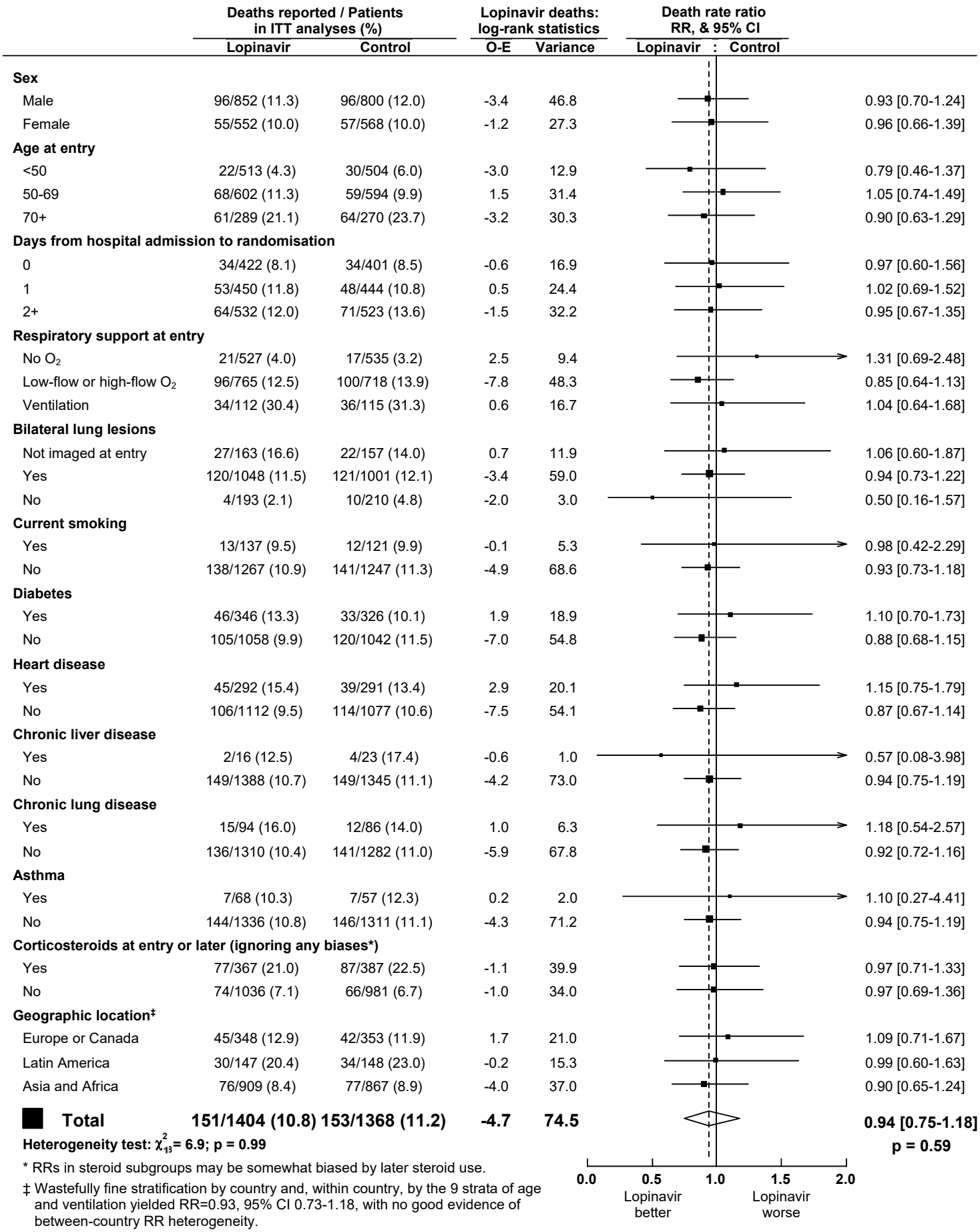
Figure S4B. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=1.19, 95% CI 0.88-1.62, with no good evidence of between-country RR heterogeneity.

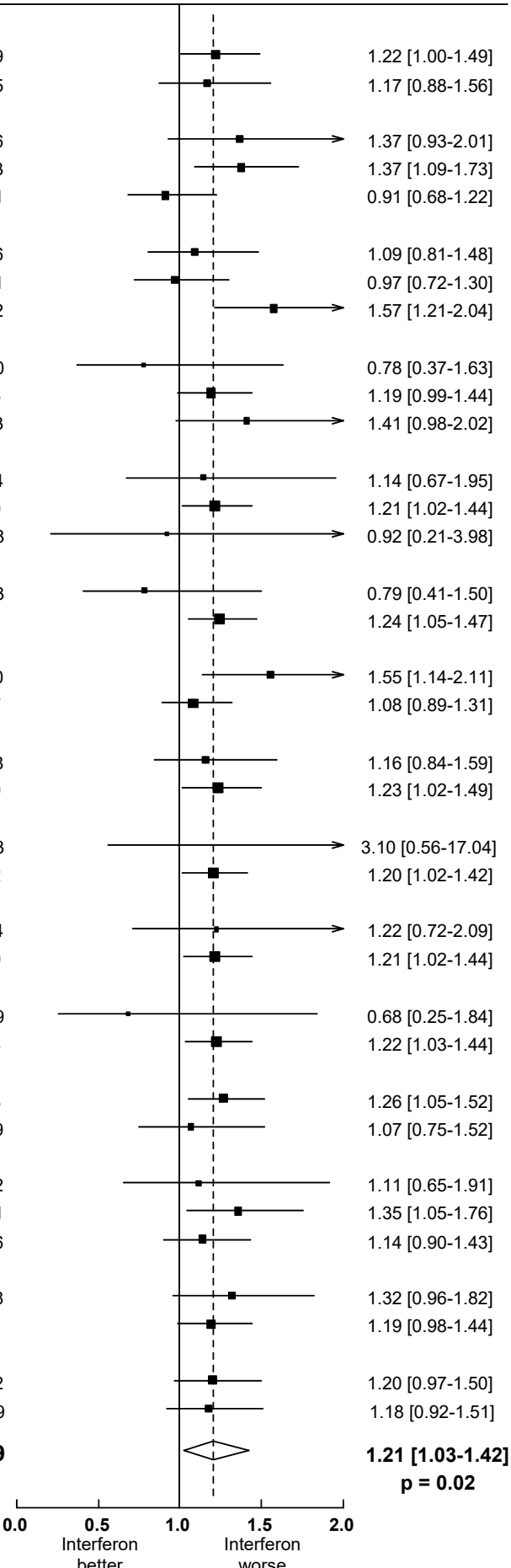
Figure S4C. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, lopinavir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=0.93, 95% CI 0.73-1.18, with no good evidence of between-country RR heterogeneity.

Figure S4D. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, interferon vs its control, by entry characteristics and by steroid use at any time*



	Deaths reported / Patients in ITT analyses (%)		Interferon deaths: log-rank statistics		Death rate ratio RR, & 95% CI
	Interferon	Control	O-E	Variance	Interferon : Control
Sex					
Male	215/1342 (16.0)	177/1331 (13.3)	19.4	96.9	1.22 [1.00-1.49]
Female	101/802 (12.6)	89/816 (10.9)	7.3	46.5	1.17 [0.88-1.56]
Age at entry					
<50	60/759 (7.9)	43/731 (5.9)	8.0	25.6	1.37 [0.93-2.01]
50-69	165/970 (17.0)	131/1017 (12.9)	23.3	73.3	1.37 [1.09-1.73]
70+	91/415 (21.9)	92/399 (23.1)	-4.2	45.1	0.91 [0.68-1.22]
Days from hospital admission to randomisation					
0	87/707 (12.3)	85/702 (12.1)	3.7	41.6	1.09 [0.81-1.48]
1	90/700 (12.9)	89/699 (12.7)	-1.4	44.1	0.97 [0.72-1.30]
2+	139/737 (18.9)	92/746 (12.3)	25.4	56.2	1.57 [1.21-2.04]
Respiratory support at entry					
No O_2	12/503 (2.4)	16/508 (3.1)	-1.8	7.0	0.78 [0.37-1.63]
Low-flow or high-flow O_2	235/1497 (15.7)	199/1503 (13.2)	18.9	107.6	1.19 [0.99-1.44]
Ventilation	69/144 (47.9)	51/136 (37.5)	10.0	29.3	1.41 [0.98-2.02]
Bilateral lung lesions					
Not imaged at entry	29/159 (18.2)	26/160 (16.2)	1.8	13.4	1.14 [0.67-1.95]
Yes	283/1857 (15.2)	235/1865 (12.6)	24.4	128.0	1.21 [1.02-1.44]
No	4/128 (3.1)	5/122 (4.1)	-0.1	1.8	0.92 [0.21-3.98]
Current smoking					
Yes	18/142 (12.7)	22/147 (15.0)	-2.2	9.3	0.79 [0.41-1.50]
No	298/2002 (14.9)	244/2000 (12.2)	29.0	134.1	1.24 [1.05-1.47]
Diabetes					
Yes	98/517 (19.0)	71/563 (12.6)	18.0	41.0	1.55 [1.14-2.11]
No	218/1627 (13.4)	195/1584 (12.3)	7.9	101.7	1.08 [0.89-1.31]
Heart disease					
Yes	82/457 (17.9)	75/487 (15.4)	5.5	37.8	1.16 [0.84-1.59]
No	234/1687 (13.9)	191/1660 (11.5)	22.0	105.0	1.23 [1.02-1.49]
Chronic liver disease					
Yes	6/14 (42.9)	5/24 (20.8)	1.5	1.3	3.10 [0.56-17.04]
No	310/2130 (14.6)	261/2123 (12.3)	25.7	141.2	1.20 [1.02-1.42]
Chronic lung disease					
Yes	30/120 (25.0)	27/110 (24.5)	2.7	13.4	1.22 [0.72-2.09]
No	286/2024 (14.1)	239/2037 (11.7)	25.1	129.9	1.21 [1.02-1.44]
Asthma					
Yes	6/79 (7.6)	12/105 (11.4)	-1.5	3.9	0.68 [0.25-1.84]
No	310/2065 (15.0)	254/2042 (12.4)	27.9	139.4	1.22 [1.03-1.44]
Corticosteroids at entry or later (ignoring any biases*)					
Yes	249/1232 (20.2)	207/1286 (16.1)	26.3	112.3	1.26 [1.05-1.52]
No	67/912 (7.3)	59/861 (6.9)	2.0	30.9	1.07 [0.75-1.52]
Geographic location‡					
Europe or Canada	29/268 (10.8)	25/256 (9.8)	1.4	13.2	1.11 [0.65-1.91]
Latin America	132/493 (26.8)	101/495 (20.4)	17.3	57.1	1.35 [1.05-1.76]
Asia and Africa	155/1383 (11.2)	140/1396 (10.0)	9.4	72.6	1.14 [0.90-1.43]
Control Type					
Lopinavir	86/648 (13.3)	69/677 (10.2)	10.5	37.8	1.32 [0.96-1.82]
Standard care	230/1496 (15.4)	197/1470 (13.4)	18.4	105.1	1.19 [0.98-1.44]
Scheduled Interferon regimen					
Subcutaneous	181/1679 (10.8)	149/1683 (8.9)	15.1	81.2	1.20 [0.97-1.50]
Intravenous†	135/465 (29.0)	117/464 (25.2)	10.1	61.9	1.18 [0.92-1.51]
Total	**316/2144 (14.7)**	**266/2147 (12.4)**	**27.1**	**143.9**	**1.21 [1.03-1.42]**

Heterogeneity test: χ^2_{20} = 24.2; p = 0.23 **p = 0.02**

* RRs in steroid subgroups may be somewhat biased by later steroid use.

† Possible only if high-flow oxygen or ventilation was being given (and the country had been supplied with intravenous interferon)

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=1.25, 95% CI 1.06-1.49, with no good evidence of between-country RR heterogeneity.

Figure S5A-S5D. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, for (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon, each vs its control

Analyses in subgroups of age are stratified by oxygen use, and vice-versa, so each total is stratified for both factors.

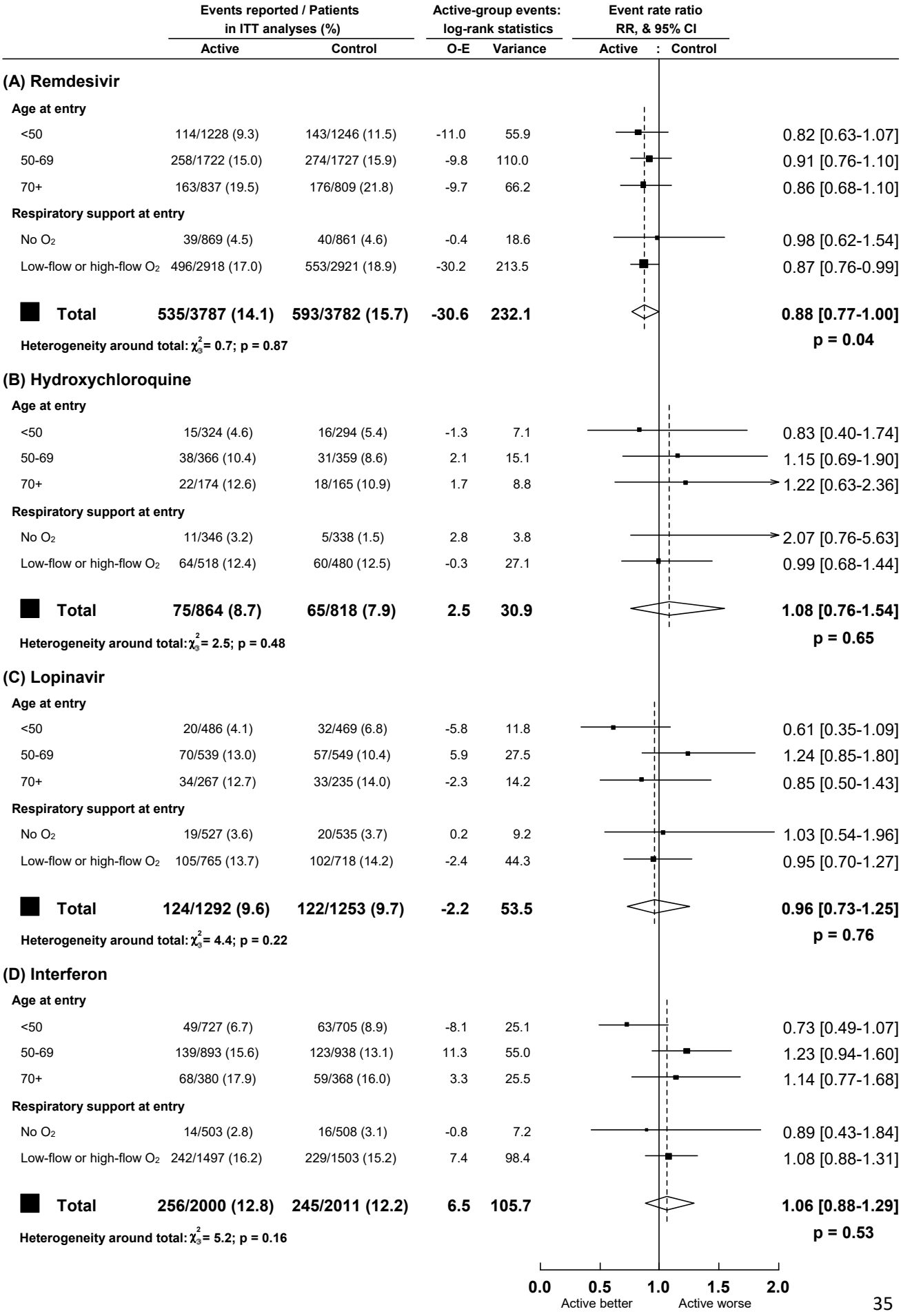
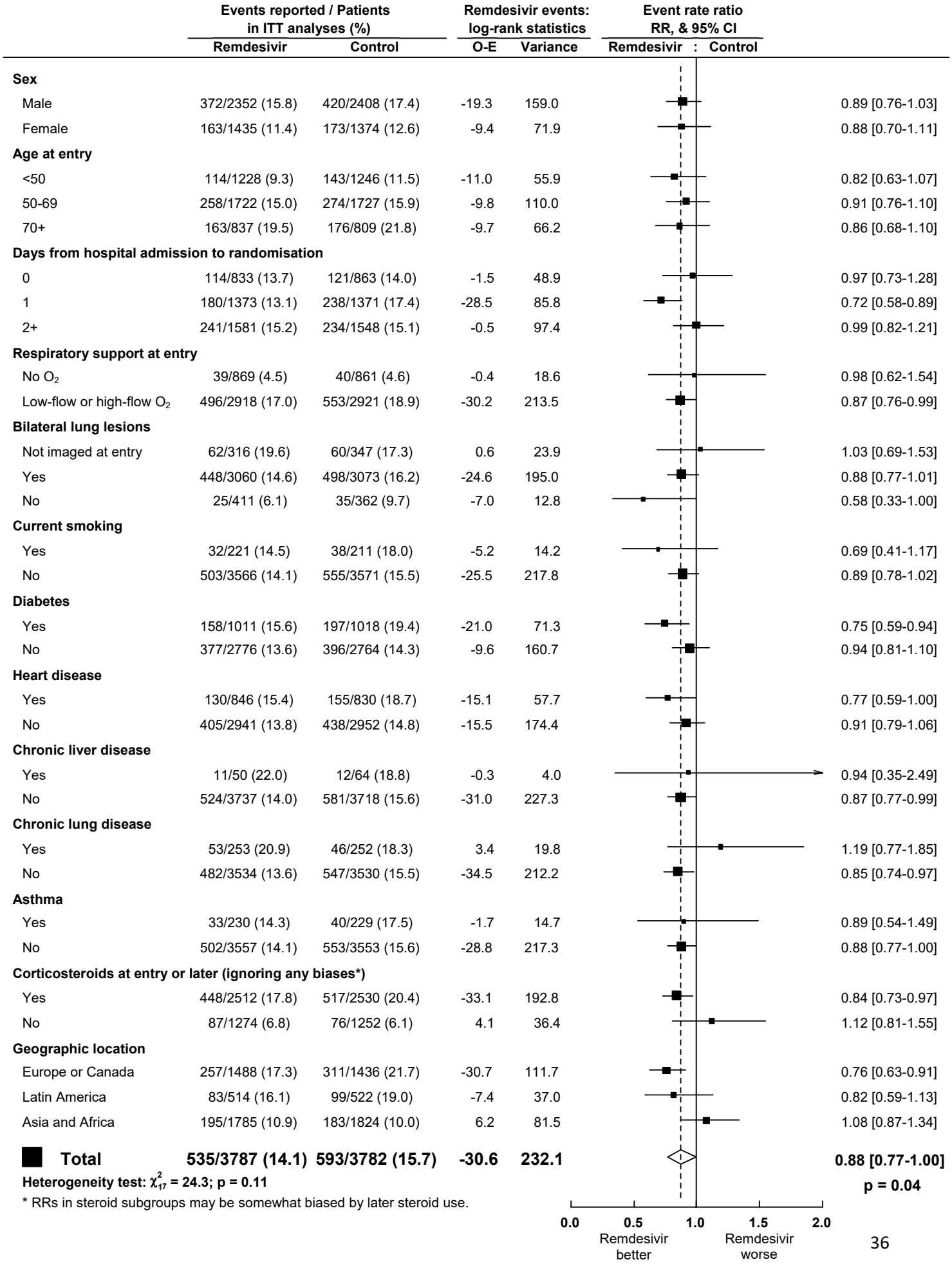


Figure S6A. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

Figure S6B. Rate ratios for initiation of ventilation in those not already ventilated at entry, hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*

	Events reported / Patients in ITT analyses (%)		Hydroxychlor. events: log-rank statistics		Event rate ratio RR, & 95% CI
	Hydroxychloroquine	Control	O-E	Variance	Hydroxychlor. : Control
Sex					
Male	49/515 (9.5)	38/473 (8.0)	3.3	19.0	1.19 [0.76-1.86]
Female	26/349 (7.4)	27/345 (7.8)	-1.0	11.9	0.92 [0.52-1.62]
Age at entry					
<50	15/324 (4.6)	16/294 (5.4)	-1.3	7.1	0.83 [0.40-1.74]
50-69	38/366 (10.4)	31/359 (8.6)	2.1	15.1	1.15 [0.69-1.90]
70+	22/174 (12.6)	18/165 (10.9)	1.7	8.8	1.22 [0.63-2.36]
Days from hospital admission to randomisation					
0	18/285 (6.3)	10/270 (3.7)	3.6	6.5	1.75 [0.81-3.78]
1	29/284 (10.2)	33/276 (12.0)	-1.7	13.2	0.88 [0.51-1.51]
2+	28/295 (9.5)	22/272 (8.1)	2.0	10.7	1.21 [0.66-2.20]
Respiratory support at entry					
No O_2	11/346 (3.2)	5/338 (1.5)	2.8	3.8	2.07 [0.76-5.63]
Low-flow or high-flow O_2	64/518 (12.4)	60/480 (12.5)	-0.3	27.1	0.99 [0.68-1.44]
Bilateral lung lesions					
Not imaged at entry	21/87 (24.1)	15/76 (19.7)	1.4	6.7	1.23 [0.57-2.62]
Yes	52/662 (7.9)	48/622 (7.7)	0.4	22.6	1.02 [0.67-1.54]
No	2/115 (1.7)	2/120 (1.7)	0.0	0.9	0.98 [0.13-7.57]
Current smoking					
Yes	4/83 (4.8)	5/72 (6.9)	-0.1	1.8	0.94 [0.22-3.97]
No	71/781 (9.1)	60/746 (8.0)	3.4	28.9	1.12 [0.78-1.62]
Diabetes					
Yes	14/174 (8.0)	16/180 (8.9)	-1.3	6.7	0.82 [0.39-1.76]
No	61/690 (8.8)	49/638 (7.7)	4.5	24.1	1.20 [0.81-1.79]
Heart disease					
Yes	9/170 (5.3)	16/167 (9.6)	-3.9	5.7	0.50 [0.22-1.13]
No	66/694 (9.5)	49/651 (7.5)	6.5	25.1	1.30 [0.88-1.92]
Chronic liver disease					
Yes	0/12 (0.0)	1/13 (7.7)	-0.5	0.2	
No	75/852 (8.8)	64/805 (8.0)	2.9	30.7	1.10 [0.77-1.57]
Chronic lung disease					
Yes	4/54 (7.4)	4/56 (7.1)	0.1	1.8	1.05 [0.24-4.54]
No	71/810 (8.8)	61/762 (8.0)	2.3	29.1	1.08 [0.75-1.56]
Asthma					
Yes	5/44 (11.4)	2/41 (4.9)	0.9	1.5	1.84 [0.37-9.17]
No	70/820 (8.5)	63/777 (8.1)	1.4	29.4	1.05 [0.73-1.51]
Corticosteroids at entry or later (ignoring any biases*)					
Yes	20/155 (12.9)	33/162 (20.4)	-5.7	10.8	0.59 [0.32-1.07]
No	55/709 (7.8)	32/656 (4.9)	9.0	19.7	1.58 [1.01-2.46]
Geographic location					
Europe or Canada	32/245 (13.1)	31/226 (13.7)	-0.4	13.1	0.97 [0.56-1.66]
Latin America	14/88 (15.9)	10/85 (11.8)	1.1	5.0	1.25 [0.52-3.00]
Asia and Africa	29/531 (5.5)	24/507 (4.7)	1.2	12.2	1.10 [0.63-1.93]
Scheduled Hydroxychloroquine dose					
Full dose	55/753 (7.3)	43/708 (6.1)	4.0	22.2	1.20 [0.79-1.82]
Half dose (Discovery)	20/111 (18.0)	22/110 (20.0)	-1.4	8.5	0.85 [0.43-1.66]
Total	**75/864 (8.7)**	**65/818 (7.9)**	**2.5**	**30.9**	**1.08 [0.76-1.54]**

Heterogeneity test: χ^2_{15} = 19.4; p = 0.37 **p = 0.65**

* RRs in steroid subgroups may be somewhat biased by later steroid use.

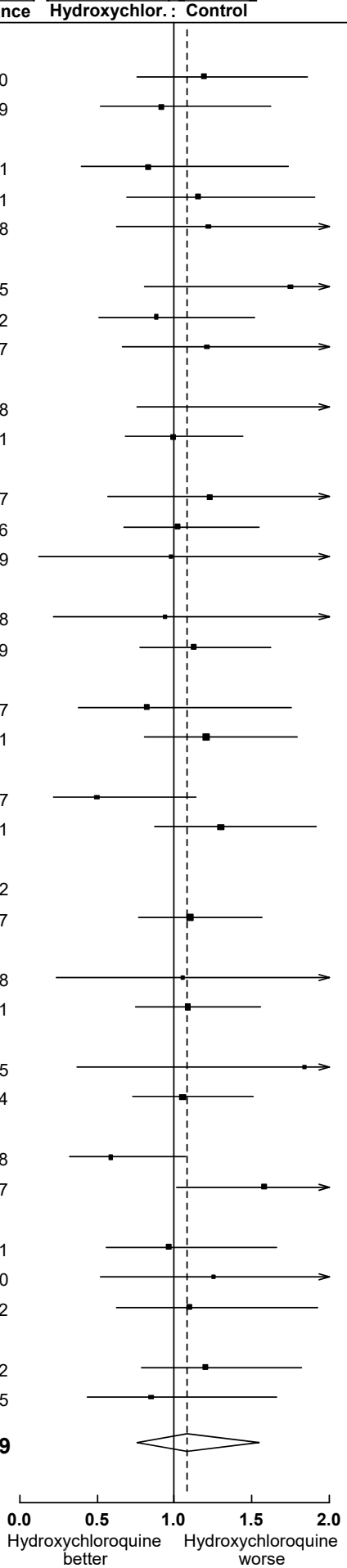
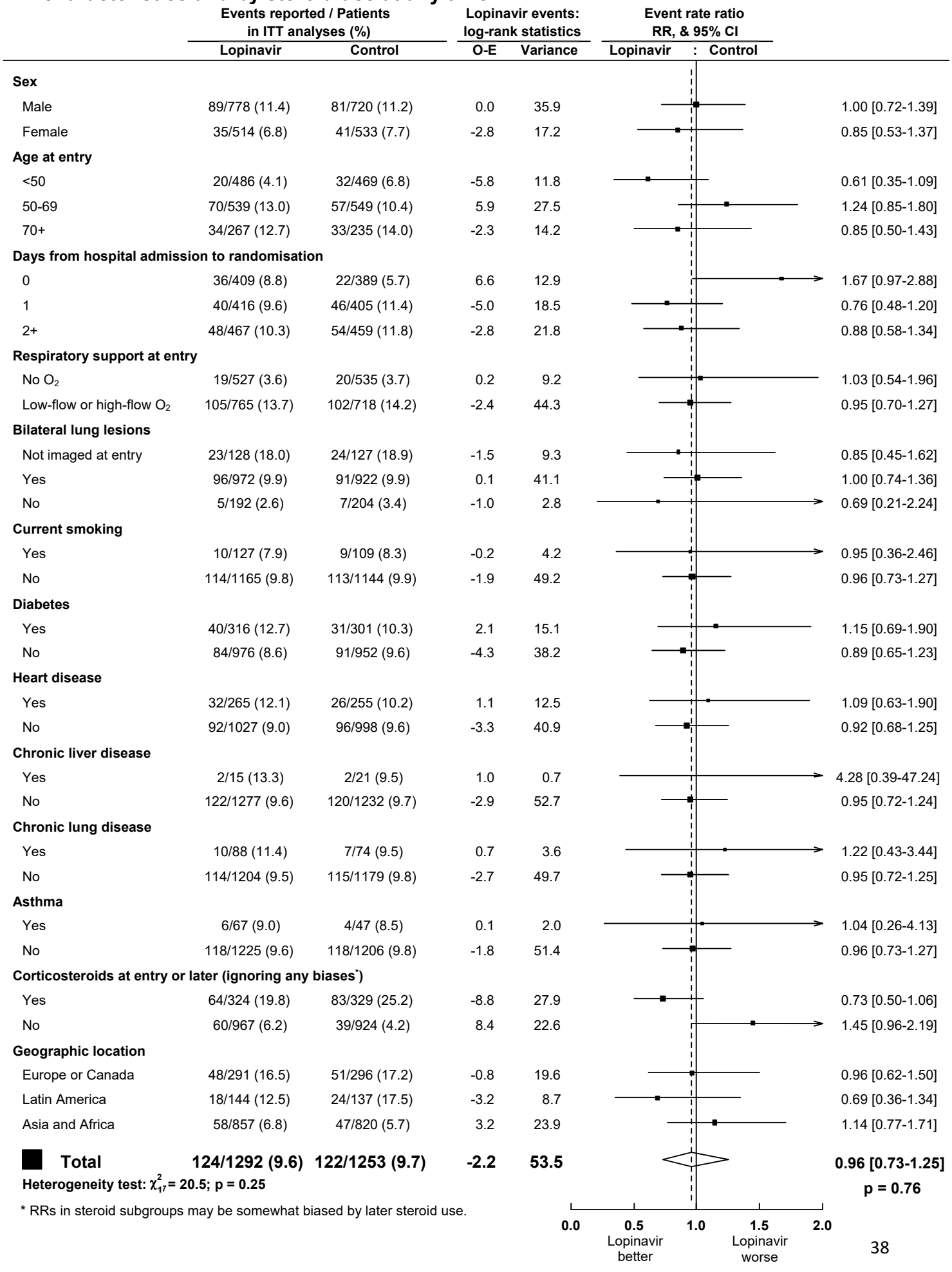
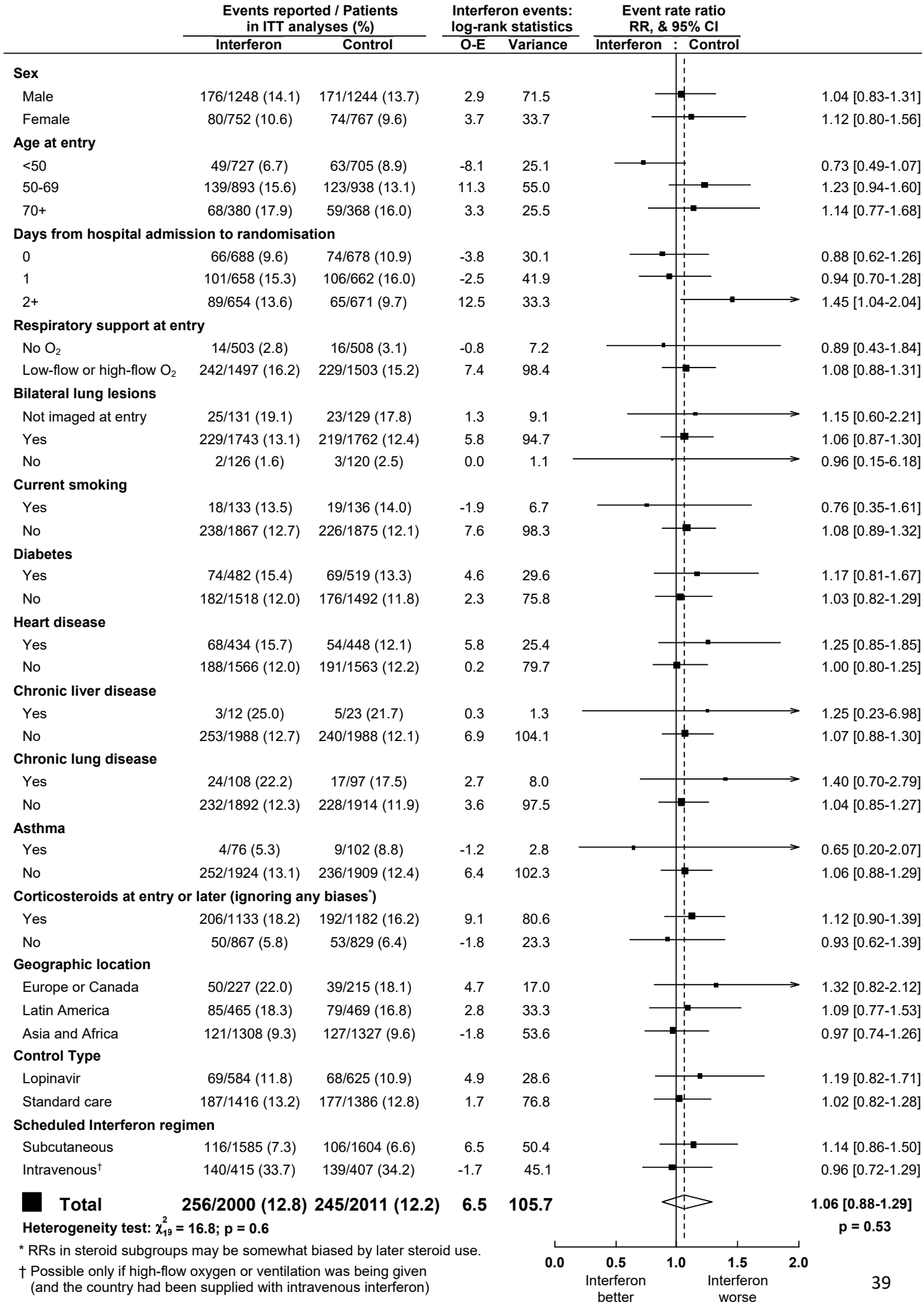


Figure S6C. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, lopinavir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

Figure S6D. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, interferon vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

† Possible only if high-flow oxygen or ventilation was being given (and the country had been supplied with intravenous interferon)

Figure S7A-D. RRs for the composite of death in hospital or initiation of ventilation: effects of (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon, each vs its control

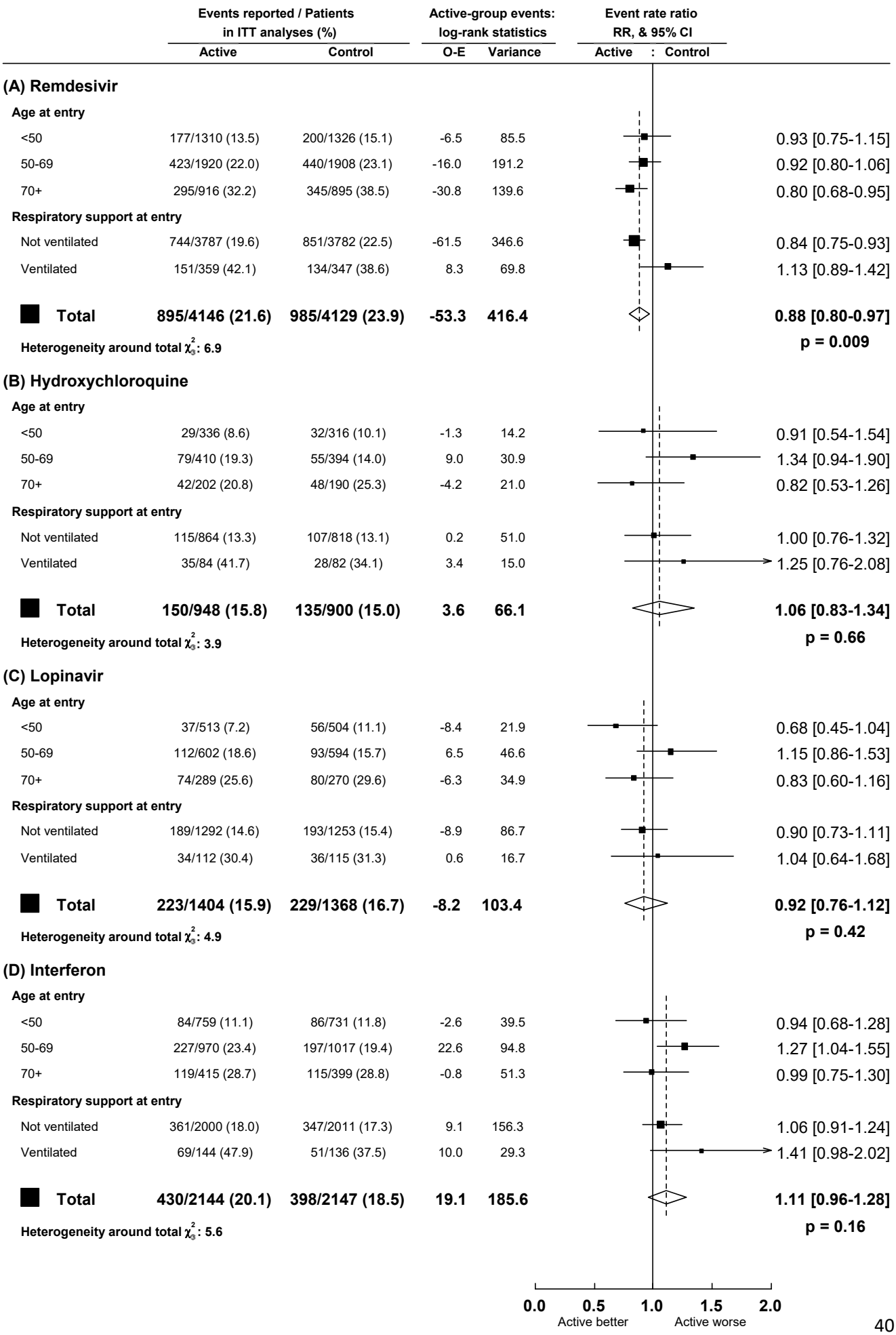
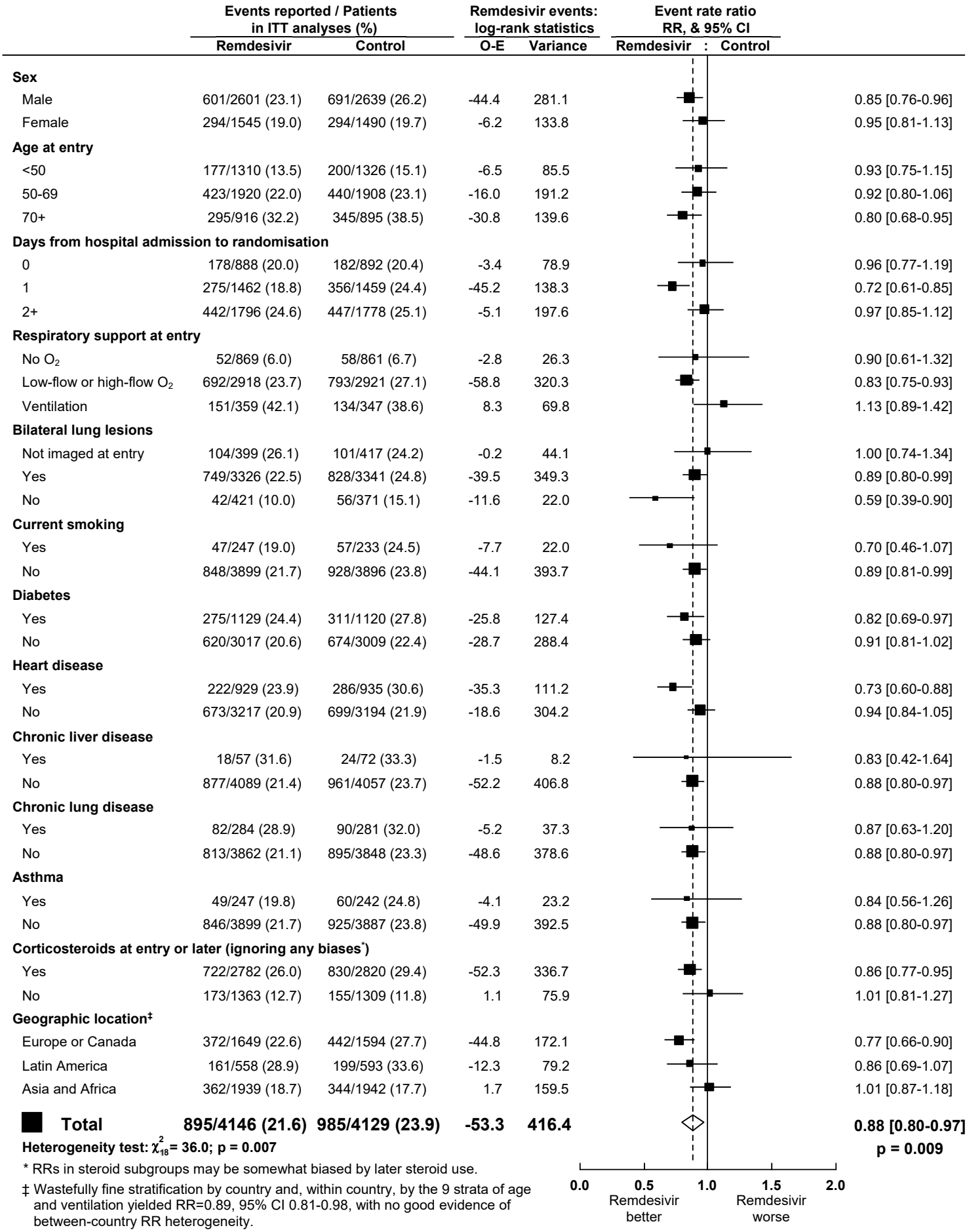


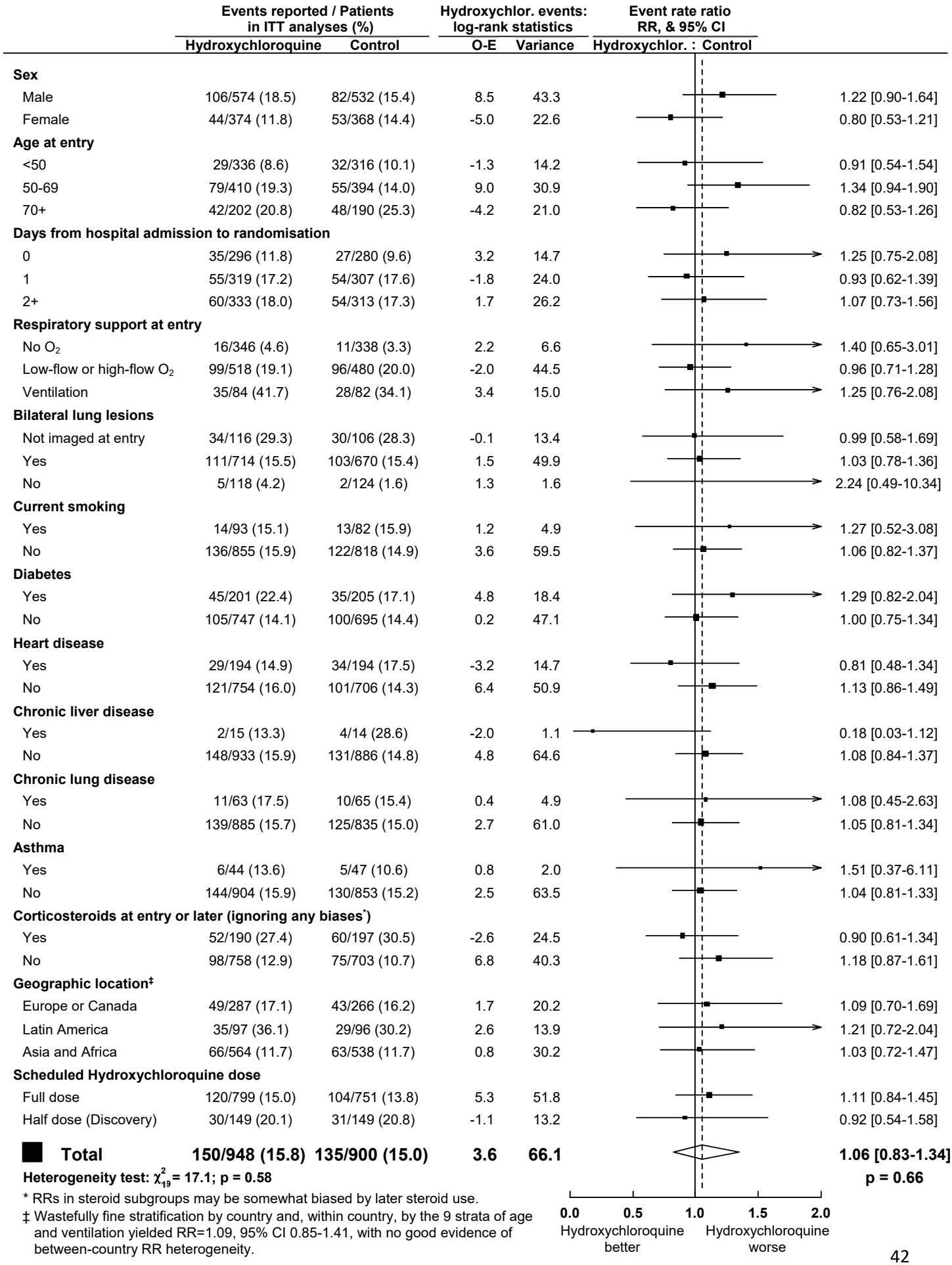
Figure S8A. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: remdesivir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=0.89, 95% CI 0.81-0.98, with no good evidence of between-country RR heterogeneity.

Figure S8B. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*

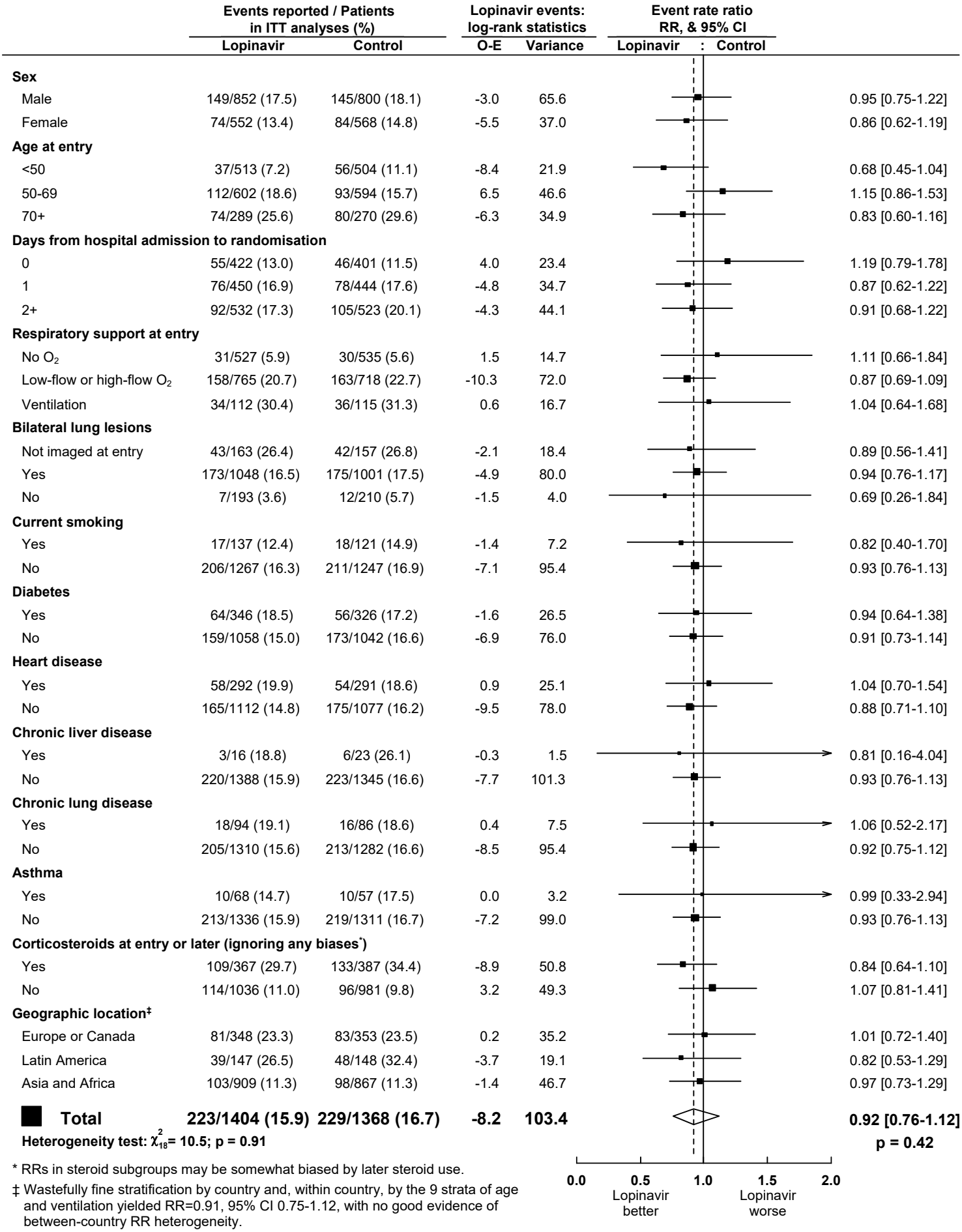


Heterogeneity test: χ^2_{19} = 17.1; p = 0.58 **p = 0.66**

* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=1.09, 95% CI 0.85-1.41, with no good evidence of between-country RR heterogeneity.

Figure S8C. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: lopinavir vs its control, by entry characteristics and by steroid use at any time*

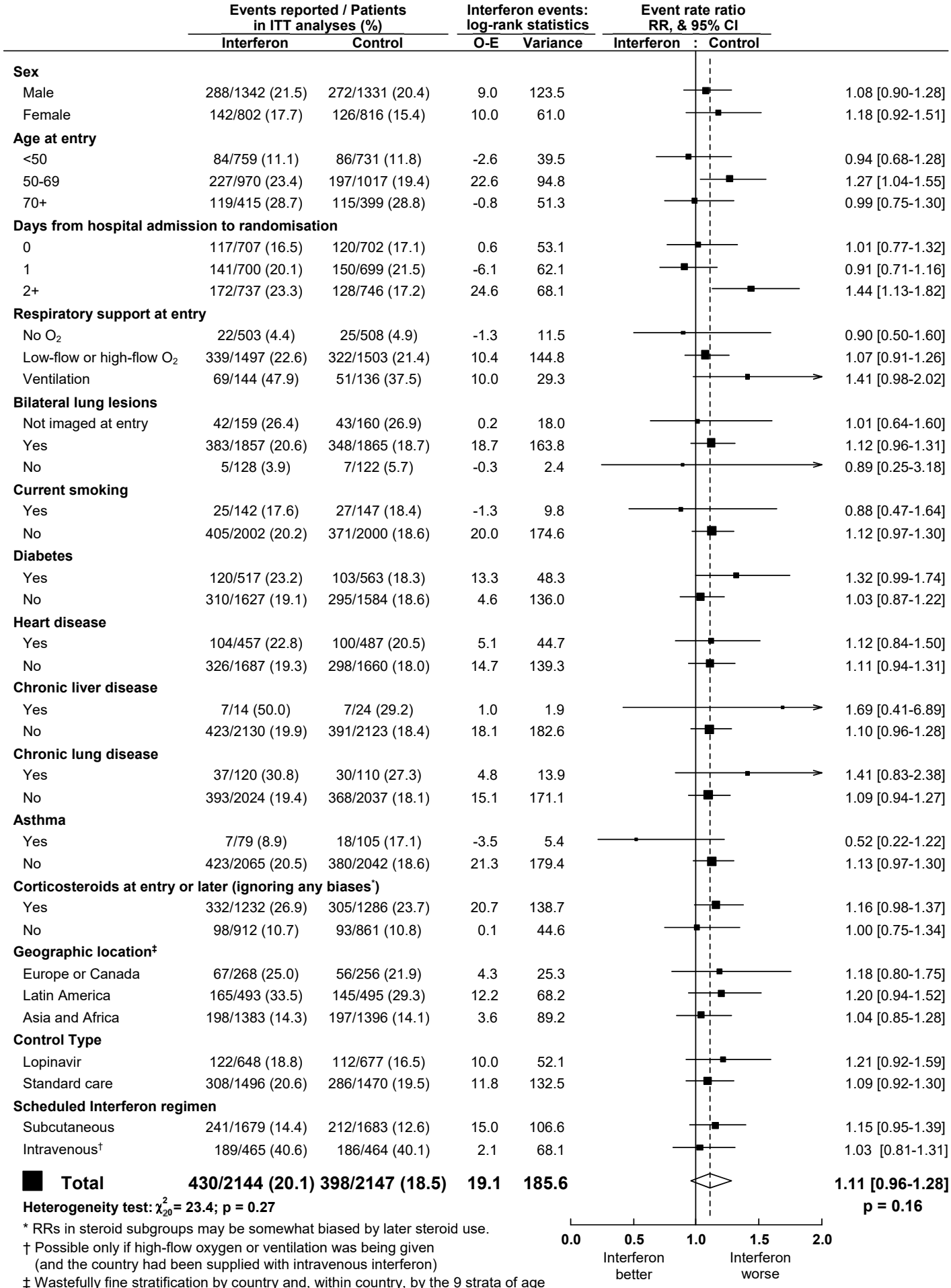


Heterogeneity test: χ^2_{18} **= 10.5; p = 0.91**

* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=0.91, 95% CI 0.75-1.12, with no good evidence of between-country RR heterogeneity.

Figure S8D. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: interferon vs its control, by entry characteristics and by steroid use at any time*

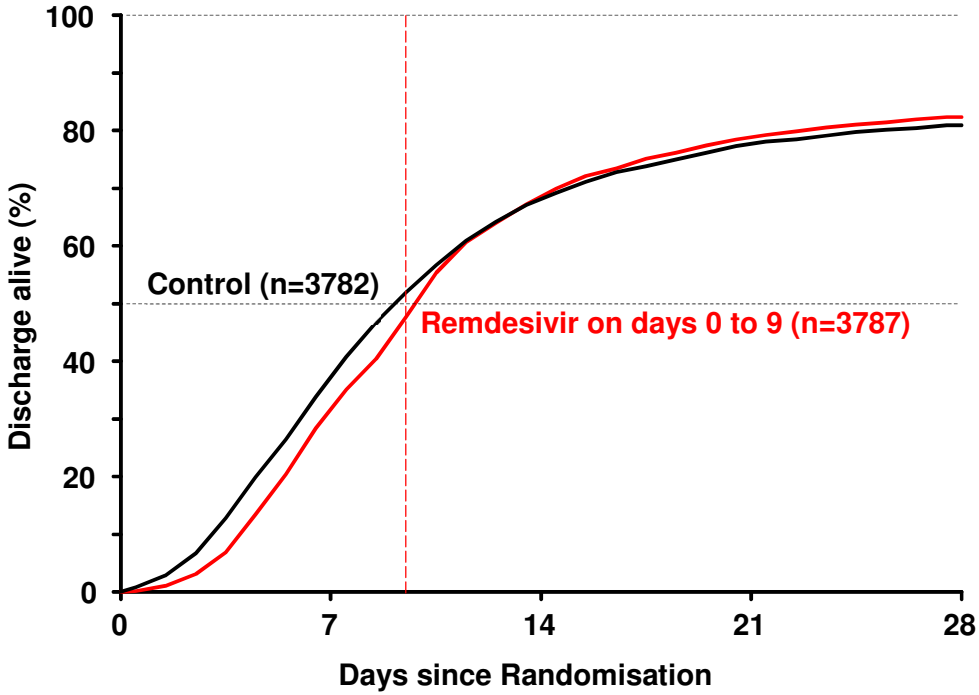


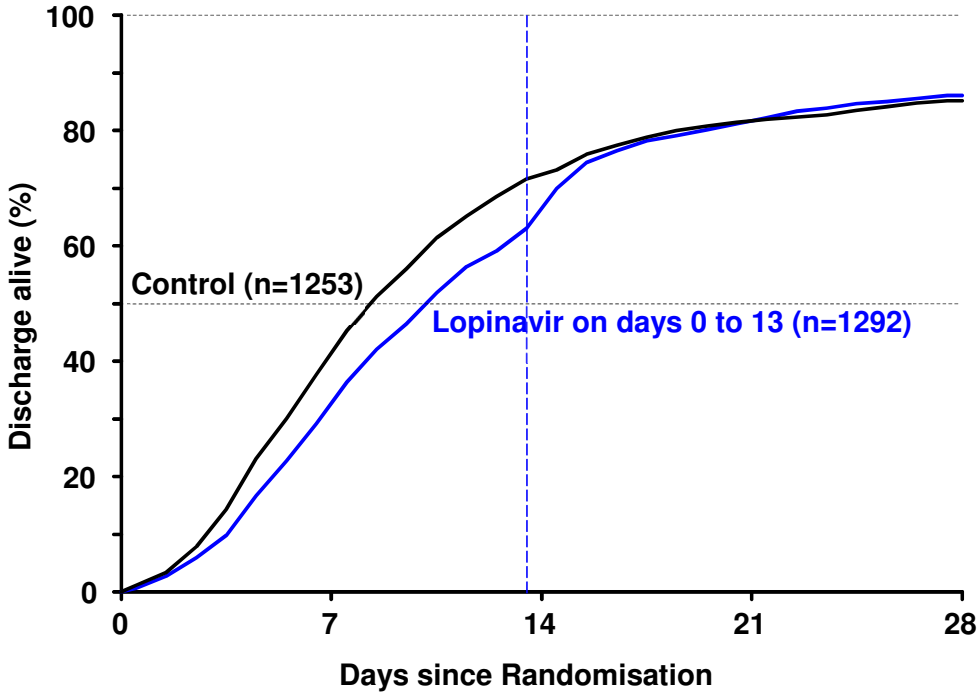
* RRs in steroid subgroups may be somewhat biased by later steroid use.

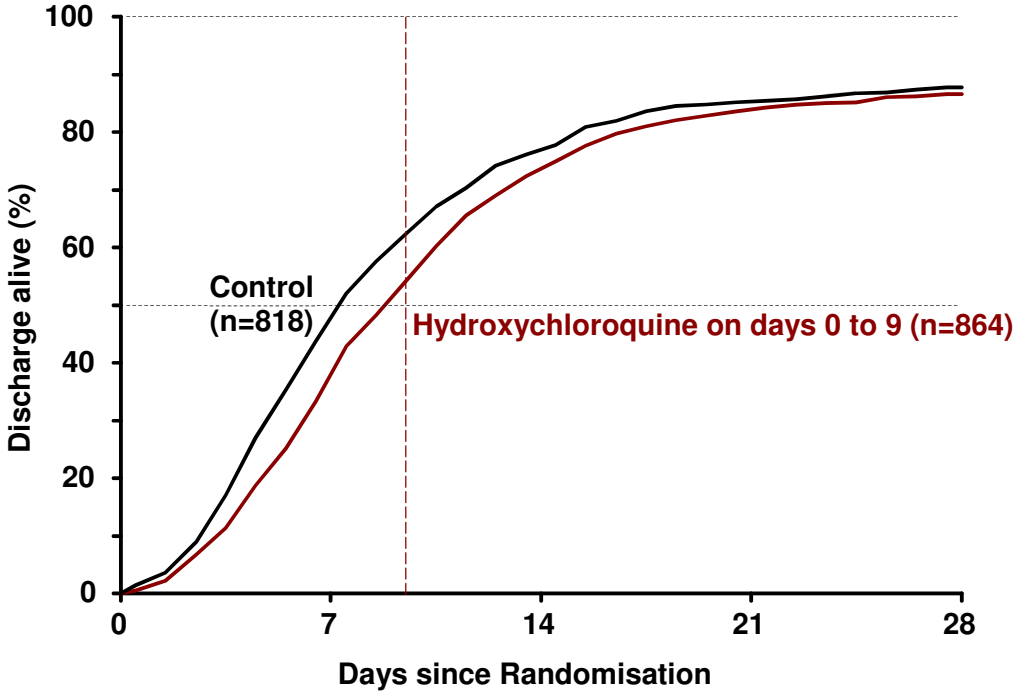
† Possible only if high-flow oxygen or ventilation was being given (and the country had been supplied with intravenous interferon)

‡ Wastefully fine stratification by country and, within country, by the 9 strata of age and ventilation yielded RR=1.13, 95% CI 0.97-1.31, with no good evidence of between-country RR heterogeneity.

Figure S9A-D. Remdesivir, Hydroxychloroquine, Lopinavir & Interferon, each vs its own control - effects on time to discharge alive in patients NOT being ventilated (no O_2, or low-flow / high-flow O_2) at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







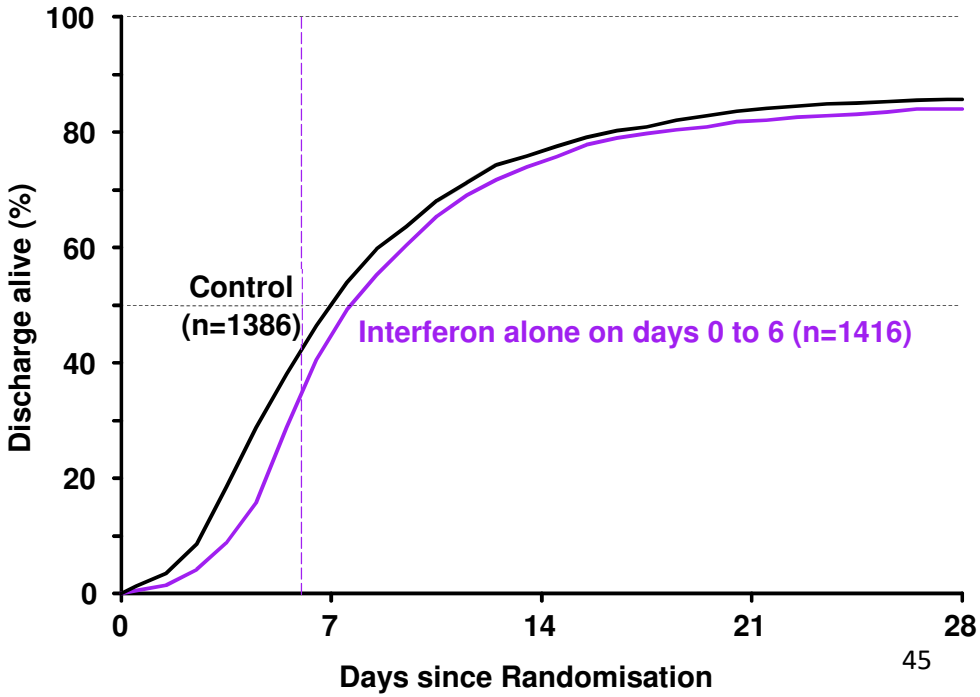
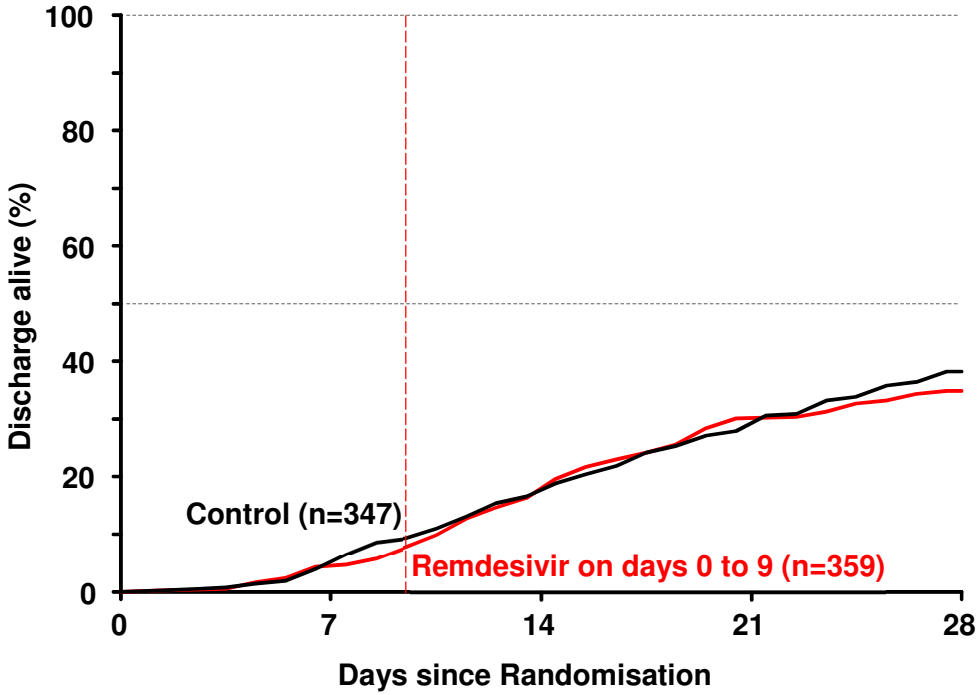
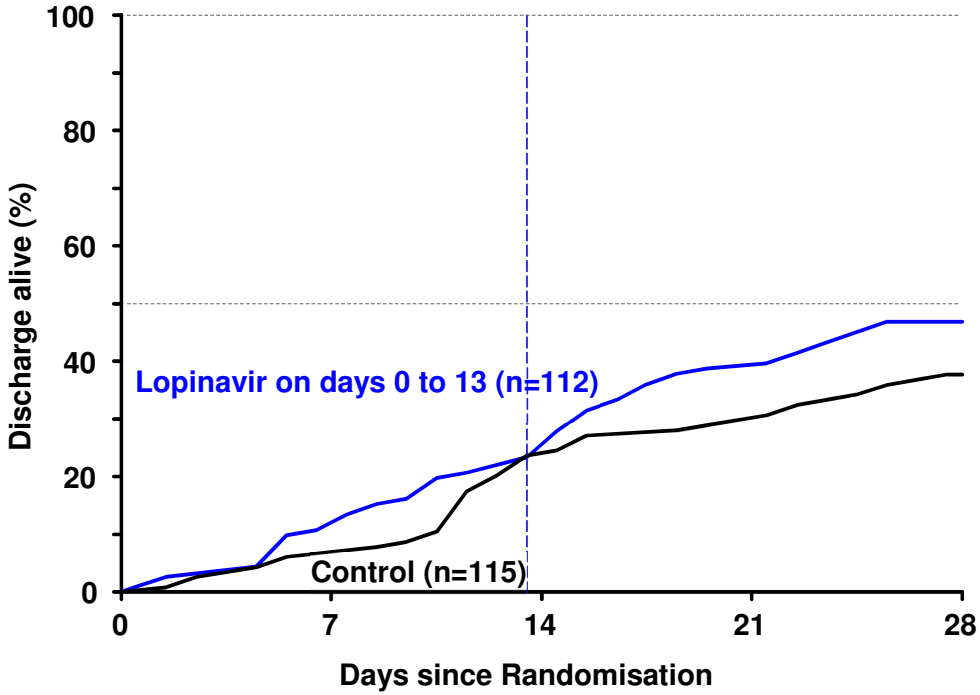
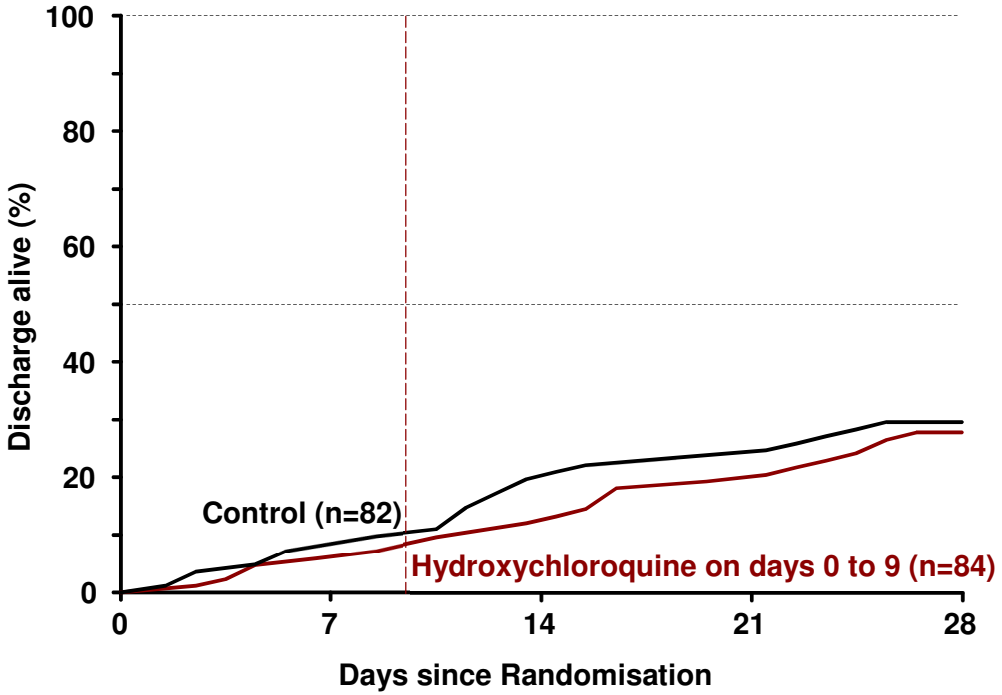


Figure S10A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own control - effects on time to discharge alive in patients already being ventilated at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







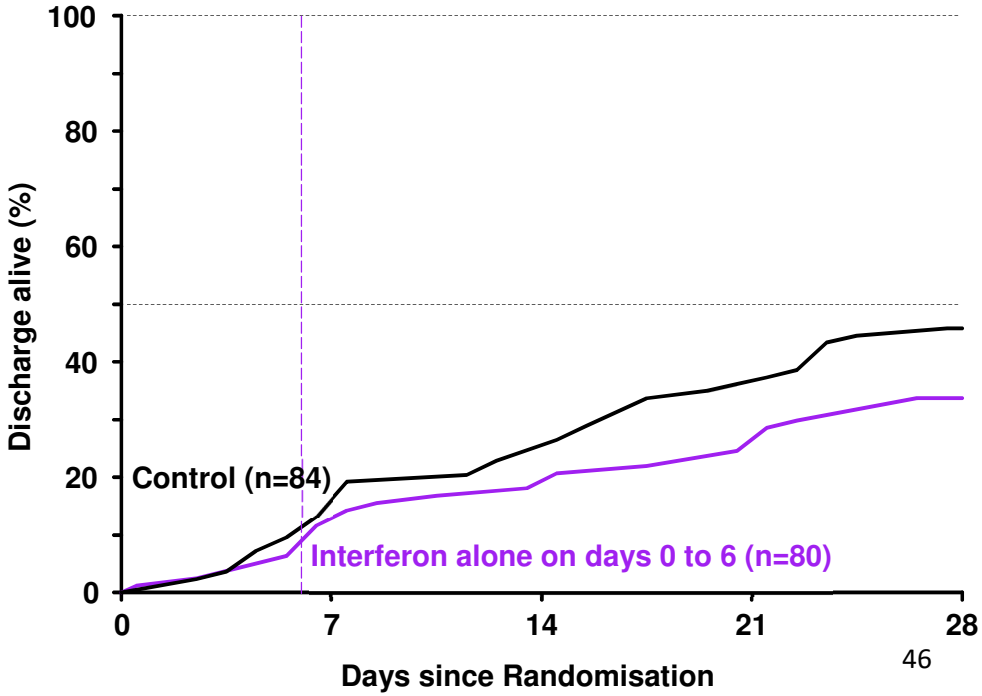
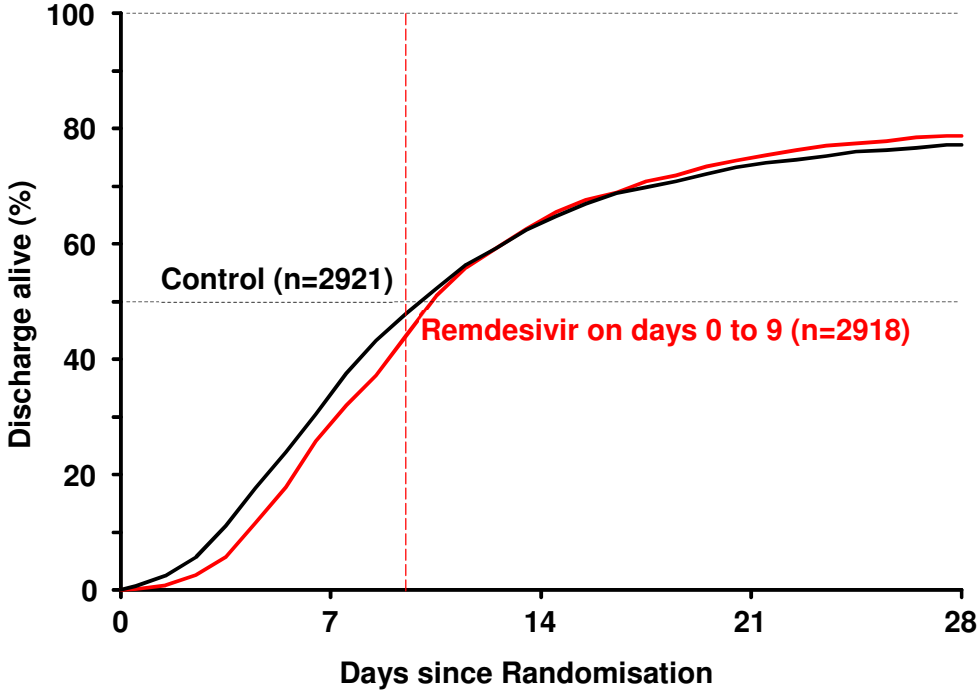
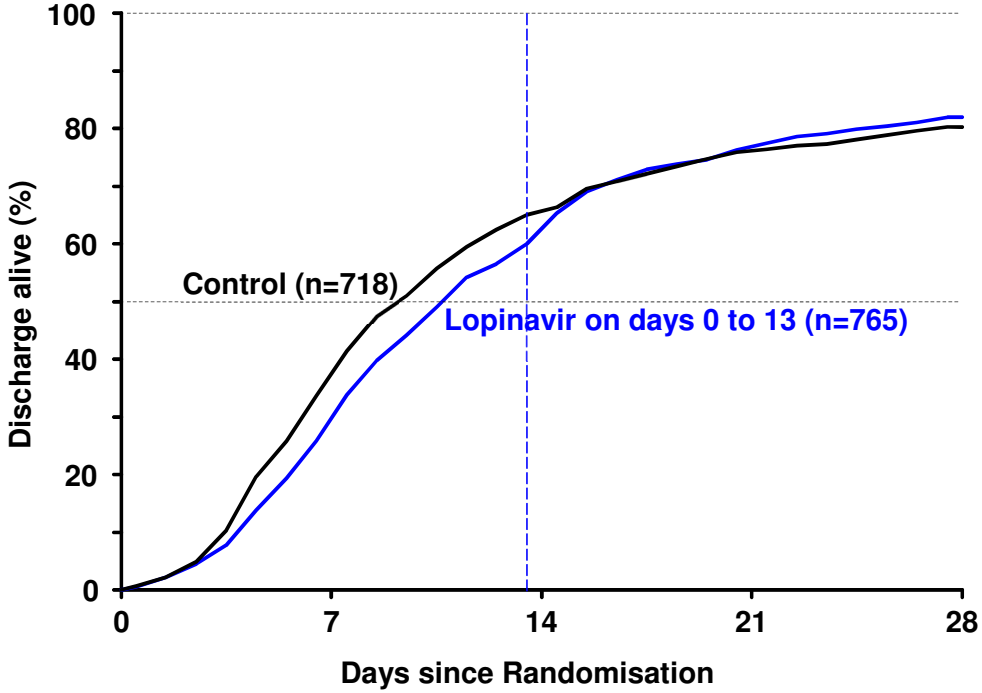
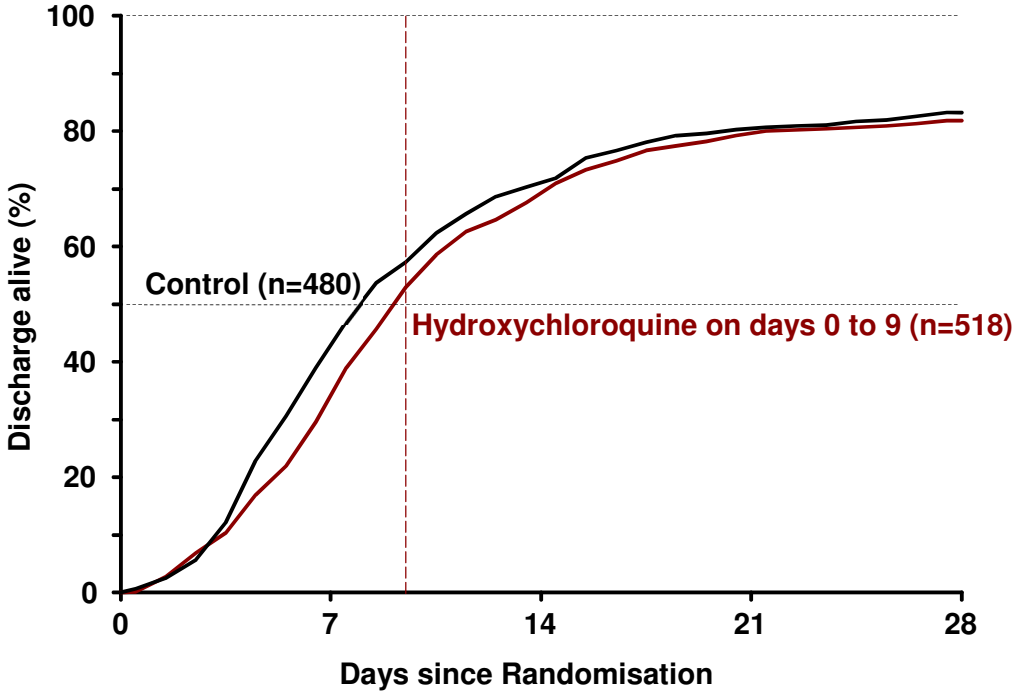


Figure S11A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients being given low-flow O_2 / high-flow O_2 at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







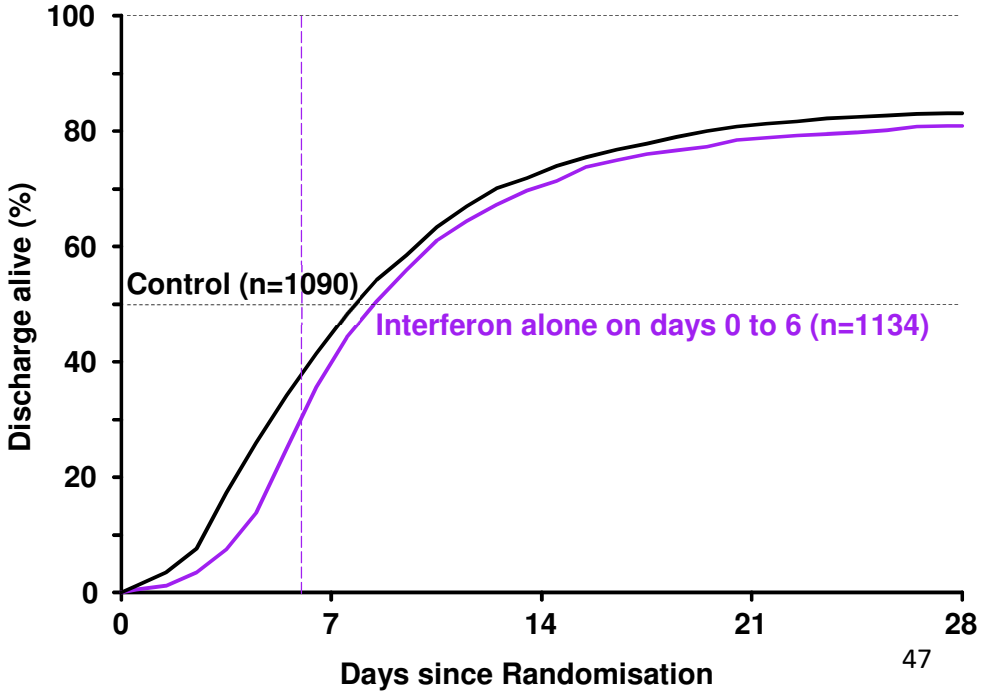
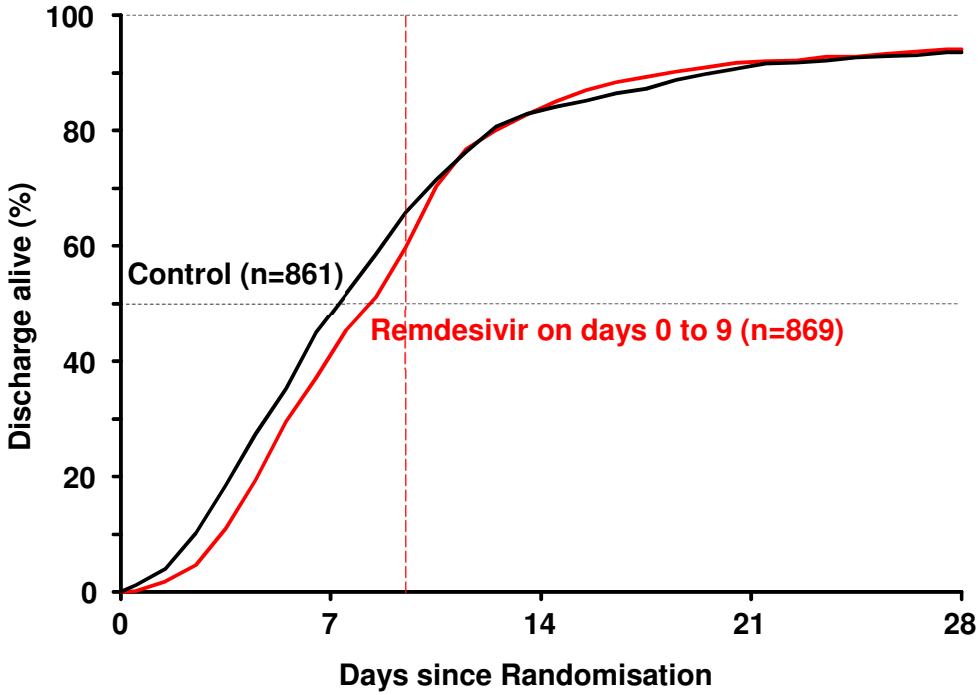
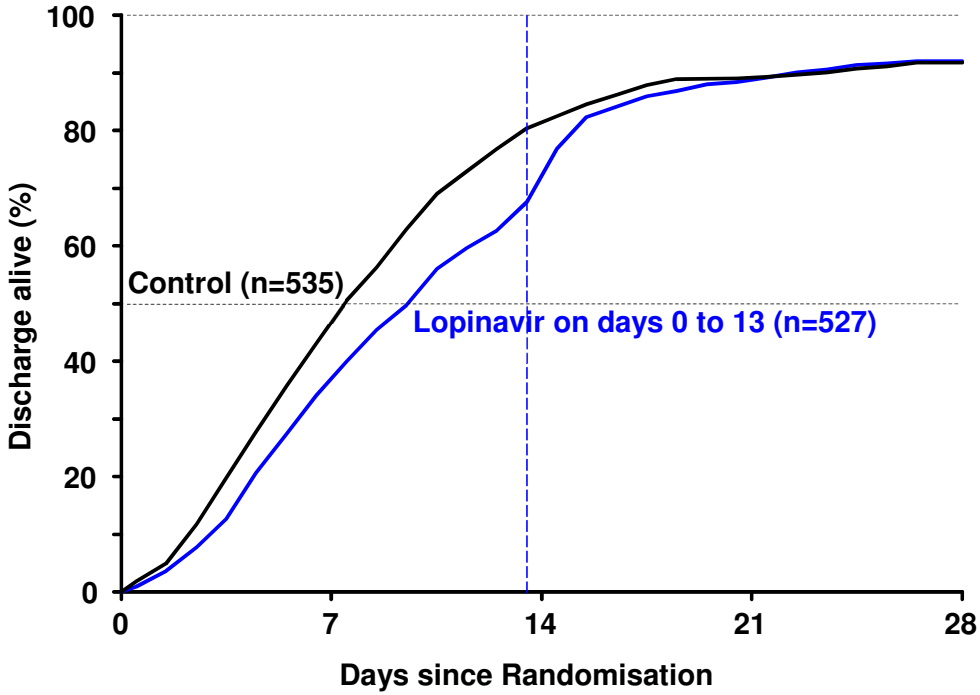
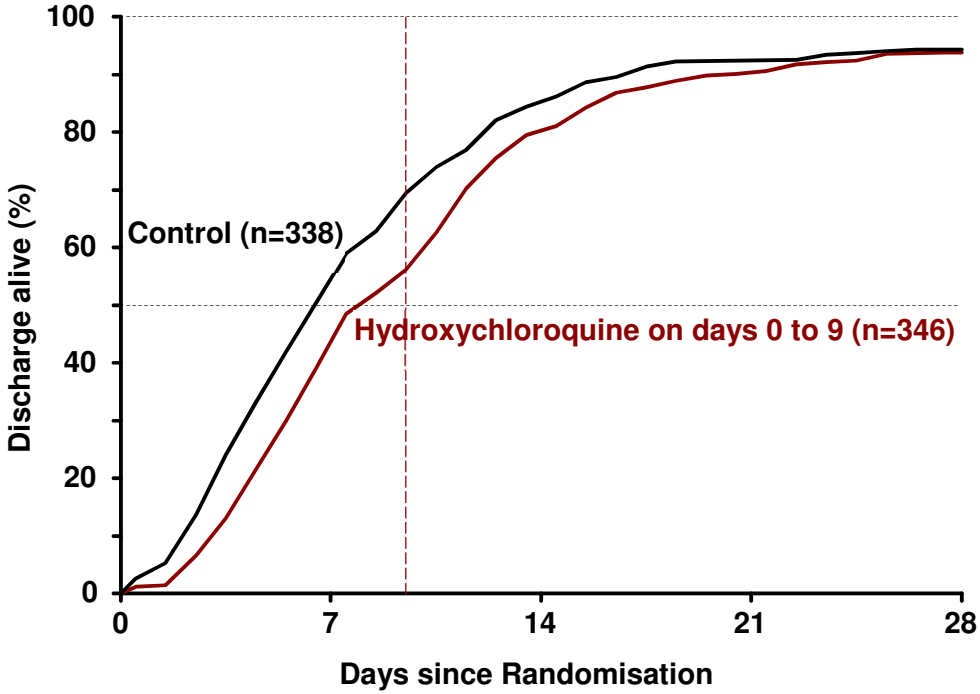


Figure S12A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients being given no O_2 at entry (Approximates "mild-to-moderate" in ACTT-1 & FDA reports.) Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







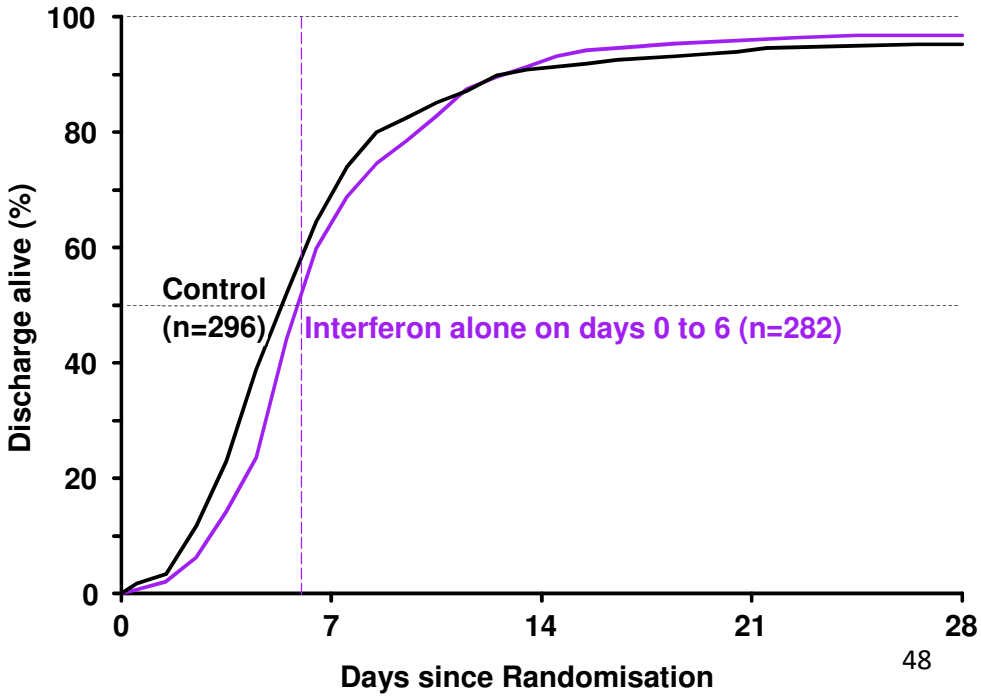
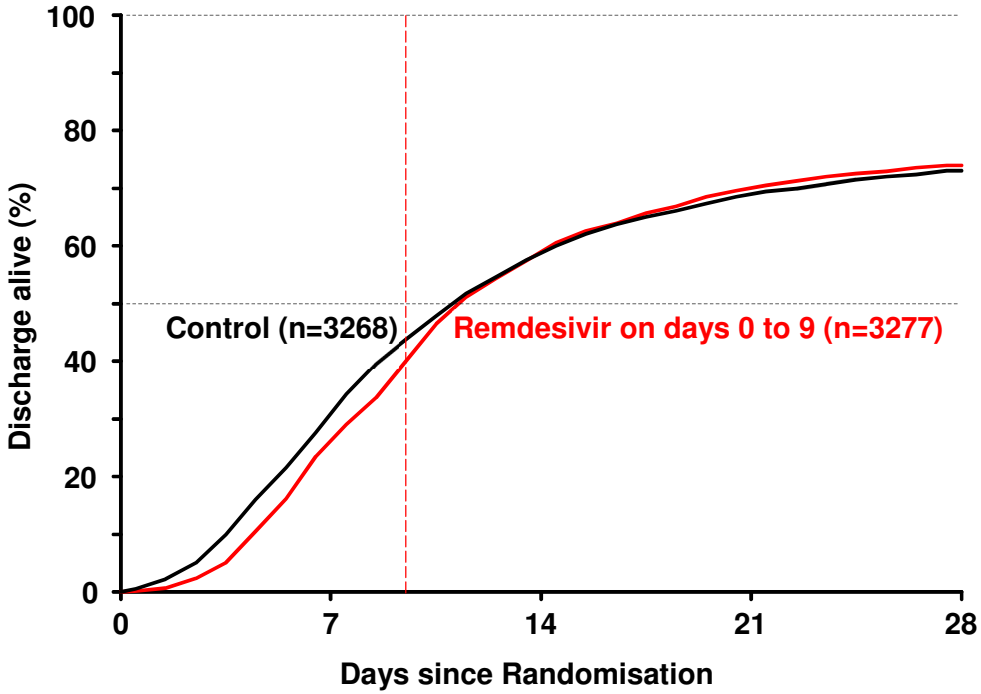
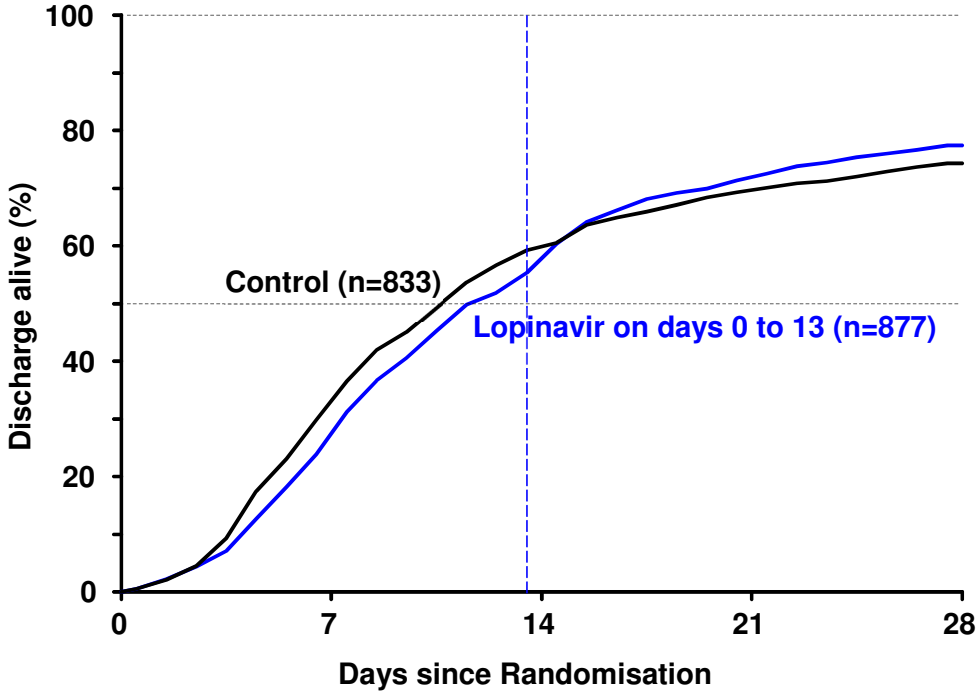
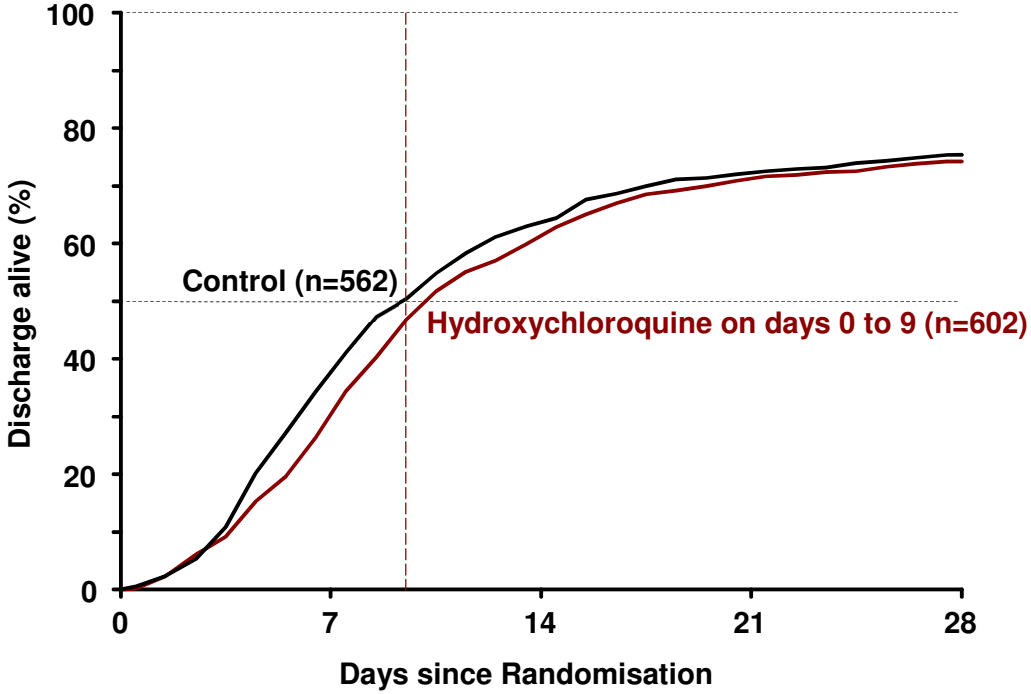


Figure S13A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients on low/high-flow O_2 or ventilated Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







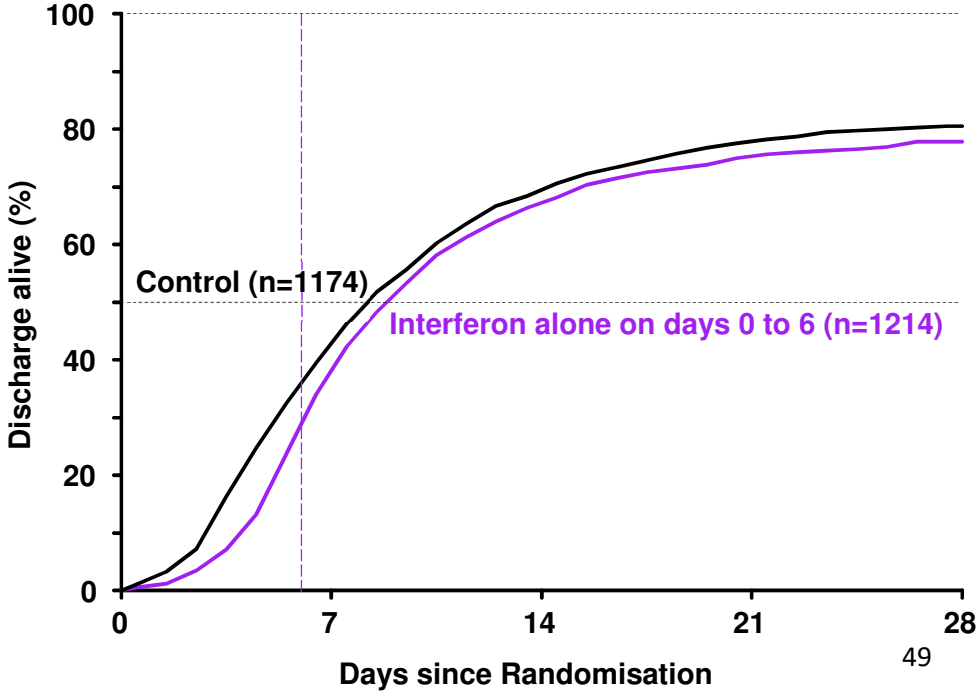
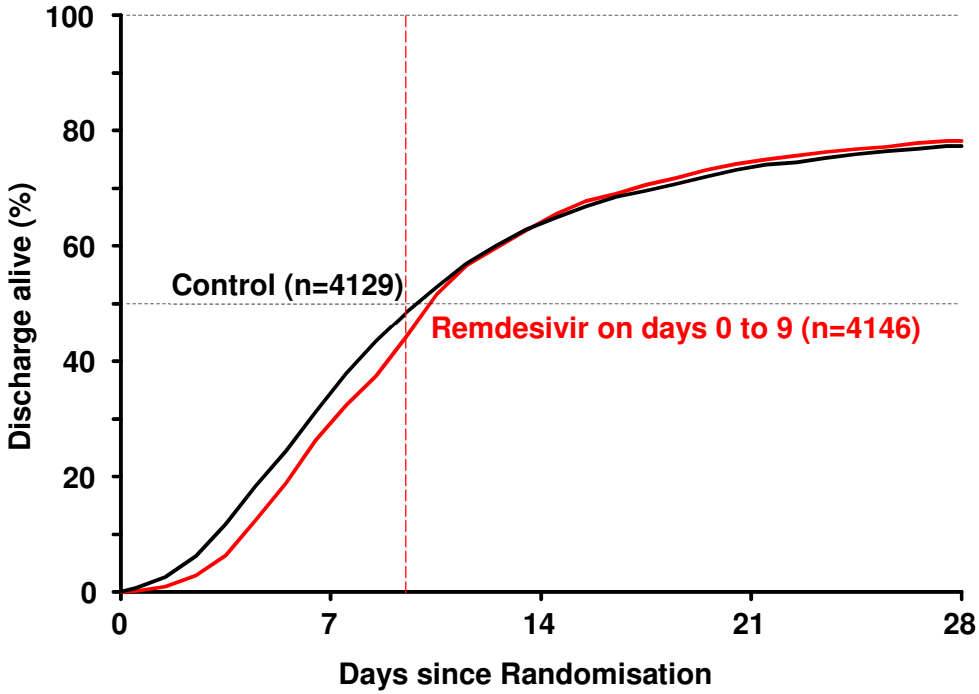
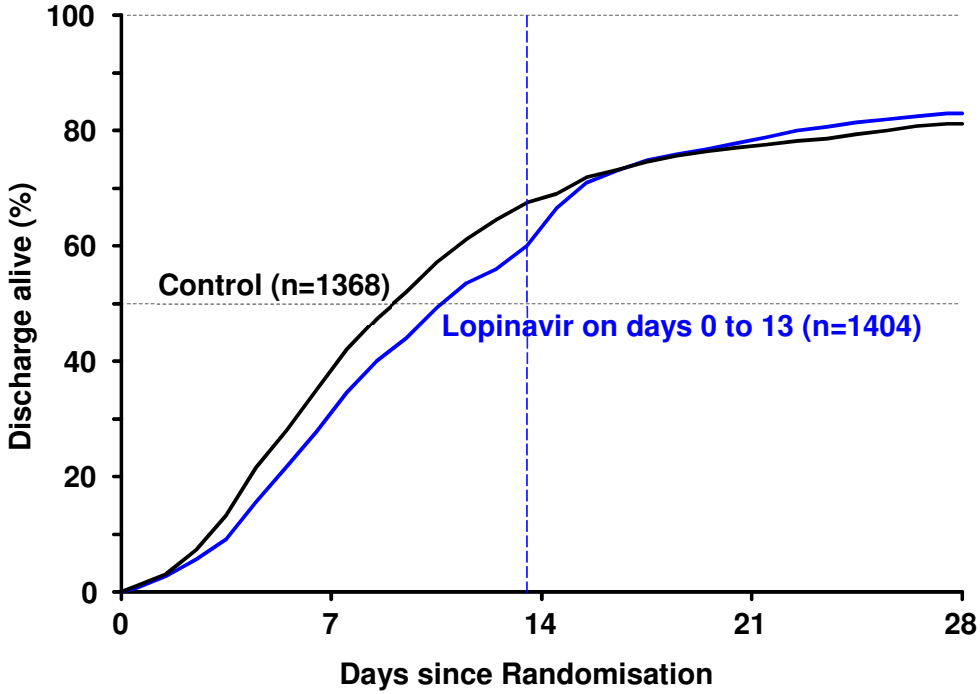
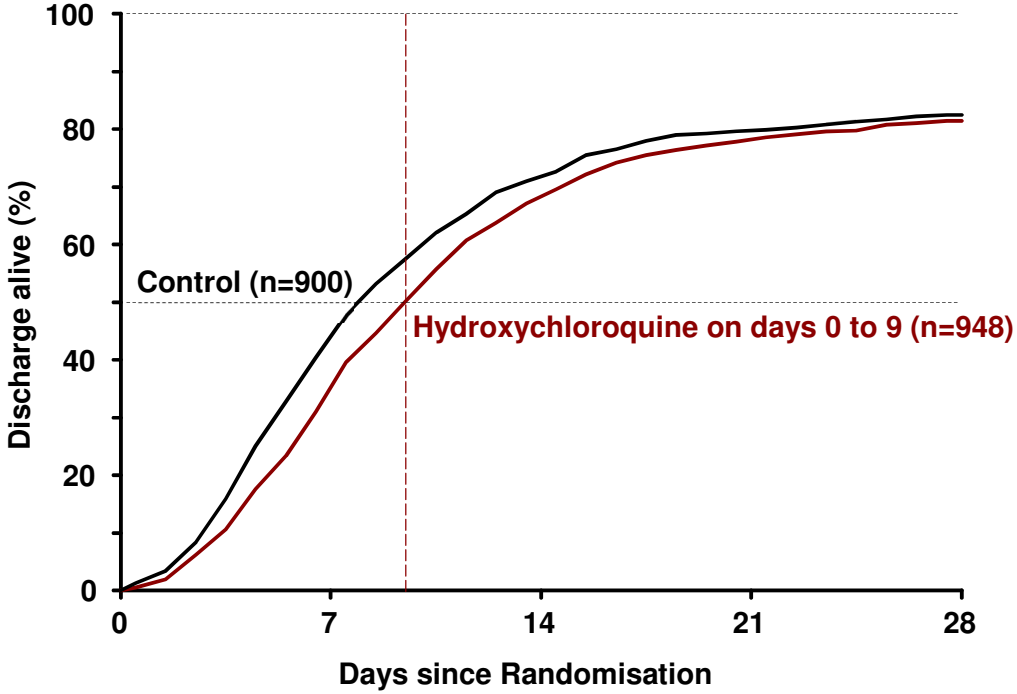


Figure S14A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in <u>all patients, regardless of respiratory support at entry</u> Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







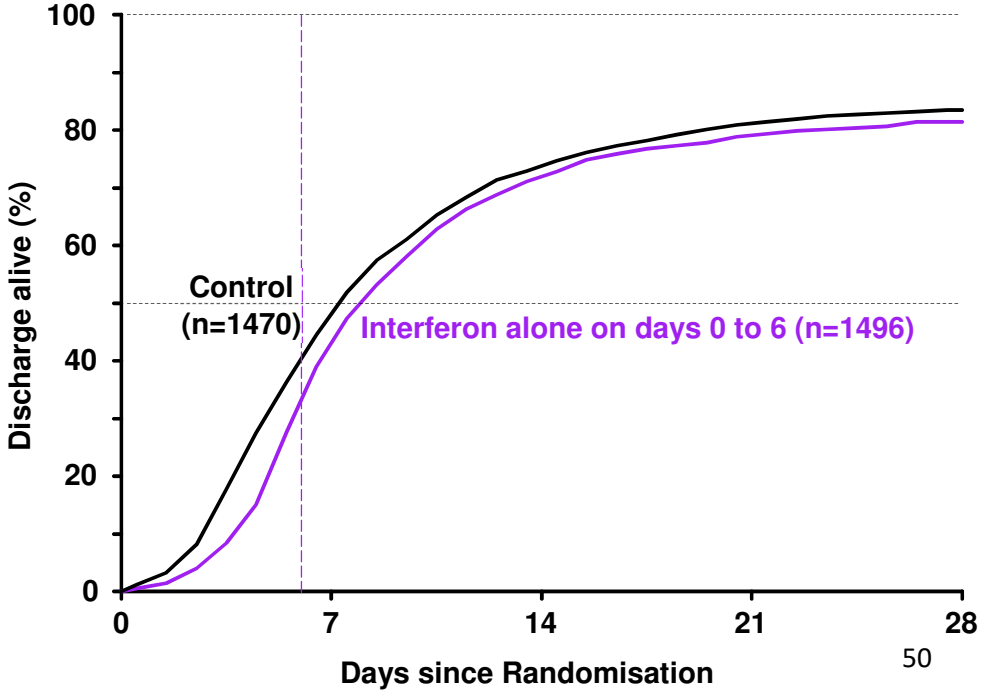
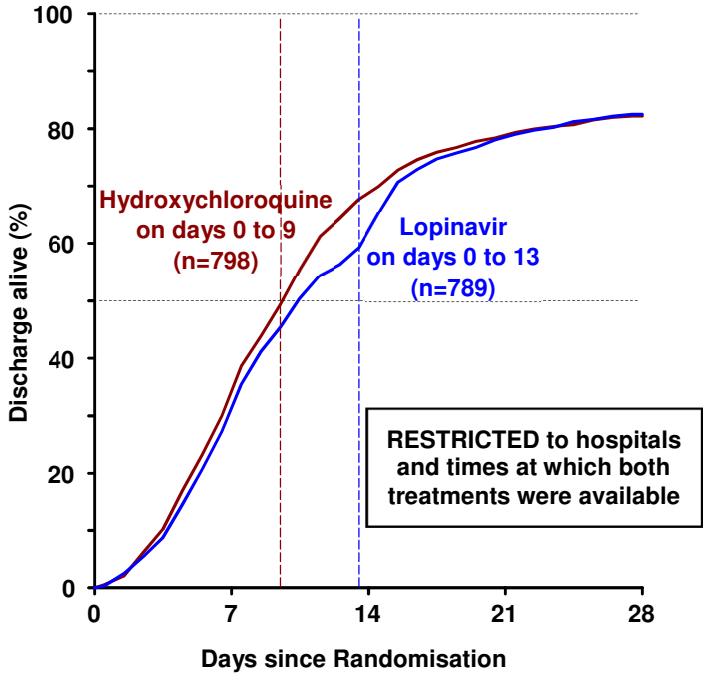
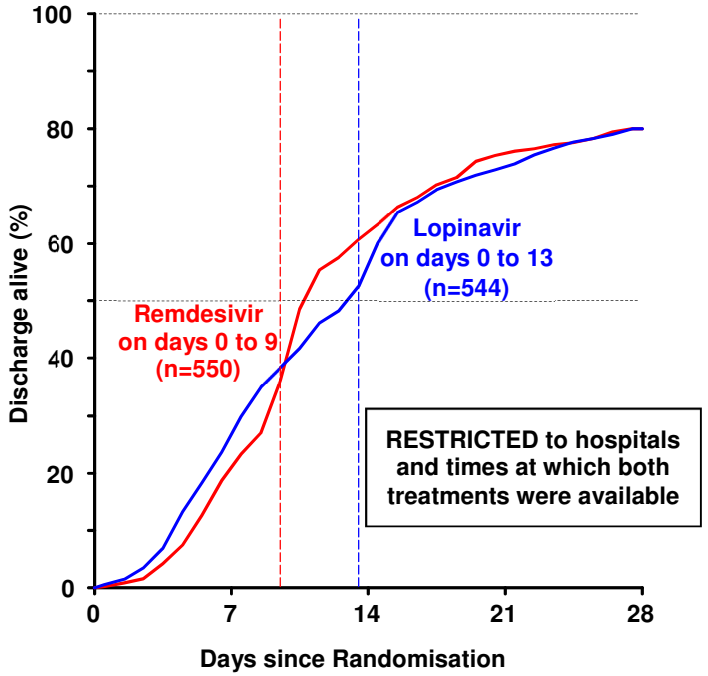
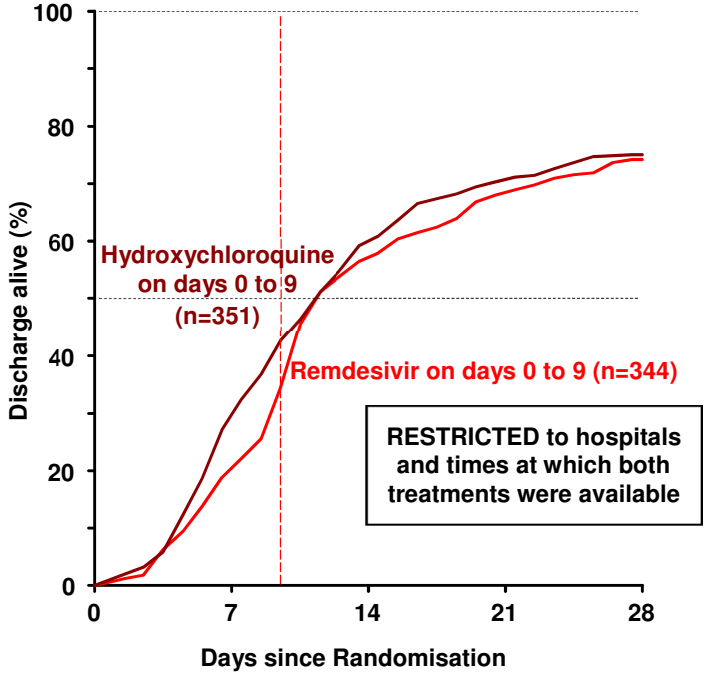


Figure S15A-D. Pairwise randomised comparisons between pairs of study drugs - effects on time to discharge alive, restricted to patients randomised where both of those two drugs were available Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital







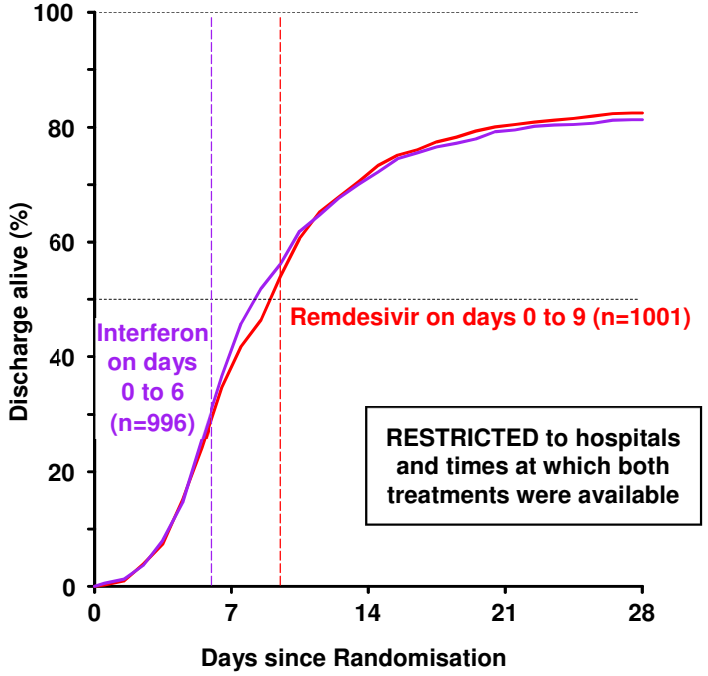
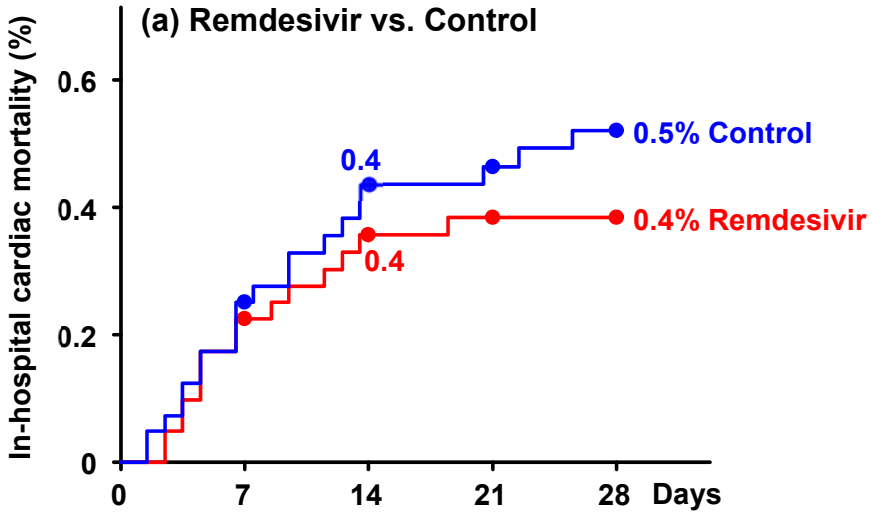
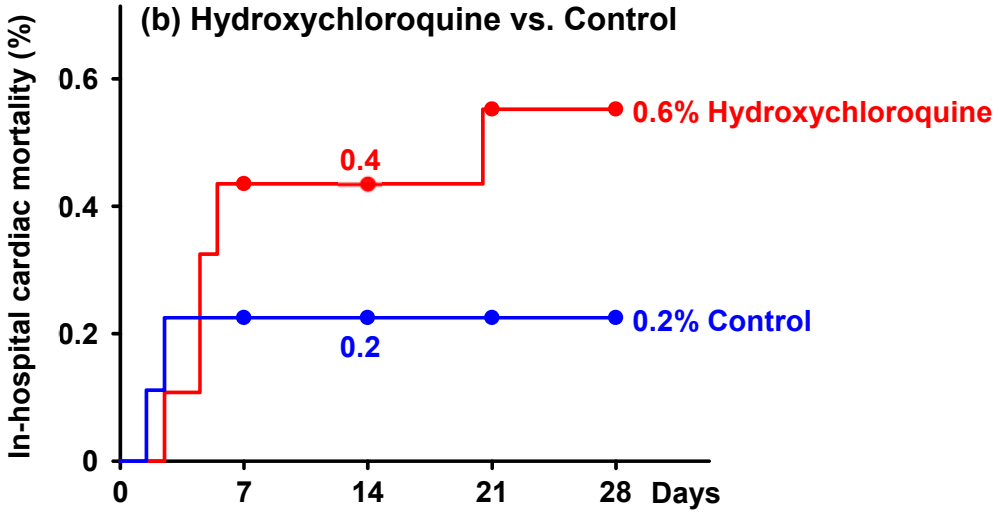


Figure S16A-D. Effects of (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon on cardiac death in hospital
(any death in hospital for which the trial's electronic death report included a cardiac cause)



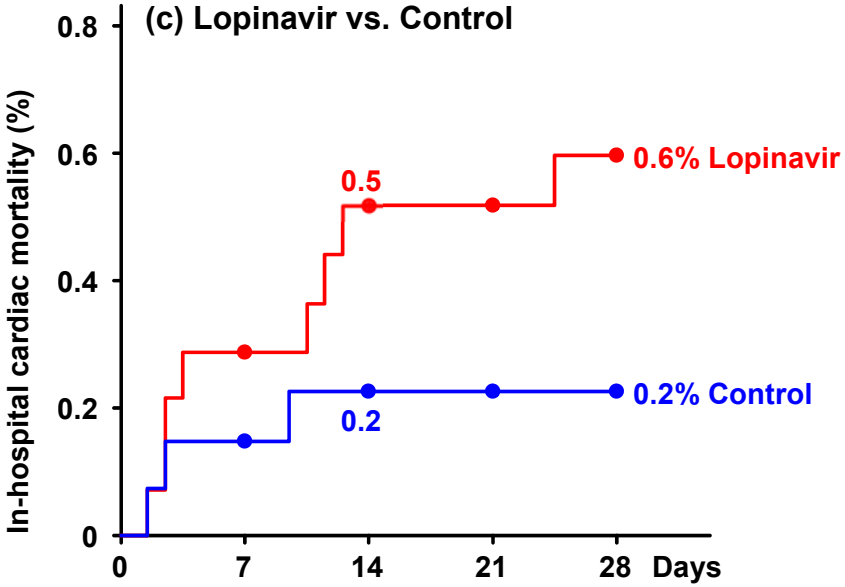
No. randomised, nos. dying, and denominators

Remdesivir	4146	9	3878	5	3703	1	3606	0	3554	2
Control	4129	10	3861	7	3665	1	3557	2	3490	0



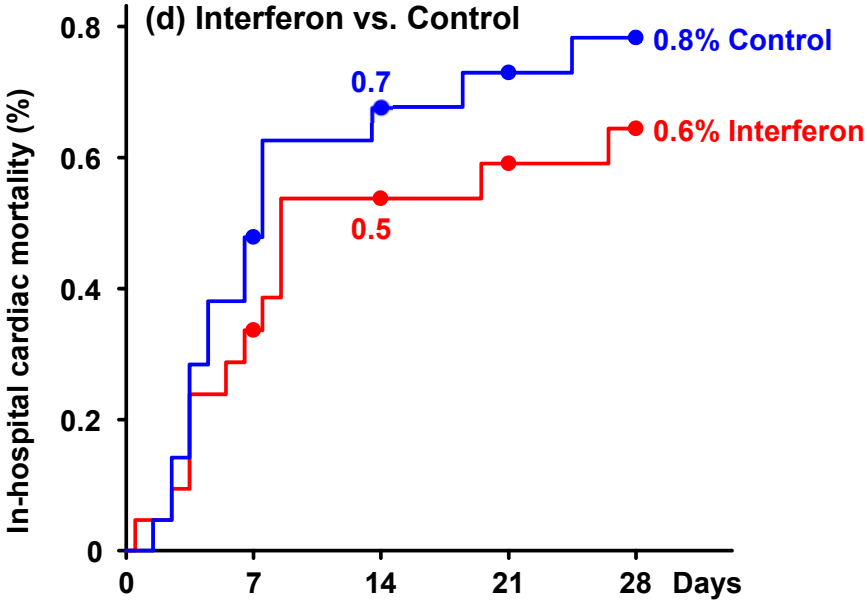
No. randomised, nos. dying, and denominators

Hydroxychlor.	948	4	890	0	858	1	845	0	841	4
Control	900	2	848	0	820	0	812	0	808	1



No. randomised, nos. dying, and denominators

Lopinavir	1404	4	1334	3	1286	0	1263	1	1250	0
Control	1368	2	1292	1	1242	0	1220	0	1208	0



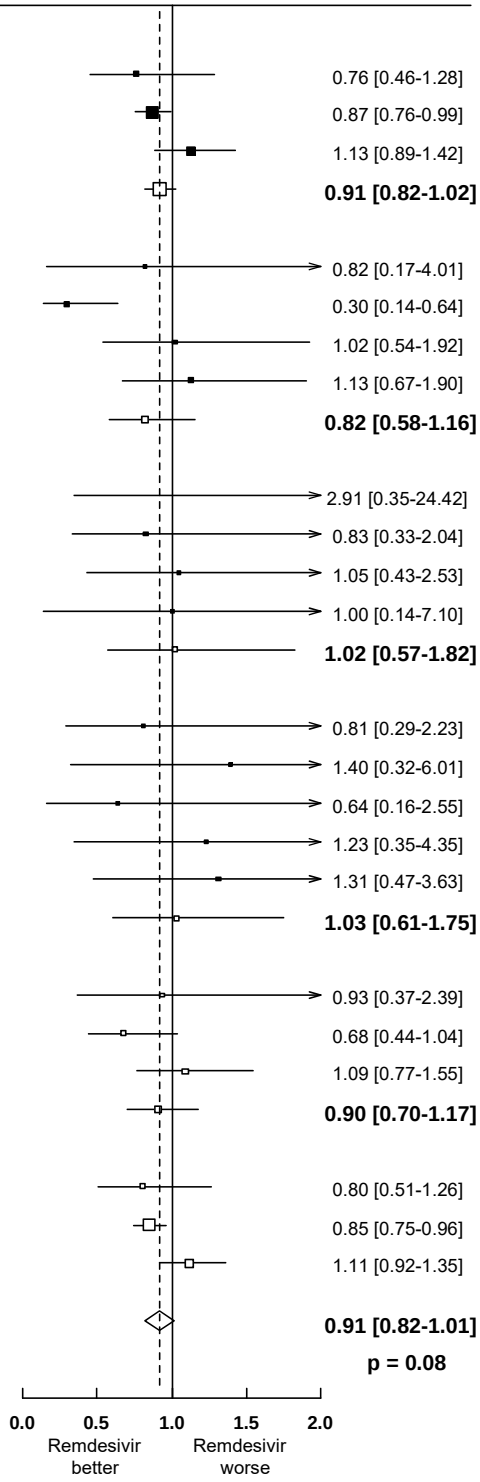
No. randomised, nos. dying, and denominators

Interferon	2144	7	1999	4	1904	1	1859	1	1828	1
Control	2147	10	2015	4	1939	1	1904	1	1880	0

Figure S17A: Remdesivir vs its control in hospitalised COVID – Meta-analysis of mortality in Solidarity, ACTT-1, & other randomised trials with some deaths

Solidarity includes in-hospital deaths before or after day 28, but other trials may stop at day 28. Statistical analyses (O-E, RR, etc) are stratified for respiratory support, but the overall % is not. The French, Canadian and Norwegian parts of Solidarity, published separately, are already included in this meta-analysis, so they are not additional to it.

Trial, and respiratory support reported at the time of randomisation	Deaths reported / No. of patients (%) Remdesivir	Control	Remdesivir deaths: Observed-Expected (O-E)**	Var (O-E)	Death rate ratio RR, and 95% CI Remdesivir : Control
Solidarity (in-hospital mortality; controls not given placebo): trend p = 0.05					
No oxygen	25/869 (2.9)	33/861 (3.8)	-3.9	14.4	0.76 [0.46-1.28]
Oxygen, not ventilated*	426/2918 (14.6)	476/2921 (16.3)	-32.0	223.5	0.87 [0.76-0.99]
Ventilated	151/359 (42.1)	134/347 (38.6)	8.3	69.8	1.13 [0.89-1.42]
Subtotal, with stratified analyses	**602/4146 (14.5)**	**643/4129 (15.6)**	**-27.6**	**307.7**	**0.91 [0.82-1.02]**
ACTT-1 (28-day mortality; controls given placebo infusions): trend p = 0.03					
No oxygen	3/75 (4.0)	3/63 (4.8)	-0.3	1.5	0.82 [0.17-4.01]
Low-flow oxygen	9/232 (3.9)	25/203 (12.3)	-8.0	6.7	0.30 [0.14-0.64]
High-flow oxygen or non-invasive ventilation	19/95 (20.0)	20/98 (20.4)	0.2	9.6	1.02 [0.54-1.92]
Invasive ventilation	28/131 (21.4)	29/154 (18.8)	1.8	14.3	1.13 [0.67-1.90]
Subtotal, with stratified analyses	**59/533 (11.1)**	**77/518 (14.9)**	**-6.4**	**32.1**	**0.82 [0.58-1.16]**
Canada, after Solidarity (in-hospital mortality; controls not given placebo): trend p = 0.75					
No oxygen	3/11 (27.3)	1/10 (10.0)	0.9	0.8	2.91 [0.35-24.42]
Low-flow oxygen	10/96 (10.4)	11/89 (12.4)	-0.9	4.7	0.83 [0.33-2.04]
High-flow oxygen or non-invasive ventilation	14/49 (28.6)	13/47 (27.7)	0.2	4.9	1.05 [0.43-2.53]
Invasive ventilation	4/14 (28.6)	2/7 (28.6)	0.0	1.0	1.00 [0.14-7.10]
Subtotal, with stratified analyses	**31/170 (18.2)**	**27/153 (17.6)**	**0.2**	**11.4**	**1.02 [0.57-1.82]**
Other trials (28-day mortality; only Wuhan was placebo-controlled): trend p = 0.55					
Wuhan: (a) low-flow oxygen	11/129 (8.5)	(7/68) x2† (10.3)	-0.8	3.7	0.81 [0.29-2.23]
(b) high-flow oxygen or ventilation	11/29 (37.9)	(3/10) x2† (30.0)	0.6	1.8	1.40 [0.32-6.01]
SIMPLE: no oxygen	5/384 (1.3)	(4/200) x2† (2.0)	-0.9	2.0	0.64 [0.16-2.55]
Amritsar: no ventilation	6/41 (14.6)	5/41 (12.2)	0.5	2.4	1.23 [0.35-4.35]
Egypt: mild/moderate	9/100 (9.0)	7/100 (7.0)	1.0	3.7	1.31 [0.47-3.63]
Subtotal, with stratified analyses	**42/683 (6.1)**	**40/697† (5.7)**	**0.4**	**13.6**	**1.03 [0.61-1.75]**
Summation of relevant strata from all other trials except Solidarity: trend p = 0.23					
No oxygen	11/470 (2.3)	12/473† (2.5)	-0.3	4.4	0.93 [0.37-2.39]
Low-flow oxygen	45/598 (7.5)	62/569† (10.9)	-8.2	21.1	0.68 [0.44-1.04]
High-flow oxygen or ventilation	76/318 (23.9)	70/326† (21.5)	2.8	31.6	1.09 [0.77-1.55]
Stratified total	**132/1386 (9.5)**	**144/1368† (10.5)**	**-5.7**	**57.1**	**0.90 [0.70-1.17]**
Meta-analysis (by summation of relevant strata from Solidarity and all other trials): trend p = 0.02					
No oxygen	36/1339 (2.7)	45/1334† (3.4)	-4.2	18.8	0.80 [0.51-1.26]
On oxygen, no ventilation; includes high-flow oxygen only in Solidarity*	471/3516 (13.4)	538/3490† (15.4)	-40.2	244.6	0.85 [0.75-0.96]
Ventilation; includes high-flow oxygen in studies other than Solidarity	227/677 (33.5)	204/673† (30.3)	11.0	101.4	1.11 [0.92-1.35]
Total (all trials), with stratified analyses	**734/5532 (13.3)**	**787/5497† (14.3)**	**-33.4**	**364.8**	**0.91 [0.82-1.01]**
					p = 0.08



* High-flow and low-flow oxygen were not recorded separately at entry into Solidarity

** Age-stratified log-rank O-E for Solidarity, O-E from 2x2 tables for small trials, and w.loge HR for ACTT-1 strata (with the weight w being the inverse of the variance of loge HR, obtained from the 95% CI for the Hazard Ratio). If V is the variance of the logrank statistic O-E then RR is got from taking $\log_e$ RR to be (O-E)/V with Normal variance 1/V. Summation of (O-E) and V yields the stratified total (ie, the inverse-variance-weighted average of the separate $\log_e$ RR values).

‡ After Solidarity ended, its Canadian centres continued randomising remdesivir vs its control until 1 April, 2021.

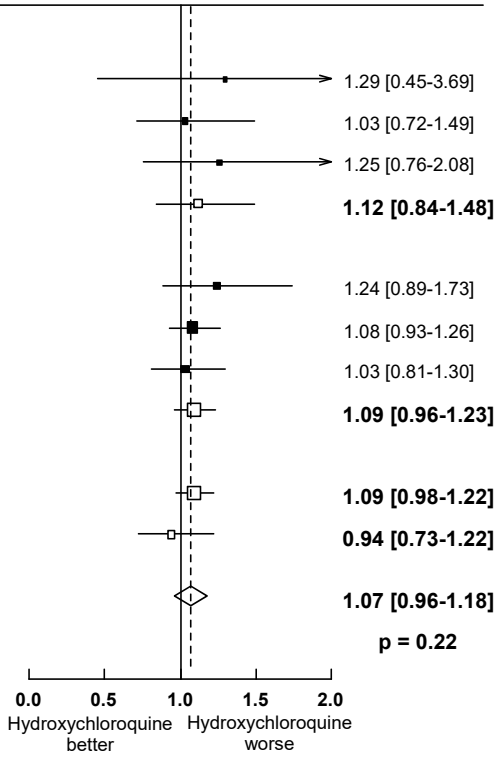
† For balance, in studies with only half as many allocated control as remdesivir the controls count twice in total deaths/patients.

Figure S17B. Hydroxychloroquine vs its control in hospitalised COVID – Meta-analysis of mortality in Solidarity, Recovery, & the other RCTs with some deaths

Solidarity includes in-hospital deaths before or after day 28, but Recovery and some other trials stop at day 28. Statistical analyses (O-E, RR, etc) are stratified for respiratory support, but the overall % is not. The French, Canadian and Norwegian results, published separately, are not additional to this.

Trial, and respiratory support at the time of randomisation	Deaths reported / No. of patients (%)		Hydroxychlor. deaths: Observed-Expected		Death rate ratio RR, and 95% CI
	Hydroxychlor.	Control	(O-E)*	Var (O-E)	Hydroxychlor. : Control
Solidarity (stratified by oxygen use and by ventilation at entry)					
No oxygen	8/346 (2.3)	6/338 (1.8)	0.9	3.5	1.29 [0.45-3.69]
Low-flow or high-flow O_2	61/518 (11.8)	55/480 (11.5)	0.9	28.8	1.03 [0.72-1.49]
Ventilation (any type) or ECMO	35/84 (41.7)	28/82 (34.1)	3.4	15.0	1.25 [0.76-2.08]
Stratified total: Solidarity	**104/948 (11.0)**	**89/900 (9.9)**	**5.2**	**47.3**	**1.12 [0.84-1.48]**
Recovery (stratified by oxygen use and by ventilation at entry)					
No oxygen	58/362 (16.0)	(99/750) /2† (13.2)	7.3	34.1	1.24 [0.89-1.73]
O_2 or non-invasive ventilation	253/938 (27.0)	(475/1873) /2† (25.4)	12.4	157.9	1.08 [0.93-1.26]
Invasive ventilation or ECMO	110/261 (42.1)	(216/532) /2† (40.6)	1.9	70.6	1.03 [0.81-1.30]
Stratified total: Recovery	**421/1561 (27.0)**	**(790/3155) /2† (25.0)**	**21.7**	**262.7**	**1.09 [0.96-1.23]**
Solidarity and Recovery	**525/2509 (20.9)**	**484/2478 (19.5)**	**26.9**	**309.9**	**1.09 [0.98-1.22]**
18 small trials	**148/1452 (10.2)**	**161/1472 (10.9)**	**-3.5**	**58.1**	**0.94 [0.73-1.22]**
Stratified total	**673/3961 (17.0)**	**645/3950 (16.3)**	**23.4**	**368.0**	**1.07 [0.96-1.18]**

Heterogeneity between Solidarity, Recovery & 18 small trials: $\chi^2_2 = 1.1$; p = 0.58 **p = 0.22**



* Log-rank O-E for Solidarity and Recovery, and sum of O-E from 2x2 tables for small trials.

RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Similar use of subtotals or of totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

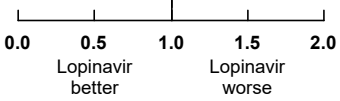
† For balance, only half the control numbers in Recovery are added into totals and subtotals

Figure S17C. Lopinavir vs its control in hospitalised COVID – Meta-analysis of mortality in Solidarity, Recovery, and the other RCT with some deaths

Solidarity includes in-hospital deaths before or after day 28, but the other trials stop at day 28. Statistical analyses (O-E, RR, etc) are stratified for respiratory support, but the overall % is not. The French, Canadian and Norwegian results, published separately, are not additional to this.

Trial, and respiratory support at the time of randomisation	Deaths reported / No. of patients (%)		Lopinavir deaths: Observed-Expected		Death rate ratio RR, and 95% CI
	Lopinavir	Control	(O-E)*	Var (O-E)	Lopinavir : Control
Solidarity (stratified by oxygen use and by ventilation at entry)					
No oxygen	21/527 (4.0)	17/535 (3.2)	2.5	9.4	1.31 [0.69-2.48]
Low-flow or high-flow O_2	96/765 (12.5)	100/718 (13.9)	-7.8	48.3	0.85 [0.64-1.13]
Ventilation (any type) or ECMO	34/112 (30.4)	36/115 (31.3)	0.6	16.7	1.04 [0.64-1.68]
Stratified total: Solidarity	**151/1404 (10.8)**	**153/1368 (11.2)**	**-4.7**	**74.5**	**0.94 [0.75-1.18]**
Recovery (stratified by oxygen use and by ventilation at entry)					
No oxygen	71/425 (16.7)	(126/896) /2† (14.1)	8.2	42.5	1.21 [0.90-1.64]
O_2 or non-invasive ventilation	279/1131 (24.7)	(586/2384) /2† (24.6)	-0.4	185.9	1.00 [0.86-1.15]
Invasive ventilation or ECMO	24/60 (40.0)	(55/144) /2† (38.2)	1.6	15.6	1.11 [0.67-1.82]
Stratified total: Recovery	**374/1616 (23.1)**	**(767/3424) /2† (22.4)**	**9.4**	**244.0**	**1.04 [0.92-1.18]**
Solidarity and Recovery	**525/3020 (17.4)**	**537/3080 (17.4)**	**4.7**	**318.5**	**1.01 [0.91-1.13]**
Wuhan trial	**19/99 (19.2)**	**25/100 (25.0)**	**-2.9**	**8.6**	**0.71 [0.37-1.39]**
Stratified total	**544/3119 (17.4)**	**562/3180 (17.7)**	**1.8**	**327.2**	**1.01 [0.90-1.12]**

Heterogeneity between Solidarity, Recovery & Wuhan trials: $\chi^2_2 = 1.6$; p = 0.45 — **p = 0.92**



* Log-rank O-E for Solidarity and Recovery, and O-E from a 2x2 table for the Wuhan trial.

RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Similar use of subtotals or of totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

† For balance, only half the control numbers in Recovery are added into totals and subtotals.

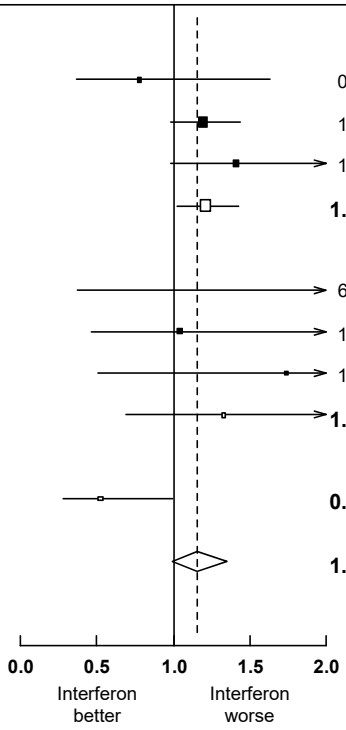
Figure S17D. Interferon-β vs its control in hospitalised COVID – Meta-analysis of mortality in Solidarity, ACTT-3, and the other RCTs with some deaths

Solidarity includes in-hospital deaths before or after day 28, but other trials may stop at day 28. Statistical analyses (O-E, RR etc) are stratified for respiratory support, but the overall % is not. The French, Canadian and Norwegian results, published separately, are not additional to this.

Trial, and respiratory support at the time of randomisation	Deaths reported / No. of patients (%)		Interferon deaths: Observed-Expected		Death rate ratio RR, and 95% CI
	Interferon	Control	(O-E)*	Var (O-E)	Interferon : Control
Solidarity (in-hospital mortality; controls not given placebo)					
No oxygen	12/503 (2.4)	16/508 (3.1)	-1.8	7.0	0.78 [0.37-1.63]
Low-flow or high-flow O_2	235/1497 (15.7)	199/1503 (13.2)	18.9	107.6	1.19 [0.99-1.44]
Ventilation (any type) or ECMO	69/144 (47.9)	51/136 (37.5)	10.0	29.3	1.41 [0.98-2.02]
Stratified total: Solidarity	316/2144 (14.7)	266/2147 (12.4)	27.1	143.9	**1.21 [1.03-1.42]**
ACTT-3 (28-day mortality; controls given placebo)					
No O_2	2/84 (2.4)	0/68 (0.0)	0.9	0.5	6.05 [0.38-96.72]
Low-flow O_2	12/368 (3.3)	12/380 (3.2)	0.2	6.0	1.04 [0.47-2.32]
High-flow O_2 or non-invasive ventilation	7/35 (20.0)	4/34 (11.8)	1.4	2.6	1.74 [0.51-5.93]
Stratified subtotal	21/487 (4.3)	16/482 (3.3)	2.5	9.0	**1.33 [0.69-2.54]**
3 small trials (unstratified†)	**24/126 (19.0)**	**39/126 (31.0)**	**-6.2**	**9.6**	**0.53 [0.28-0.99]**
Stratified total	**361/2757 (13.1)**	**321/2755 (11.7)**	**23.5**	**162.5**	**1.16 [0.99-1.35]**

Heterogeneity between Solidarity, ACTT-3 & small trials: $\chi^2_2 = 6.4$; p = 0.04 **p = 0.07**

* Log-rank O-E for Solidarity, and sum of O-E from 2x2 tables for small trials.



Note that the multivariate analysis of Solidarity in Table S3 yields RR=1.15 (p=0.06) for interferon instead of RR=1.21 (p=0.02), as in the pre-specified pairwise Kaplan-Meier and log-rank analyses. The reduction in RR on going from pairwise to multivariate analysis shows the apparently adverse effect of interferon in Solidarity was at least partly due to an adverse play of chance at randomisation.

RR is got by taking logeRR to be (O-E)/V with Normal variance 1/V. Similar use of subtotals or of totals of (O-E) and of V yields inverse-variance-weighted averages of the logeRR values.

† All 3 small trials were single-centre Iranian studies. For balance, in the one trial in which half as many were allocated control as interferon the control results are counted twice in the total number of deaths and patients. In another, 4 early deaths that were omitted as they prevented interferon completion have been restored.