

THE LANCET

Supplementary appendix

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

Supplement to: WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet* 2022; published online May 2. [https://doi.org/10.1016/S0140-6736\(22\)00519-0](https://doi.org/10.1016/S0140-6736(22)00519-0).

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Special recognition to all the research staff and medical teams in hospitals in

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Honduras: Agencia de Regulación Sanitaria (F Contreras), Hospital Atlantida la Ceiba (M Juarez); Hospital Leonardo Martinez San Pedro Sula (J Samara), Hospital Militar Tegucigalpa (TL Moreno), Hospital San Felipe Tegucigalpa (E Cruz, H Rodriguez), Instituto Cardiopulmonar Tegucigalpa (N Maradiaga), National Autonomous University of Honduras (F Herrera, S Moncada, W Murillo), Secretaria de Salud de Honduras (A Flores, R Aplicano), and PAHO (P Huerta);

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Acknowledgments

The Ministries of Health of the participating Member States and their institutions provided critical support in the implementation of the trial.

Castor EDC donated and managed their cloud-based clinical data capture and management system. Anonymized data handling and analysis was at the Universities of Berne, Bristol and Oxford. Remdesivir was donated by Gilead Sciences, Hydroxychloroquine by Mylan, Lopinavir-Ritonavir by Abbvie, Cipla and Mylan and Interferon β -1a by Merck KGaA (subcutaneous) and Faron (intravenous). Add-on studies were conducted in Canada, France, India and Norway.

The chief acknowledgement is to the thousands of patients and their families who participated in this trial and made it possible, and to the hundreds of medical staff who randomised and cared for the patients.

Funding: Solidarity was supported by in-kind effort from many sources, and by:

Brazil: Oswaldo Cruz Foundation (Fiocruz); Evandro Chagas National Institute of Infectious Diseases (INI/Fiocruz); Laboratory of Clinical Research on Aids and STDs at Evandro Chagas National Institute of Infectious Diseases (INI/Fiocruz);

Canada: Canadian Institutes of Health Research; Vancouver Coastal Health Research Institute; Northern Alberta Clinical Trials and Research Centre; Covenant Health Research Centre; St. Joseph's Health Care Foundation; The London Health Sciences Foundation, London, Ontario; The Calgary Health Trust and Calgary Centre for Clinical Research COVID-19 Fund, and the Covenant Health Research Centre; The McGill University Health Centre was supported by a grant from the McGill Interdisciplinary Initiative in Infection and Immunity (MI4) with Funding from the MUHC Foundation;

Finland: Funding support from the Academy of Finland (309387)

France: EU-RESPONSE has received funding support from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101015736;

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 Ospedaliera Integrata 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 conventional adverse effect of interferon ceased to be conventionally significant, again finding no definitely favorable or unfavorable effect of any of the 4 study drugs:

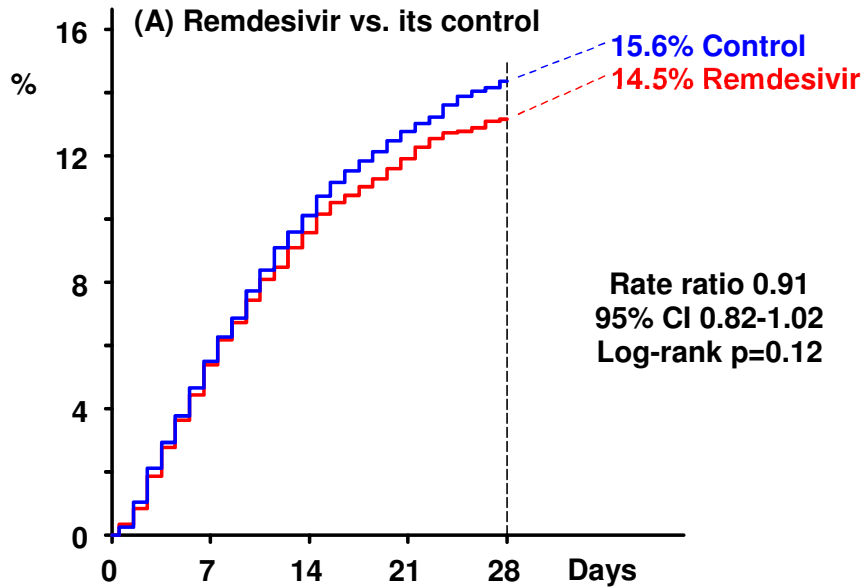
Remdesivir vs local SoC (by multivariate analysis) RR=0.93 (95% CI 0.84-1.04),

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

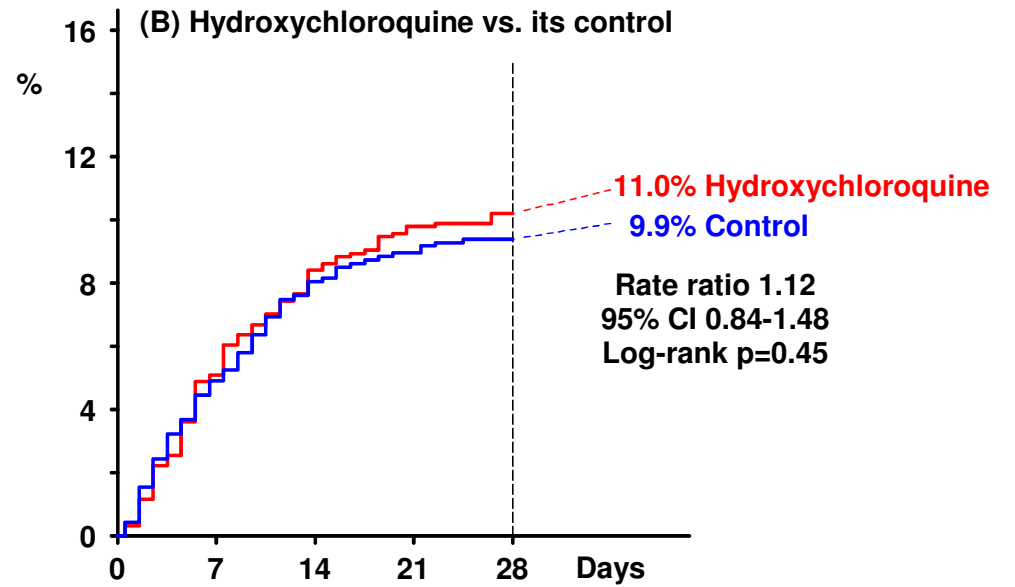
Lopinavir vs local SoC (by multivariate analysis) RR=0.93 (0.76-1.14), and

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

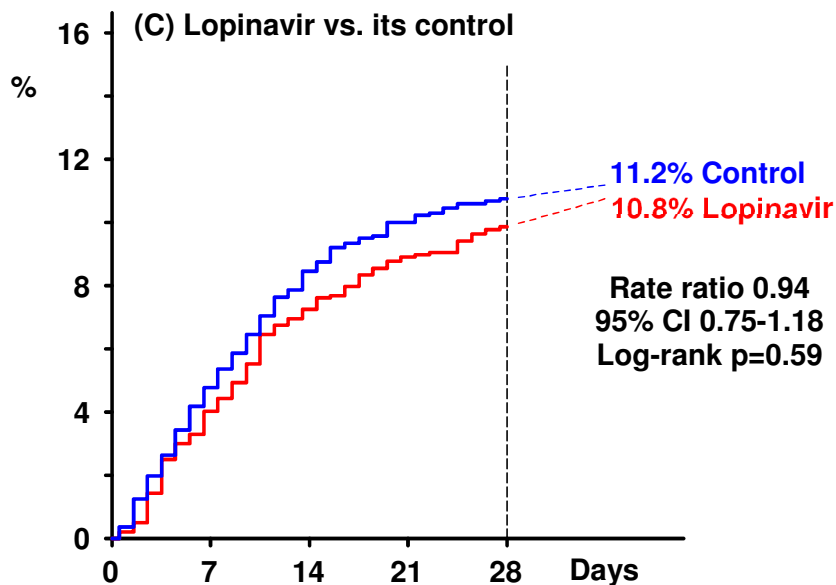
Figure S1A-S1D. Effects on in-hospital mortality of (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, and (D) interferon
Kaplan-Meier graphs, not standardised. Rate ratios (RR, 95% CI) include later in-hospital deaths, and standardise for age and ventilation at entry.



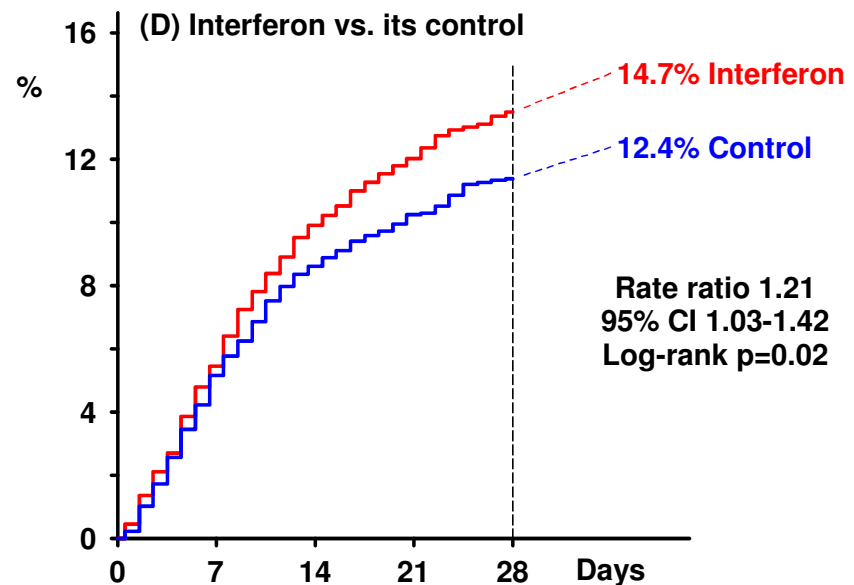
Weekly denominators (all not yet dead/lost), and numbers dying in hospital
 Remdesivir 4146 222 3878 171 3703 96 3606 51 3554 62
 Control 4129 225 3861 189 3665 108 3557 65 3490 56



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

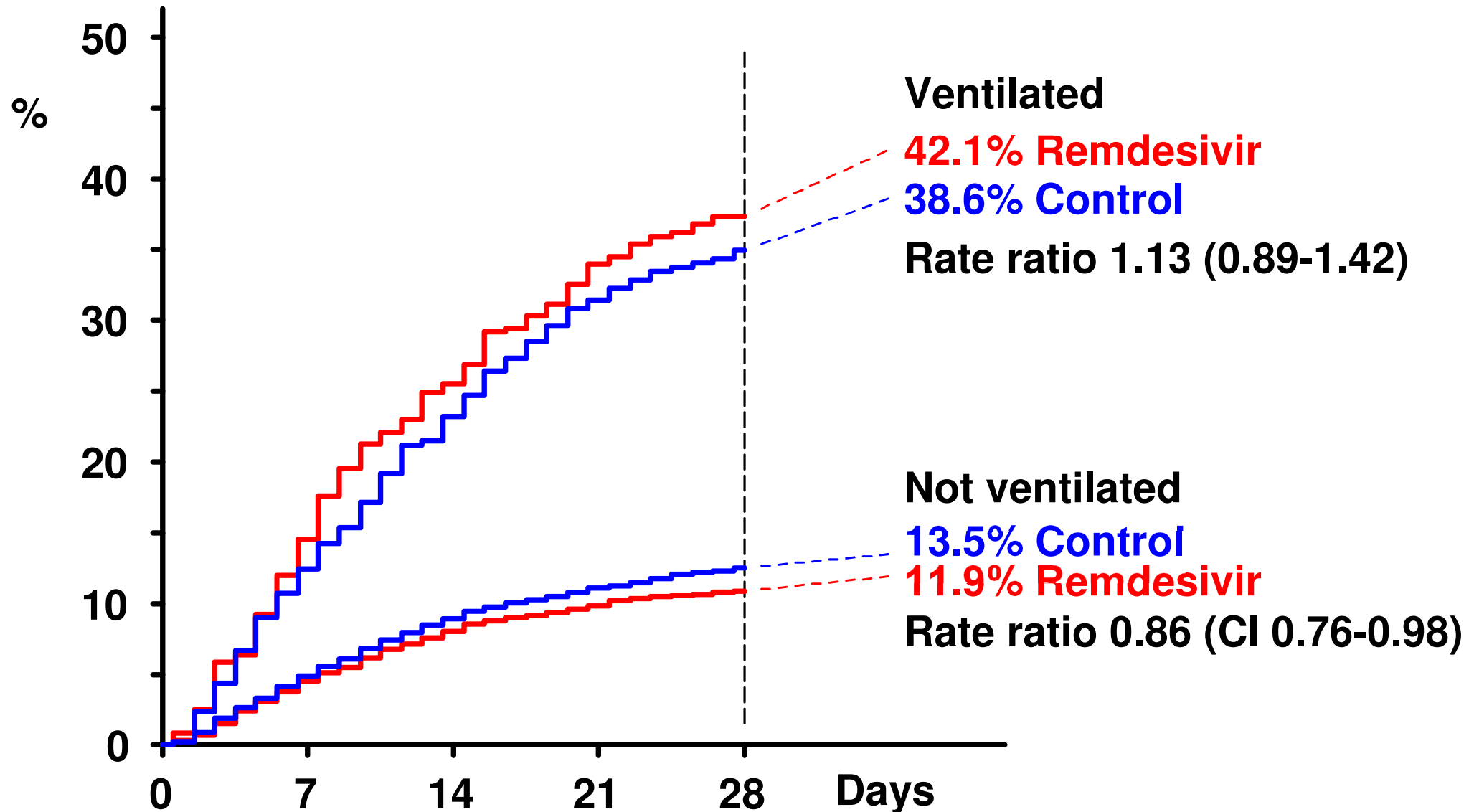


Weekly denominators (all not yet dead/lost), and numbers dying in hospital
 Lopinavir 1404 56 1334 45 1286 23 1263 13 1250 14
 Control 1368 65 1292 50 1242 21 1220 10 1208 7



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

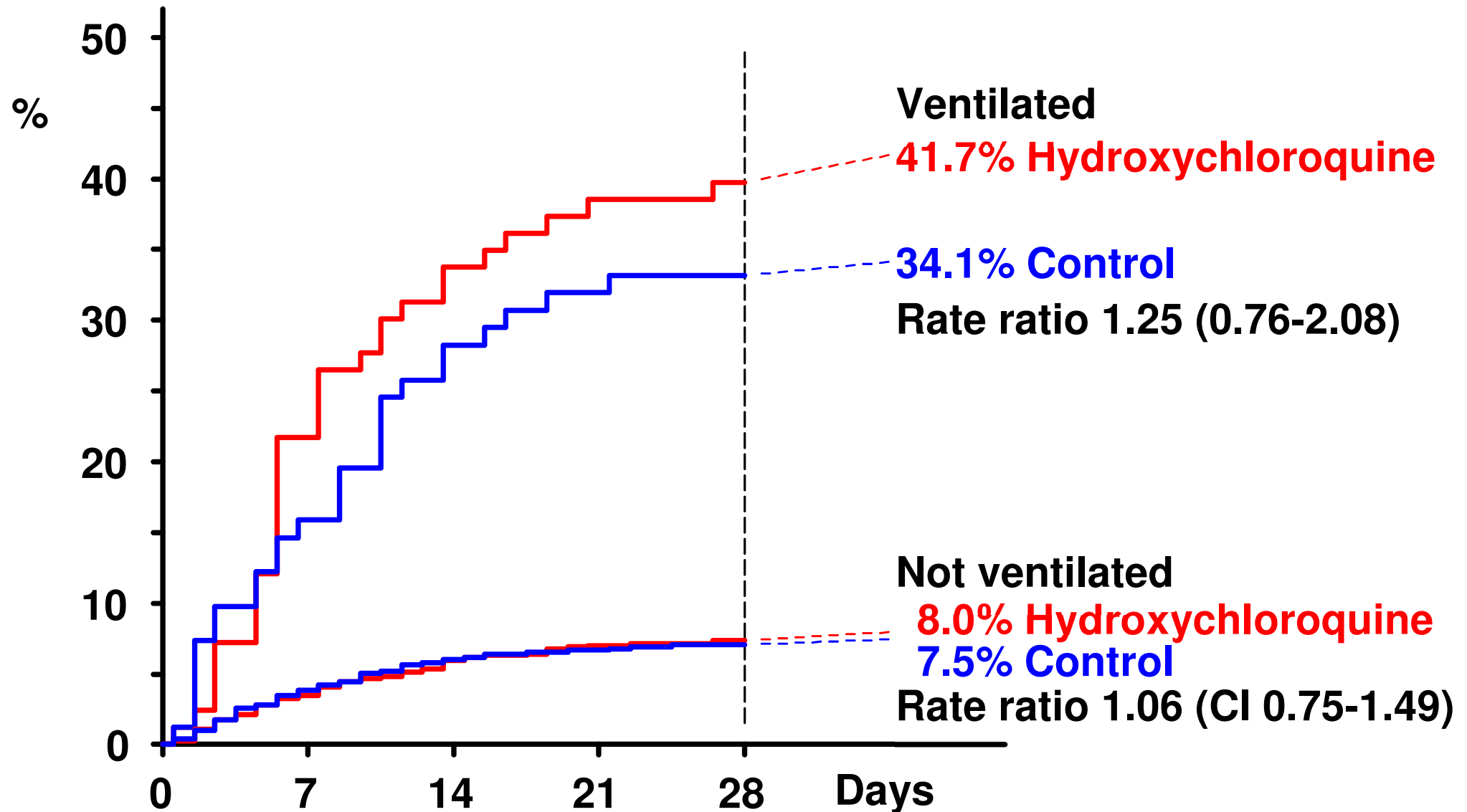
Figure S2A. Subdivision by ventilation at randomisation of the apparent effects of remdesivir on the probability of death in hospital from any cause



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

Remdesivir	359	52	305	39	264	30	234	12	222	18	Ventilated
Control	347	43	301	37	263	28	235	12	222	14	
Remdesivir	3787	170	3573	132	3439	66	3372	39	3332	44	Not ventilated
Control	3782	182	3560	152	3402	80	3322	53	3268	42	

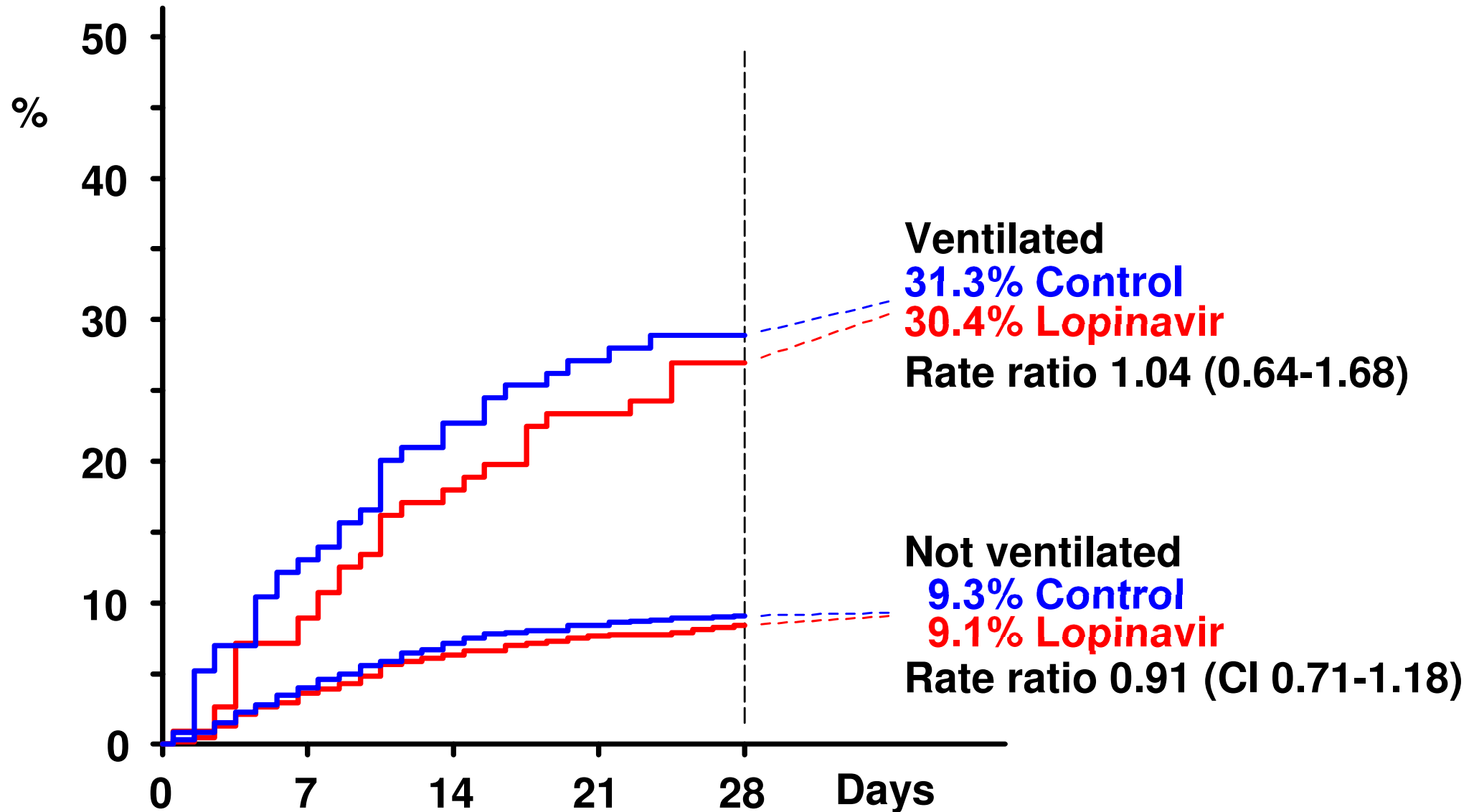
Figure S2B. Subdivision by ventilation at randomisation of the apparent effects of hydroxychloroquine on the probability of death in hospital from any cause



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

Hydroxychlor.	84	18	65	10	55	4	51	1	50	2	Ventilated
Control	82	13	68	10	58	3	55	1	54	1	
Hydroxychlor.	864	30	825	21	803	9	794	3	791	6	Not ventilated
Control	818	31	780	18	762	5	757	3	754	4	

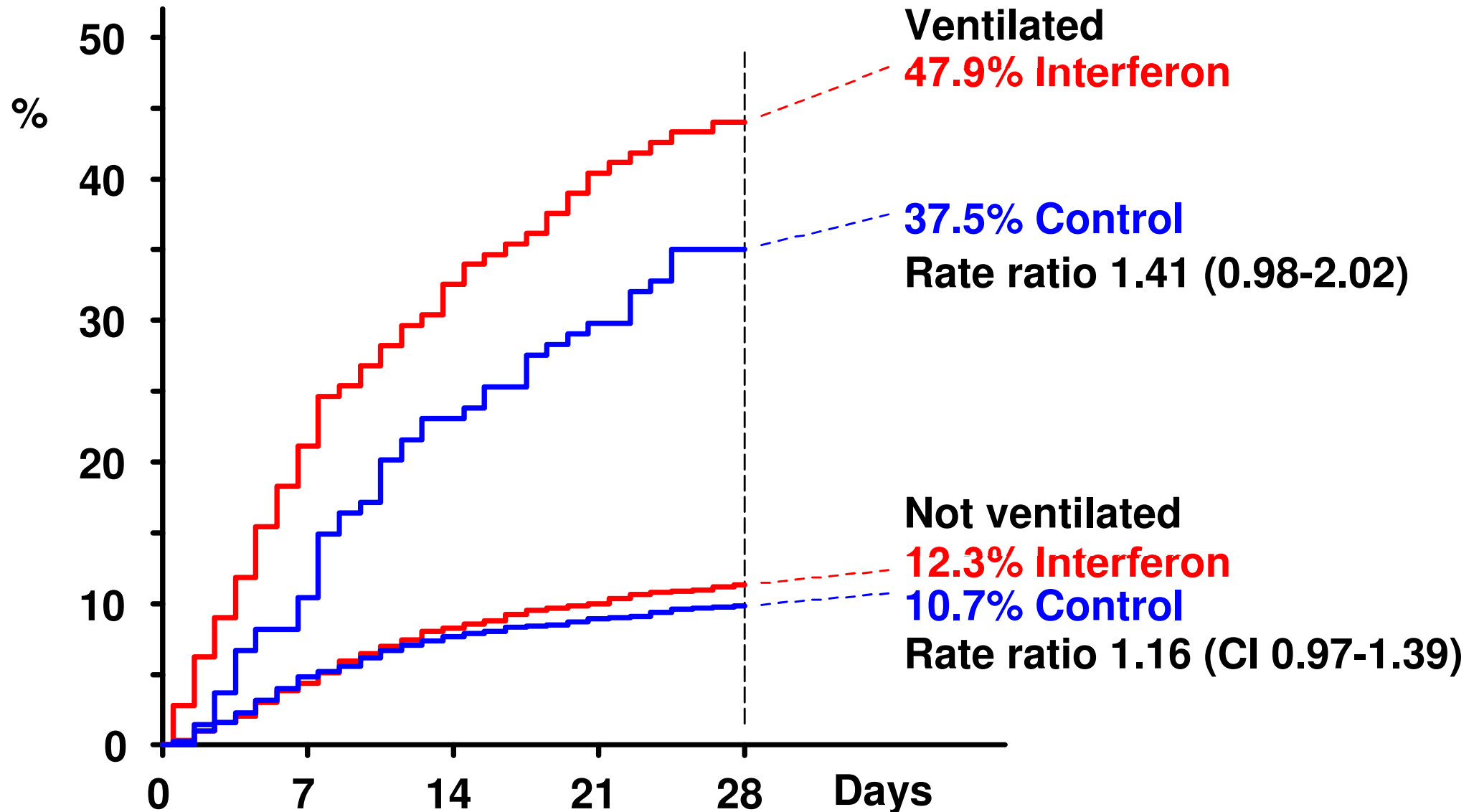
Figure S2C. Subdivision by ventilation at randomisation of the apparent effects of lopinavir on the probability of death in hospital from any cause



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

Lopinavir	112	10	101	10	91	6	85	4	81	4	Ventilated
Control	115	15	99	11	88	5	83	2	80	3	
Lopinavir	1292	46	1233	35	1195	17	1178	9	1169	10	Not ventilated
Control	1253	50	1193	39	1154	16	1137	8	1128	4	

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	Ventilated
Control	136	14	120	17	103	9	94	7	87	4	
Interferon	2000	86	1888	78	1810	34	1776	26	1750	23	Not ventilated
Control	2011	96	1895	56	1836	26	1810	17	1793	20	

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.

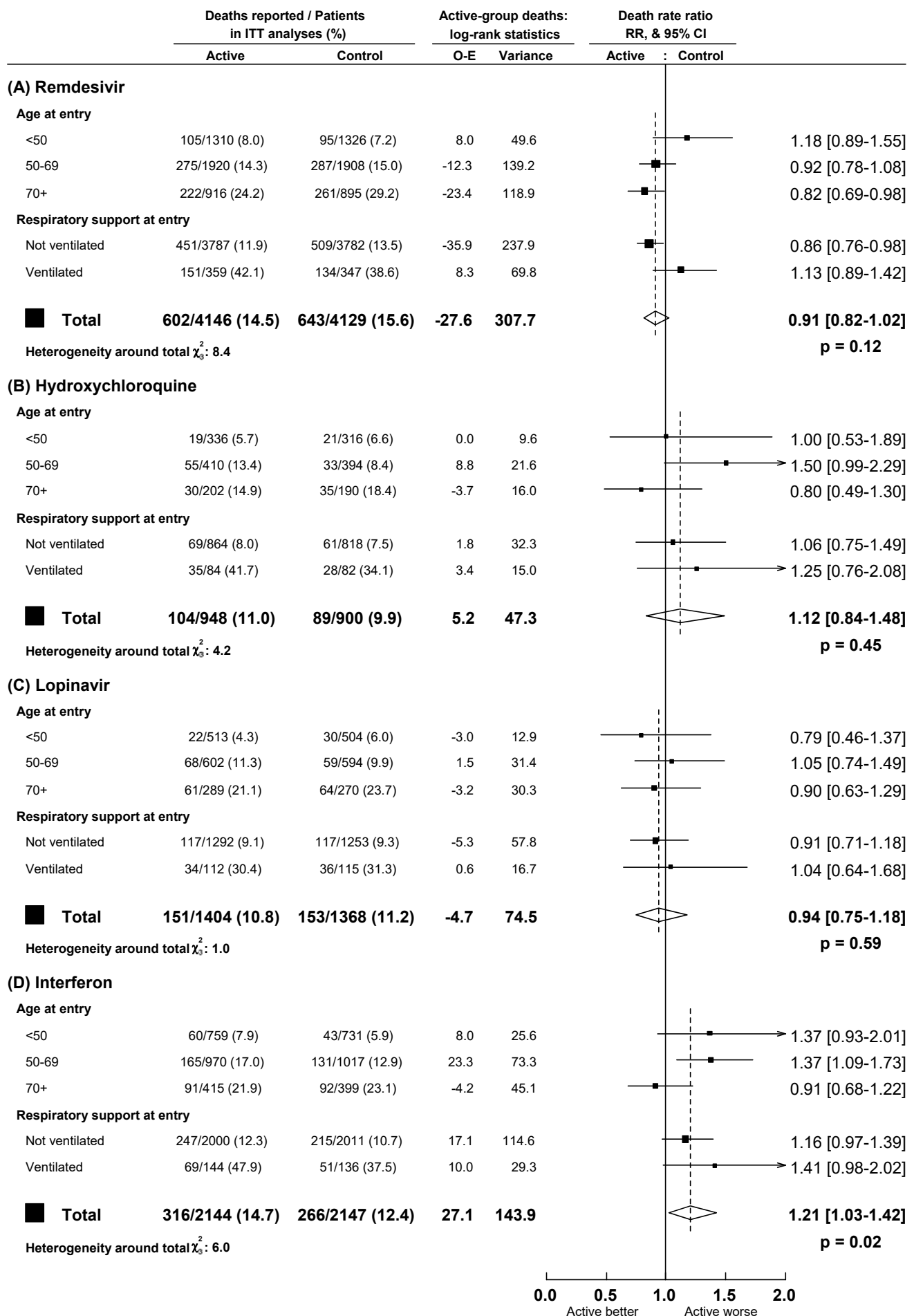


Figure S4A. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time*

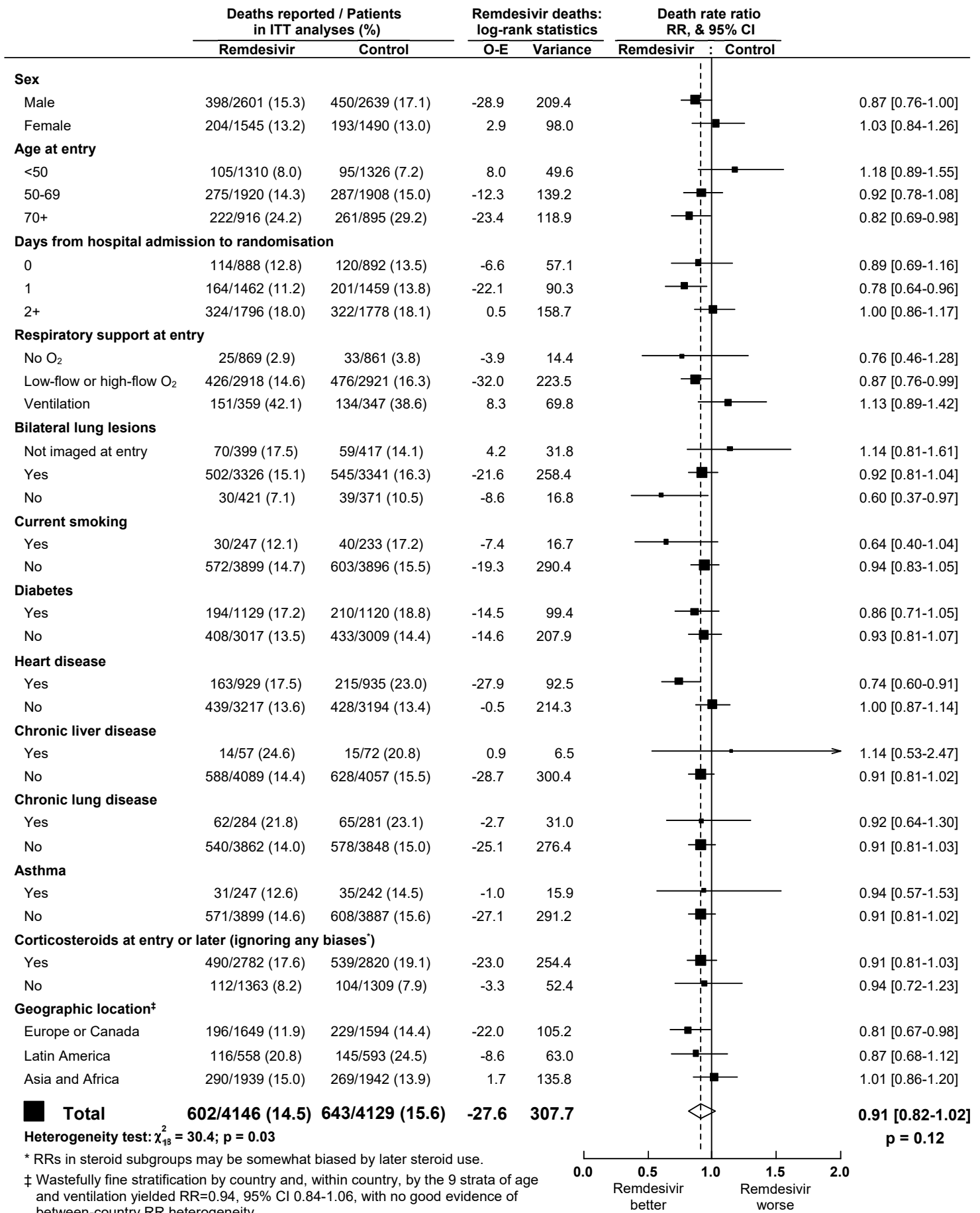


Figure S4B. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*

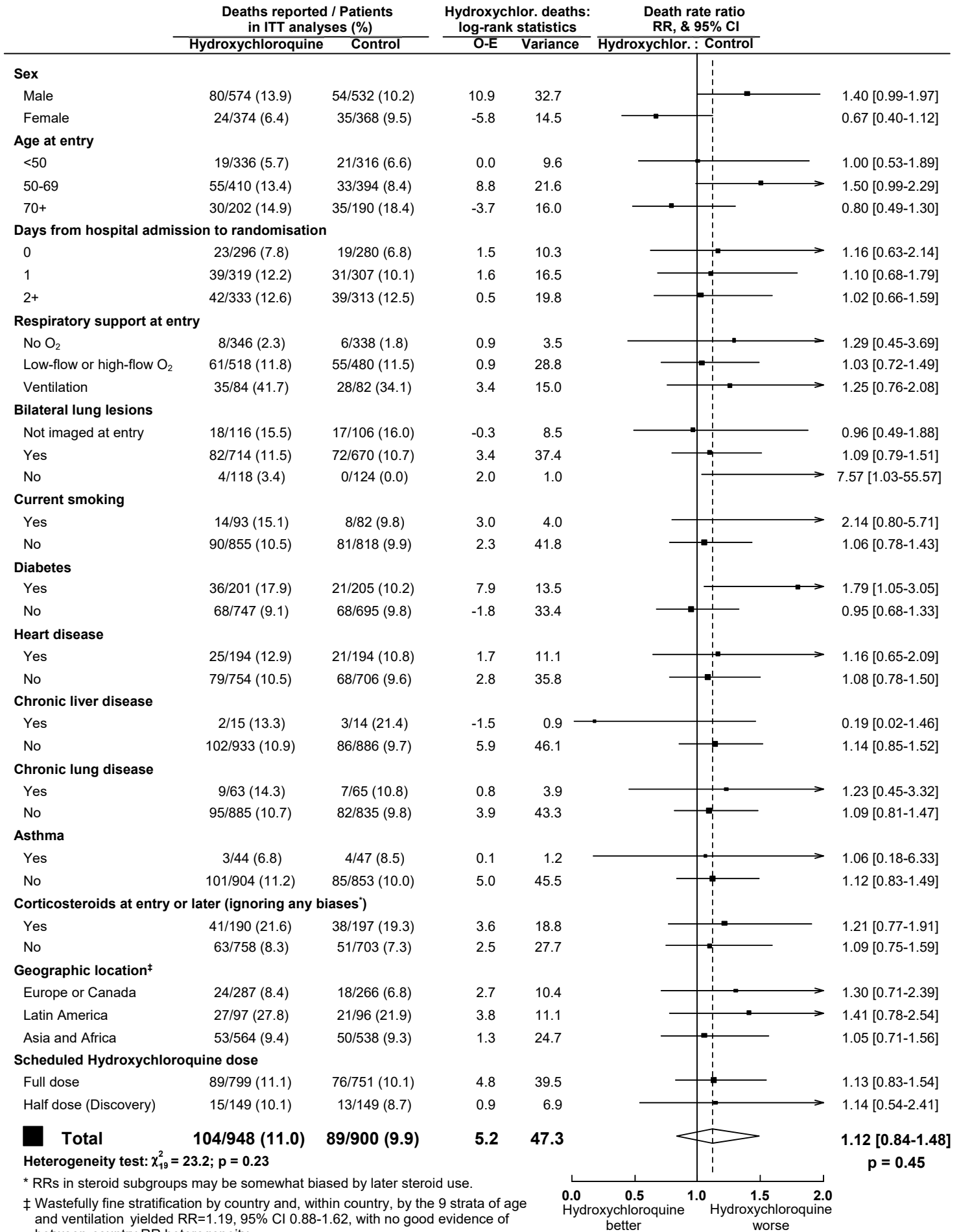


Figure S4C. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, lopinavir vs its control, by entry characteristics and by steroid use at any time*

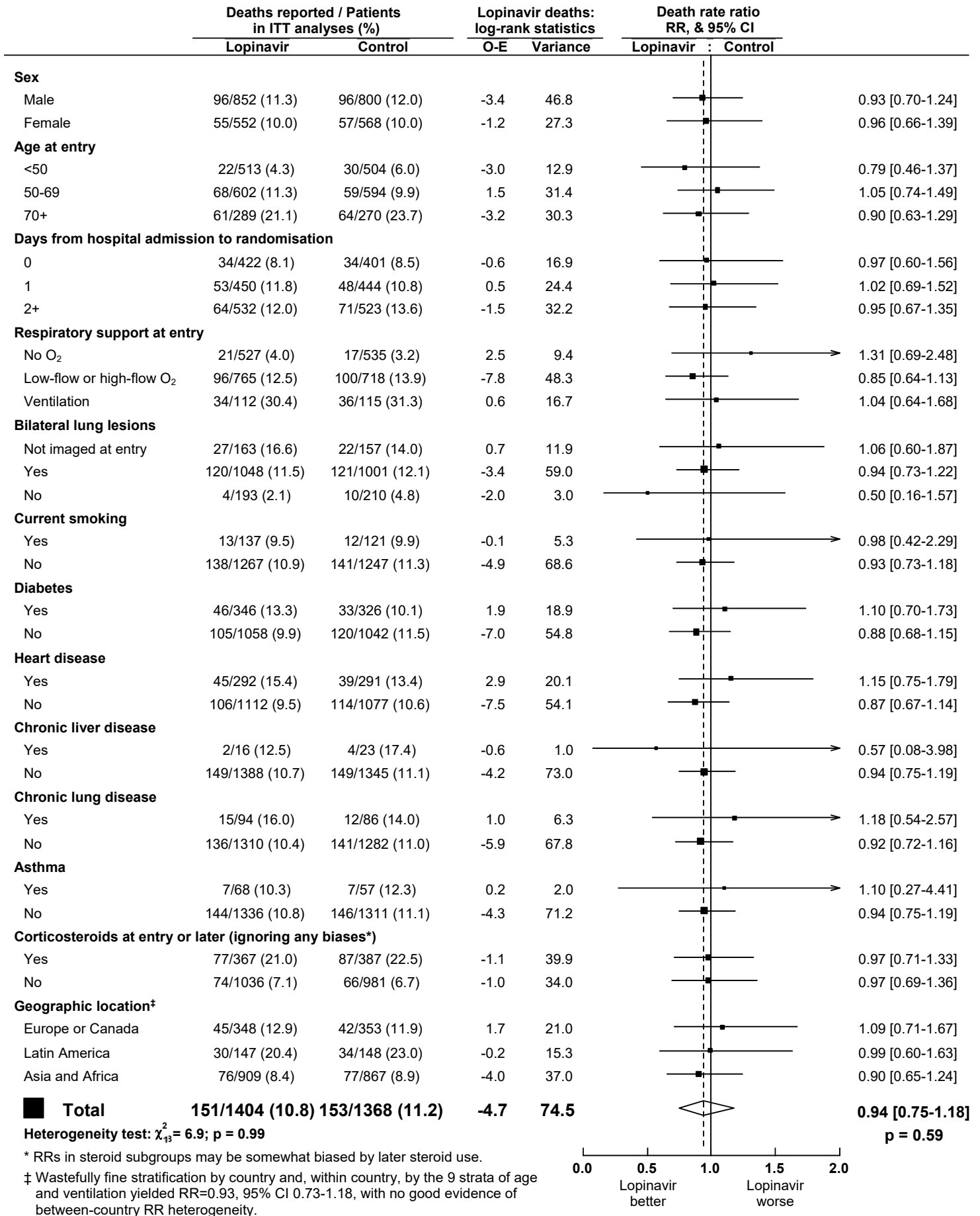


Figure S4D. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, interferon vs its control, by entry characteristics and by steroid use at any time*

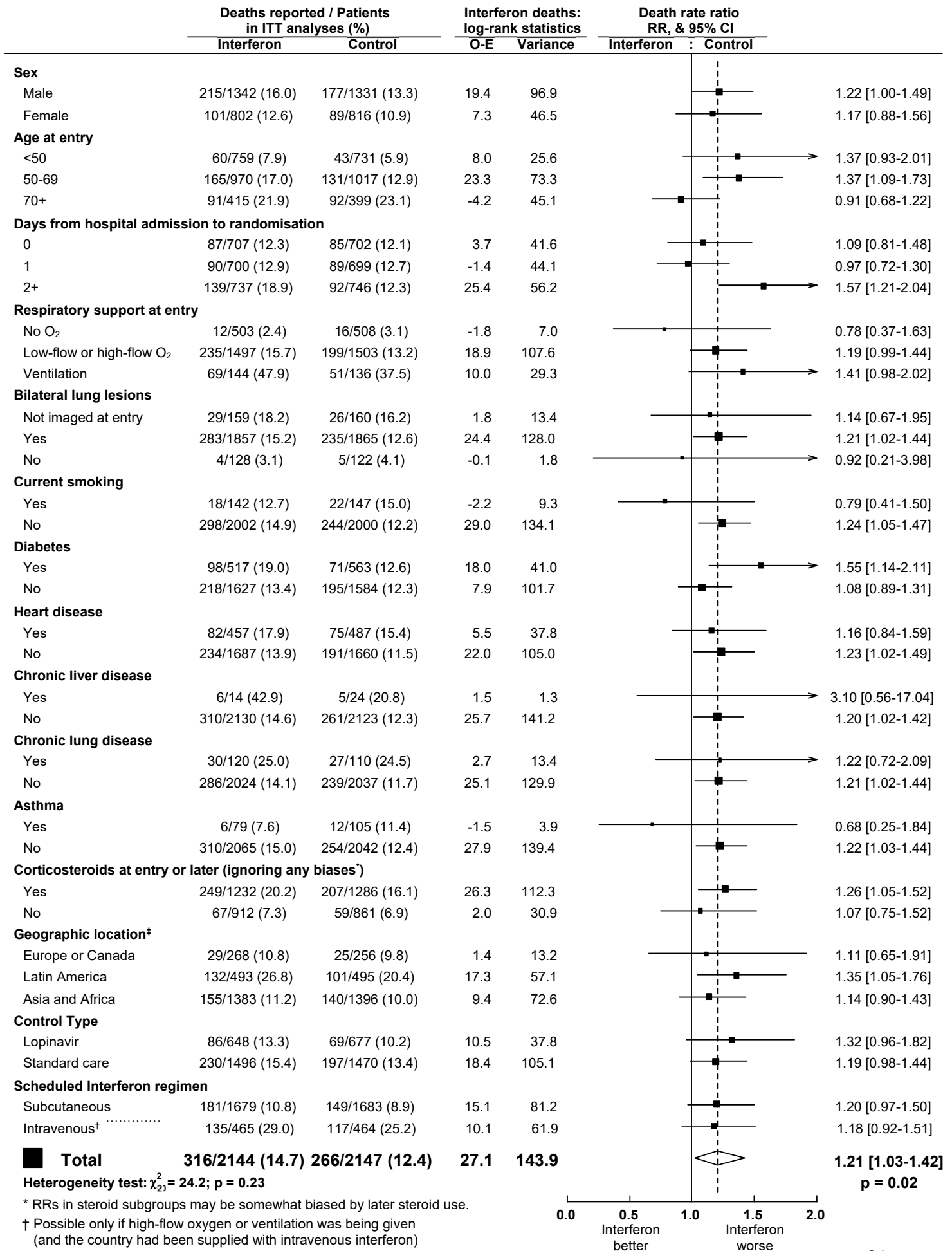


Figure S5A-S5D. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, for (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon, each vs its control

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

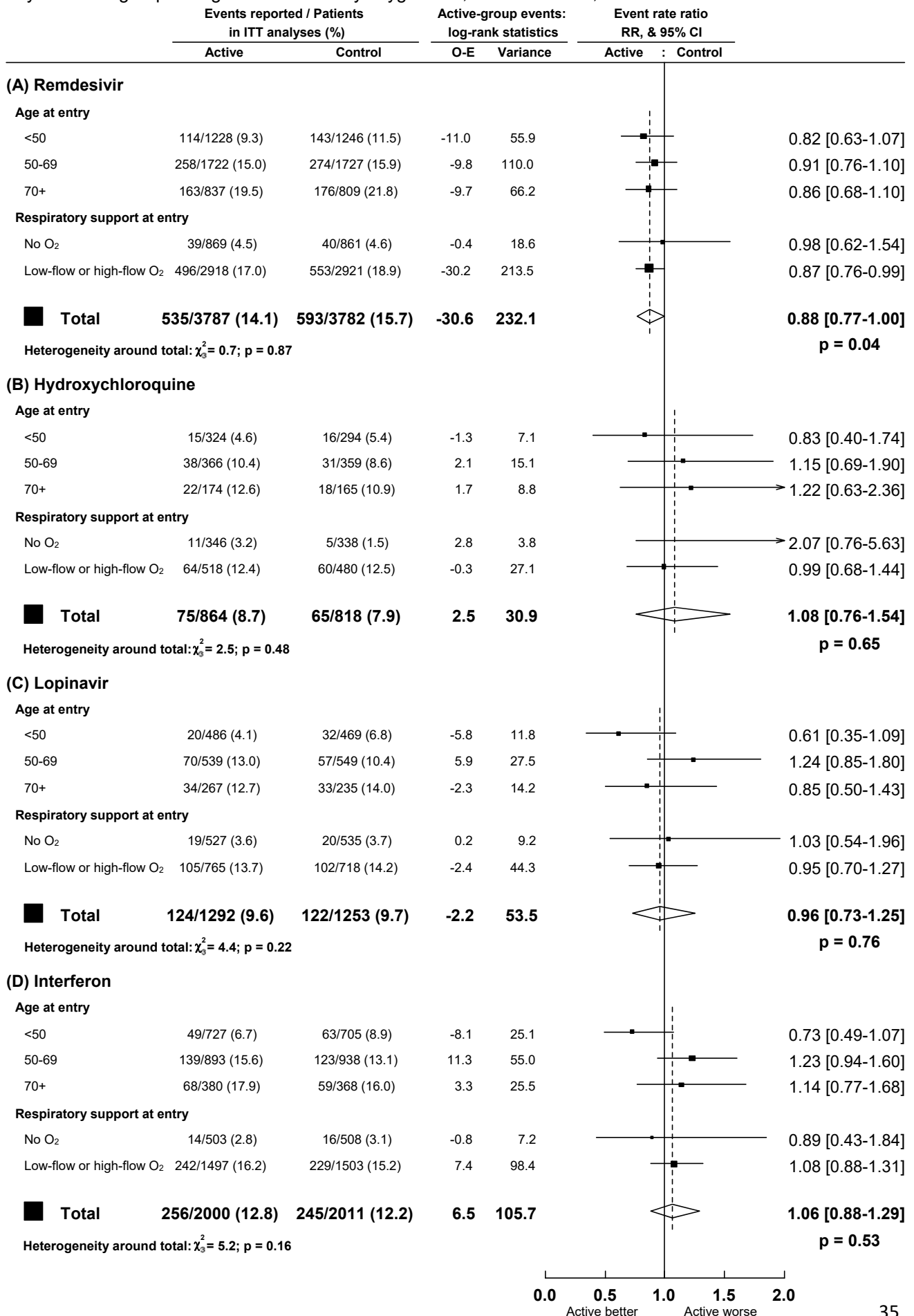


Figure S6A. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time*

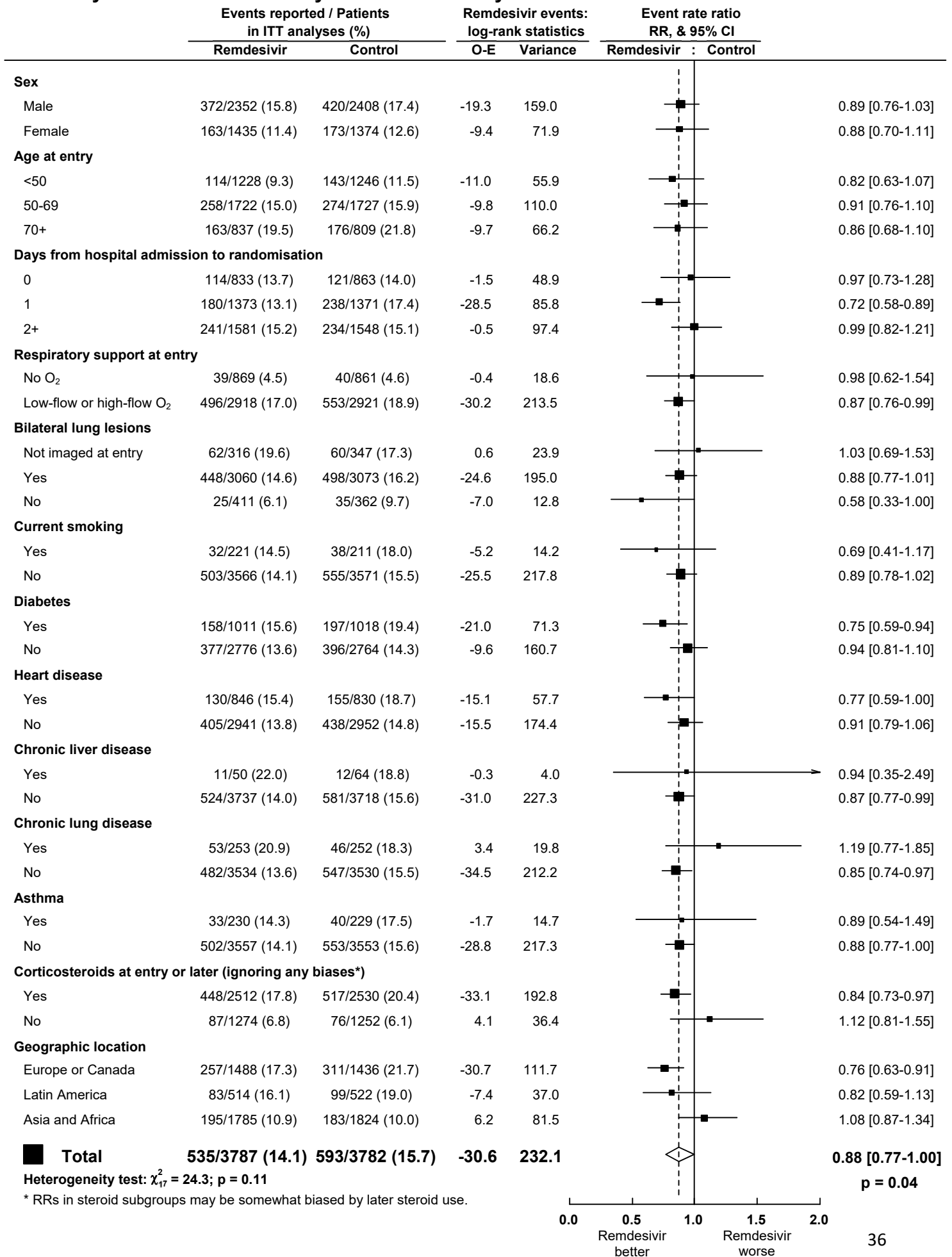


Figure S6B. Rate ratios for initiation of ventilation in those not already ventilated at entry, hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*

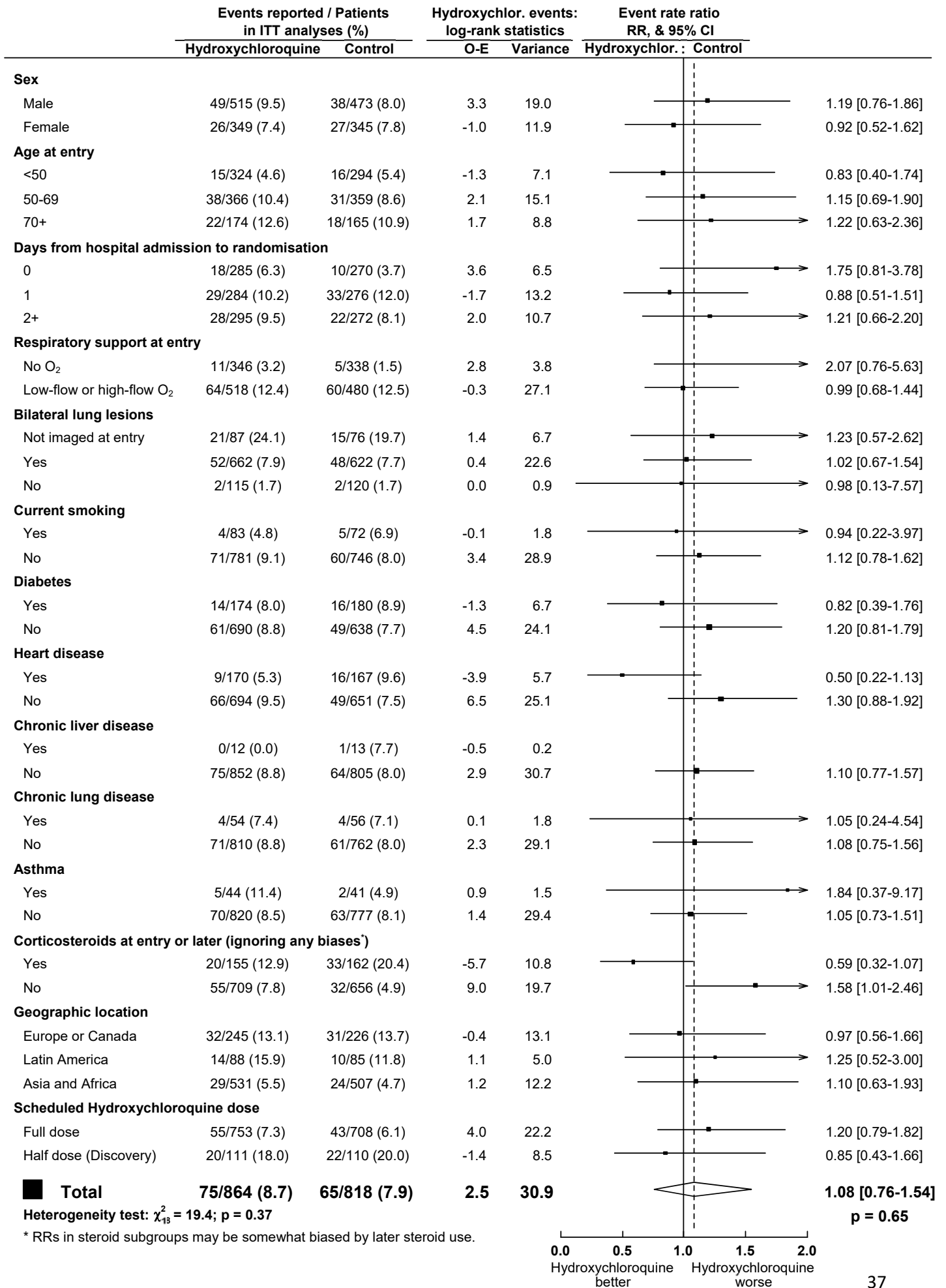


Figure S6C. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, lopinavir vs its control, by entry characteristics and by steroid use at any time*

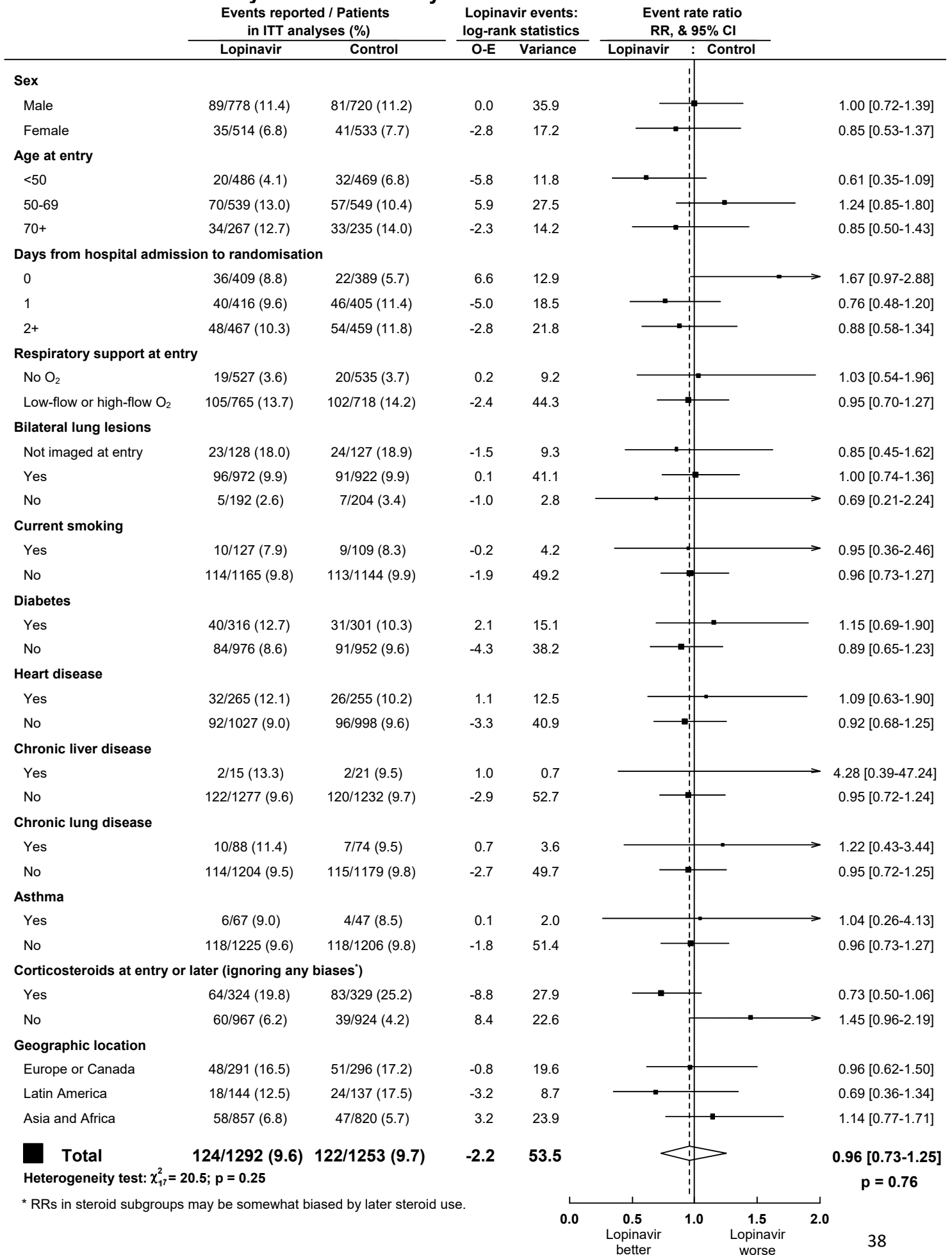


Figure S6D. Rate ratios for initiation of ventilation among those not already ventilated at entry, stratified by age and respiratory support at entry, interferon vs its control, by entry characteristics and by steroid use at any time*

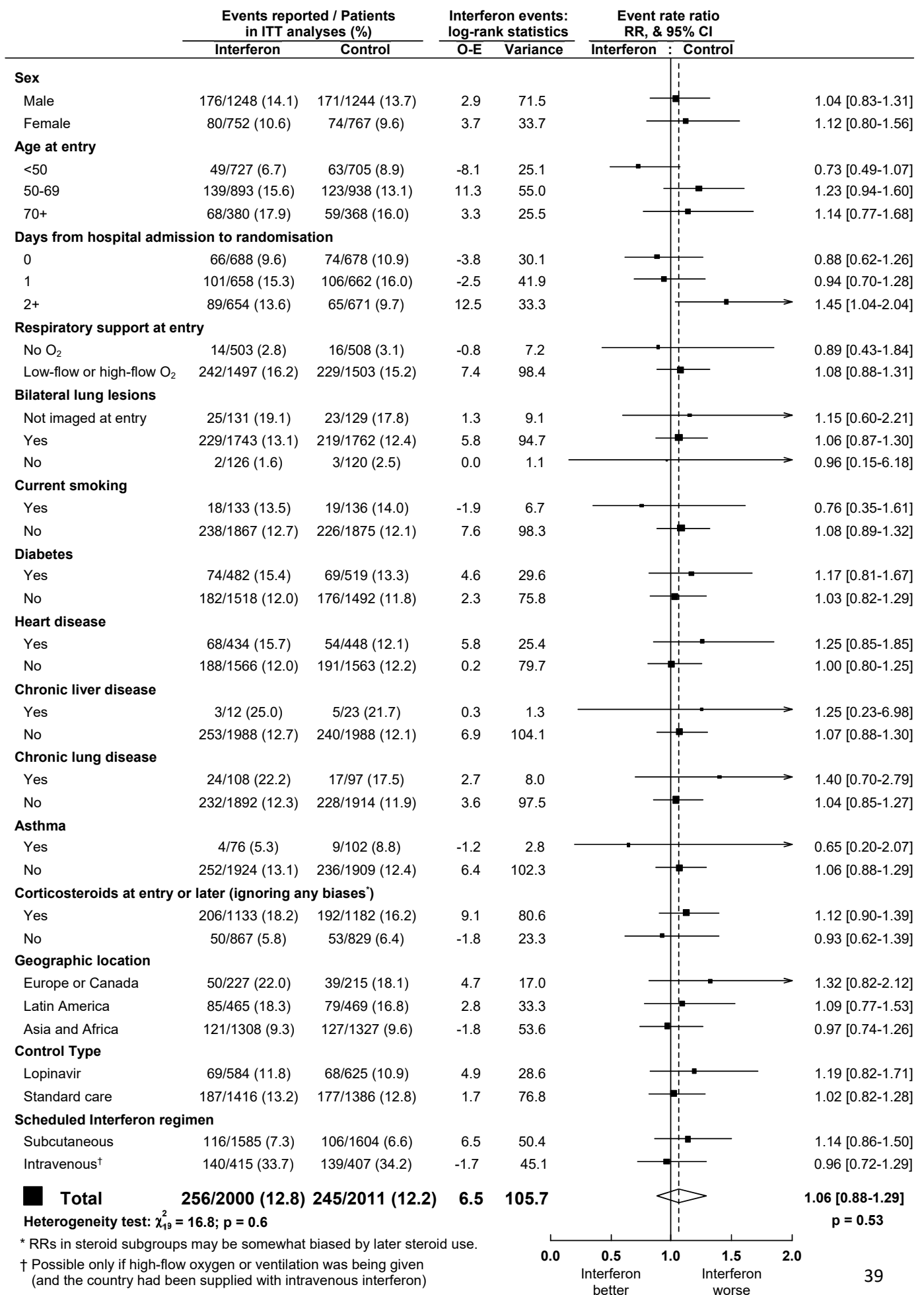


Figure S7A-D. RRs for the composite of death in hospital or initiation of ventilation: effects of (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon, each vs its control

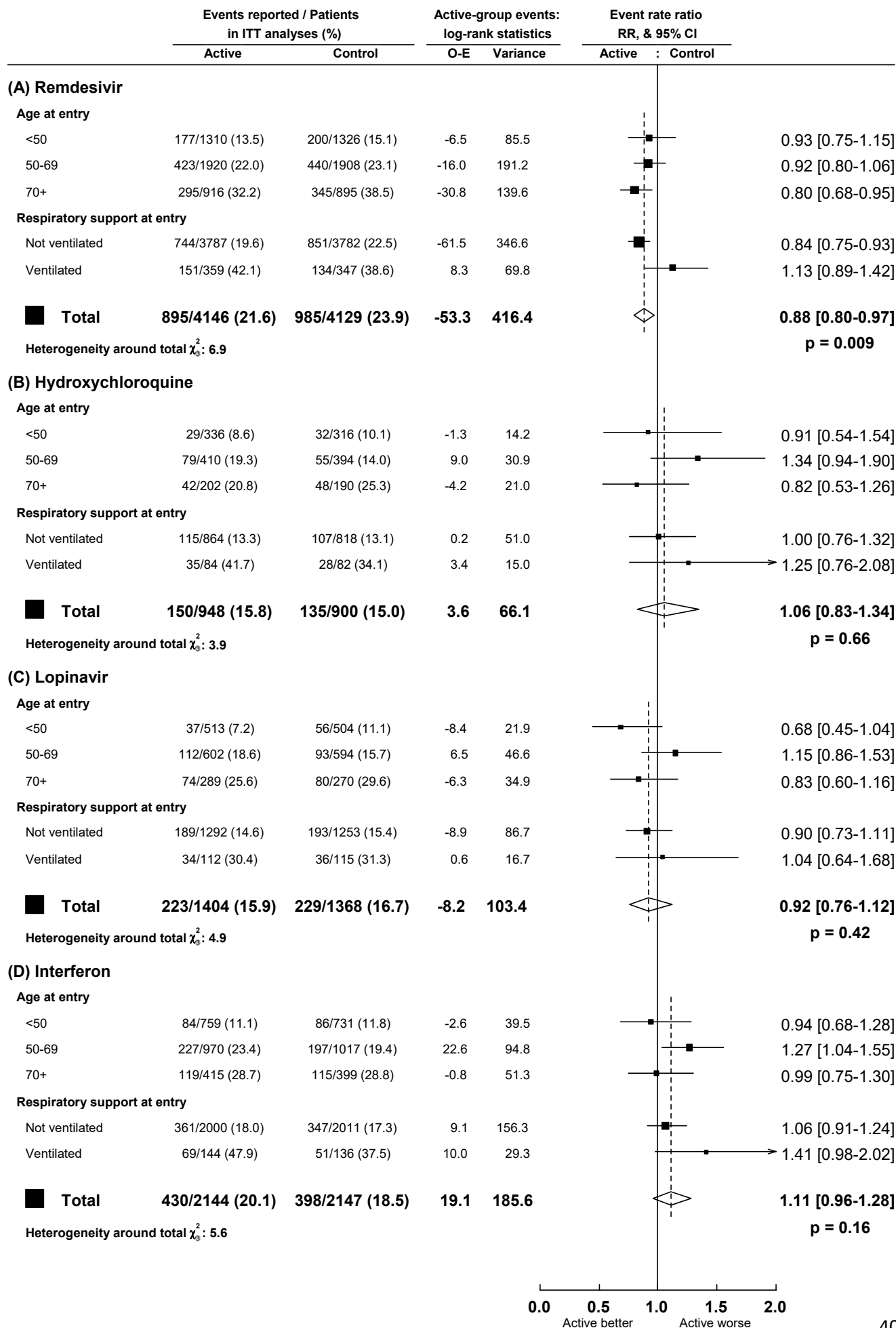


Figure S8A. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: remdesivir vs its control, by entry characteristics and by steroid use at any time*

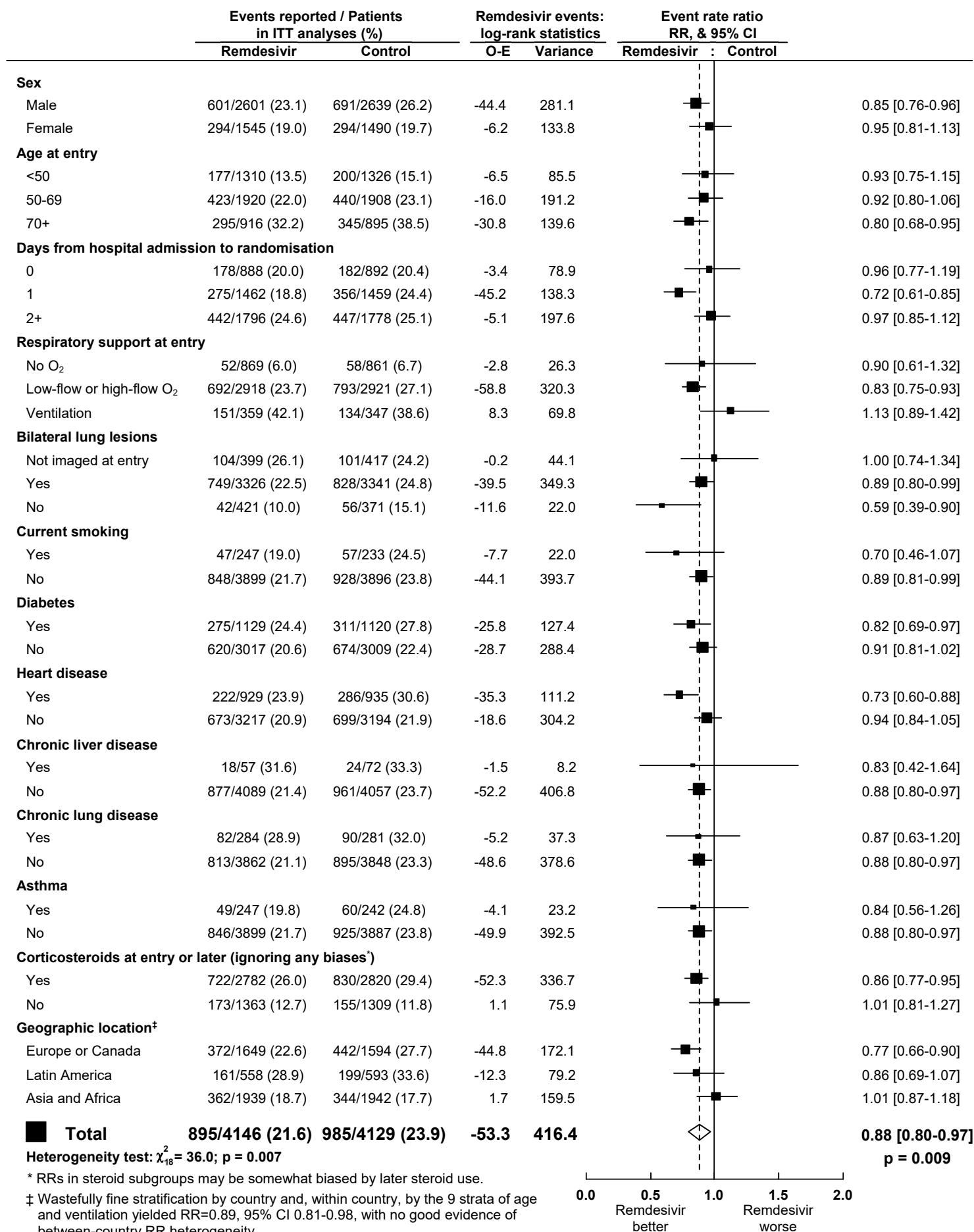


Figure S8B. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*

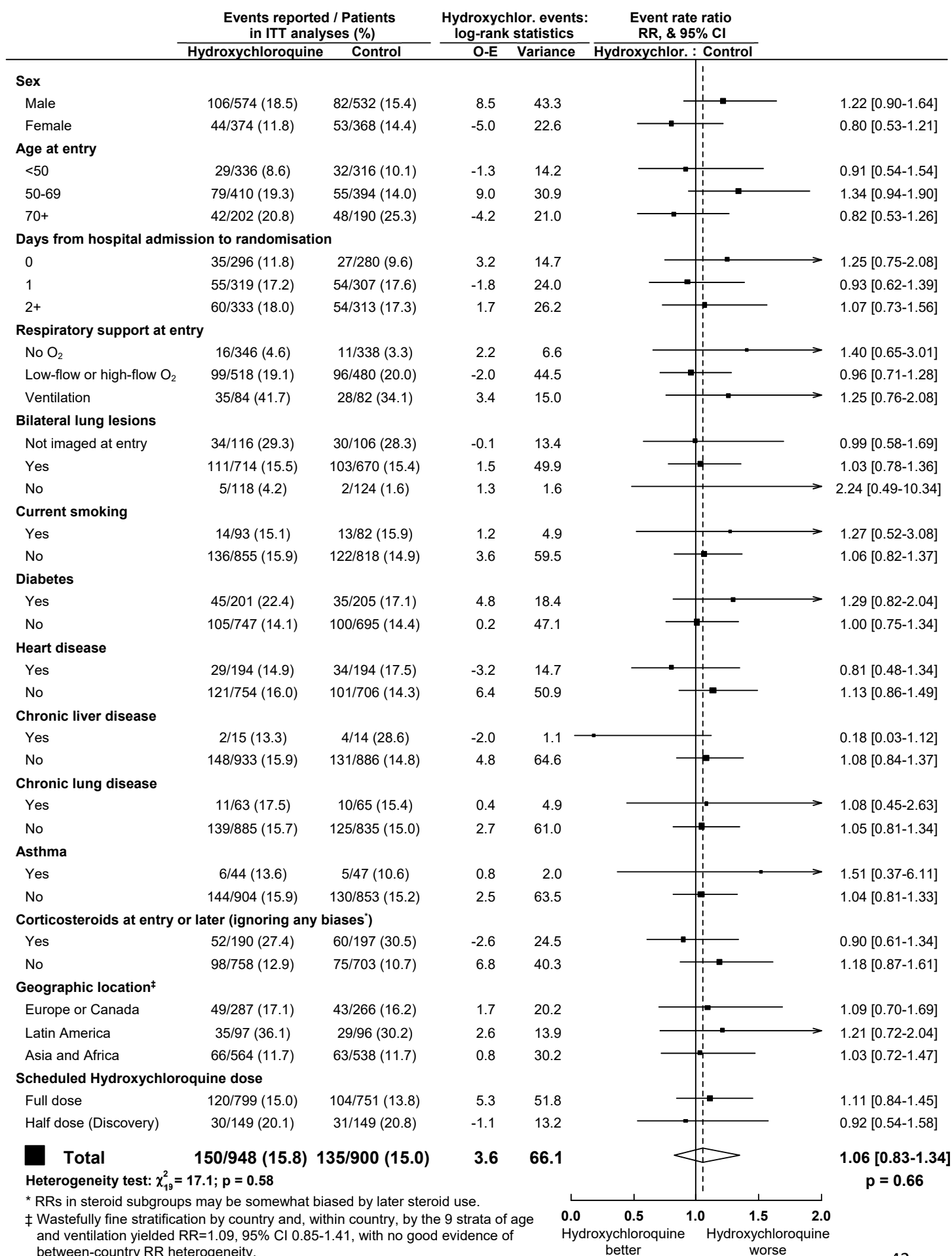
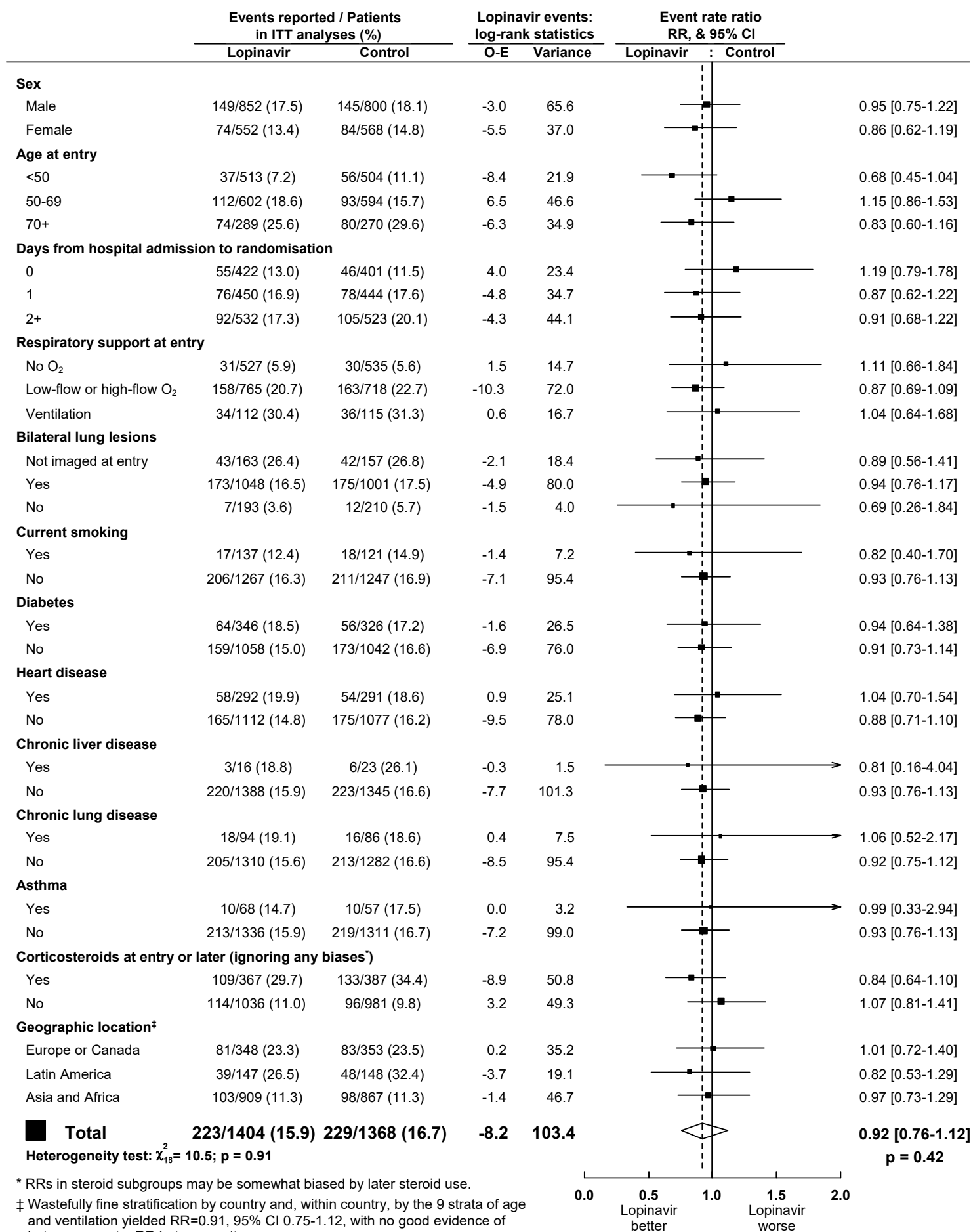


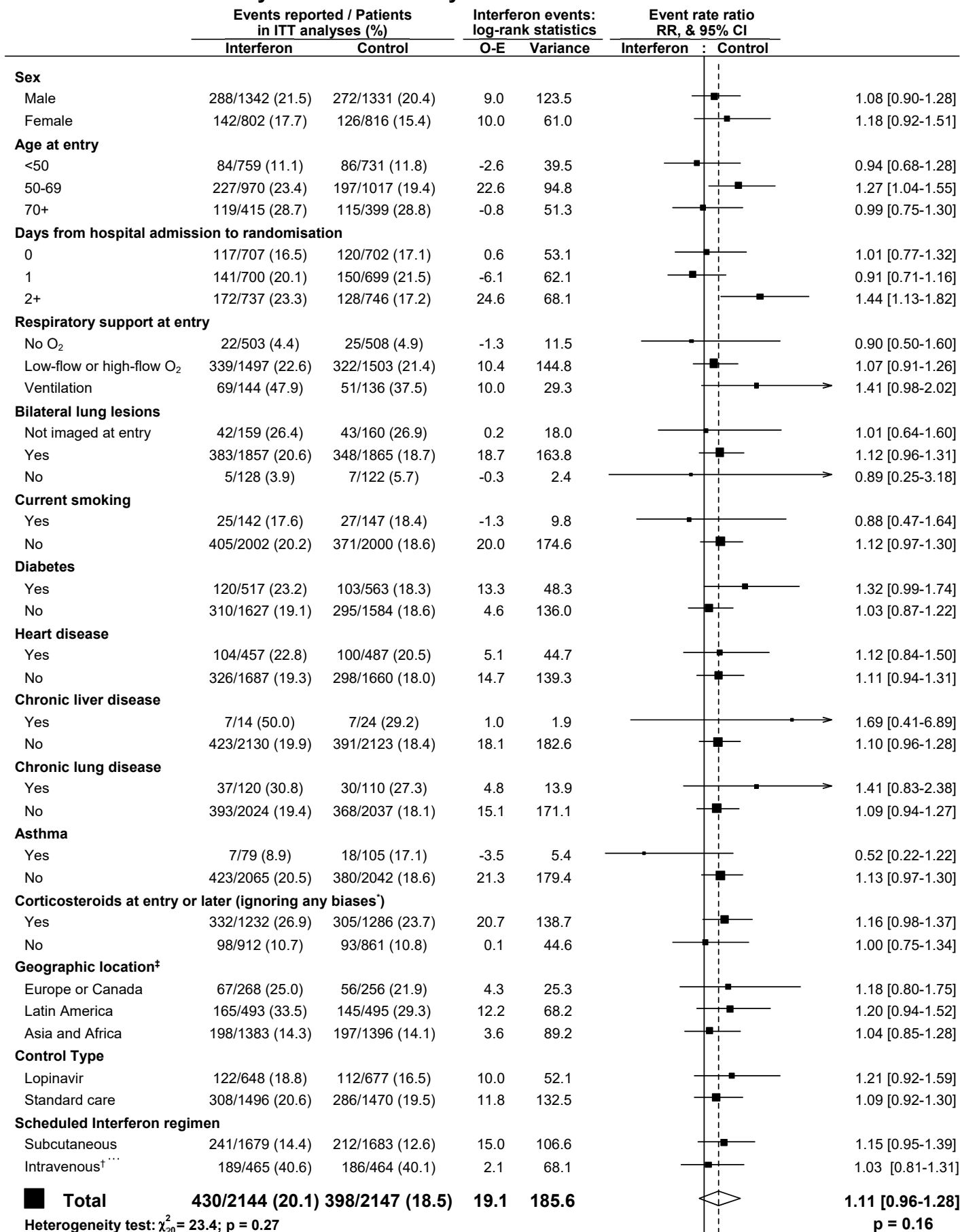
Figure S8C. RRs for the composite of death in hospital or initiation of ventilation, stratified by age and respiratory support at entry: lopinavir vs its control, by entry characteristics and by steroid use at any time*



* 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 O₂, or low-flow / high-flow O₂) at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

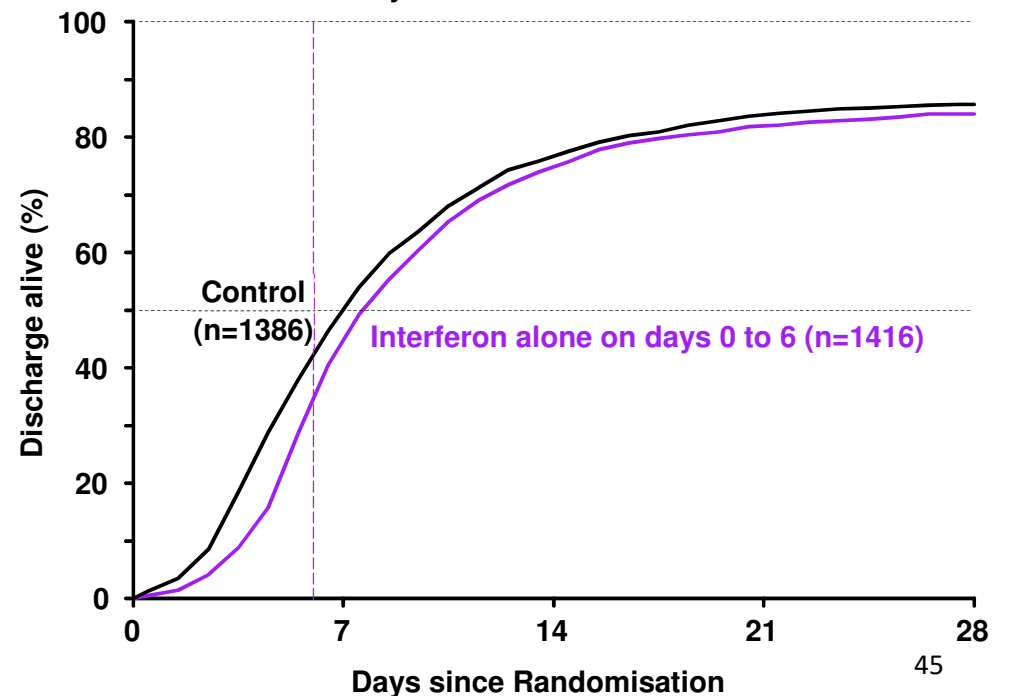
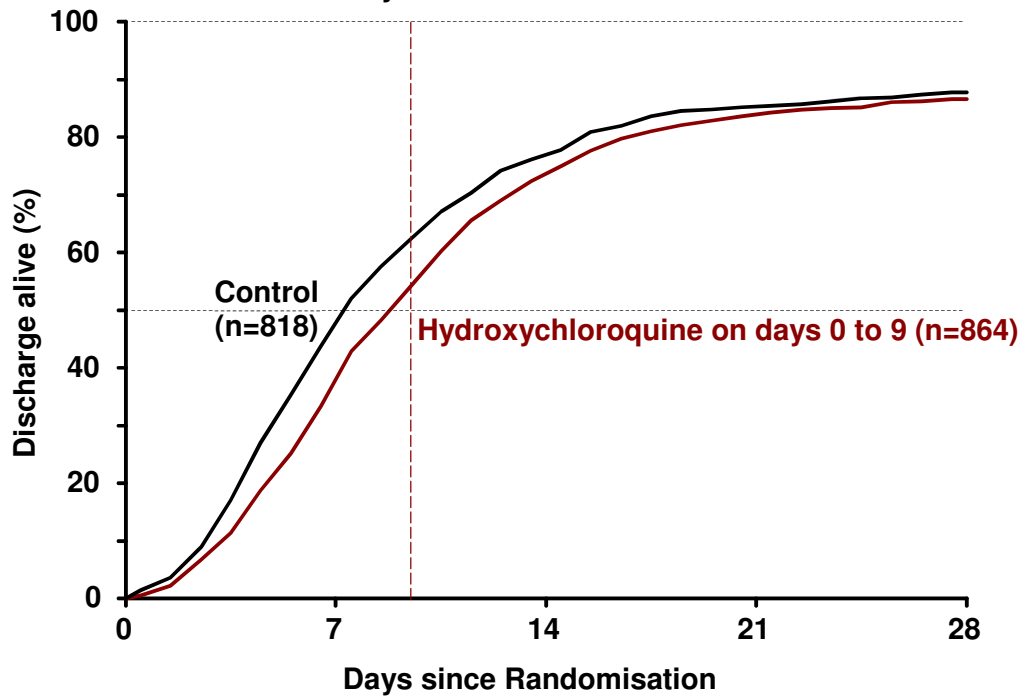
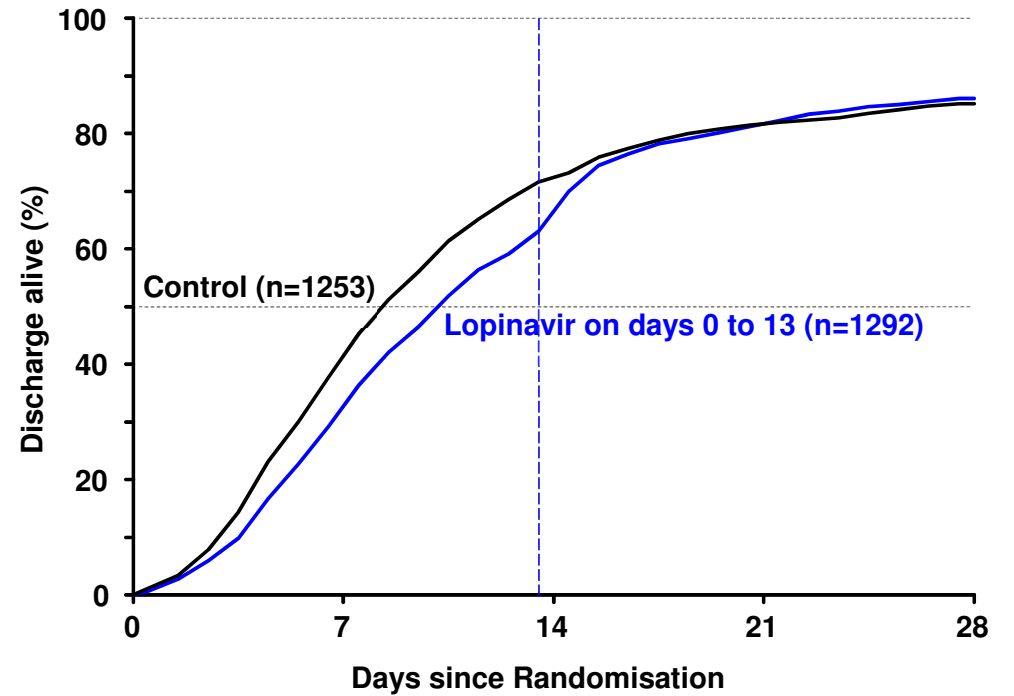
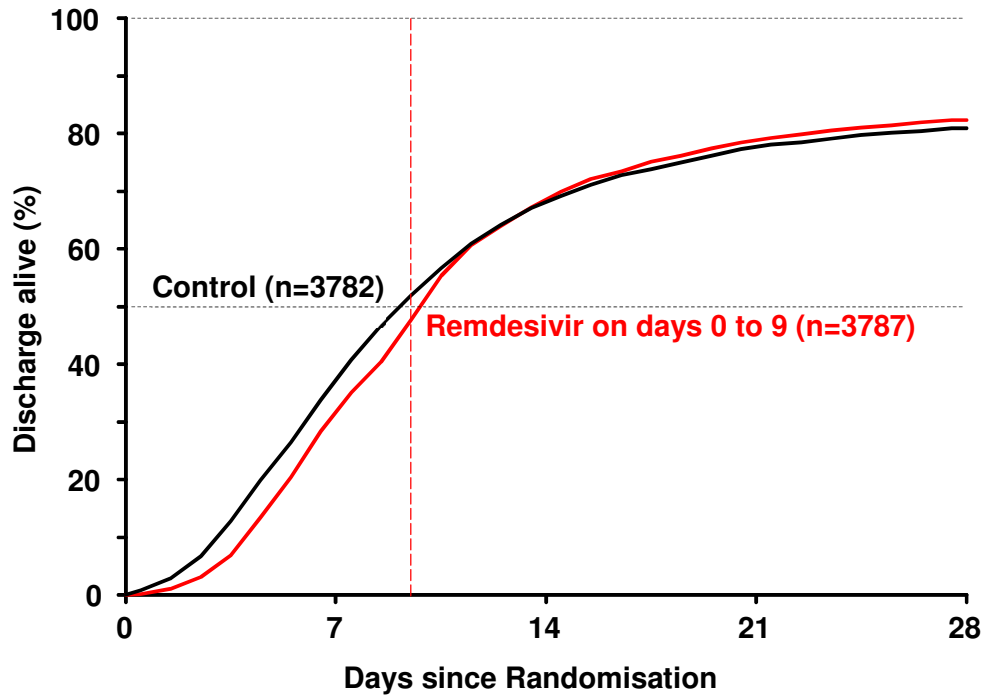


Figure S10A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own control - effects on time to discharge alive in patients already being ventilated at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

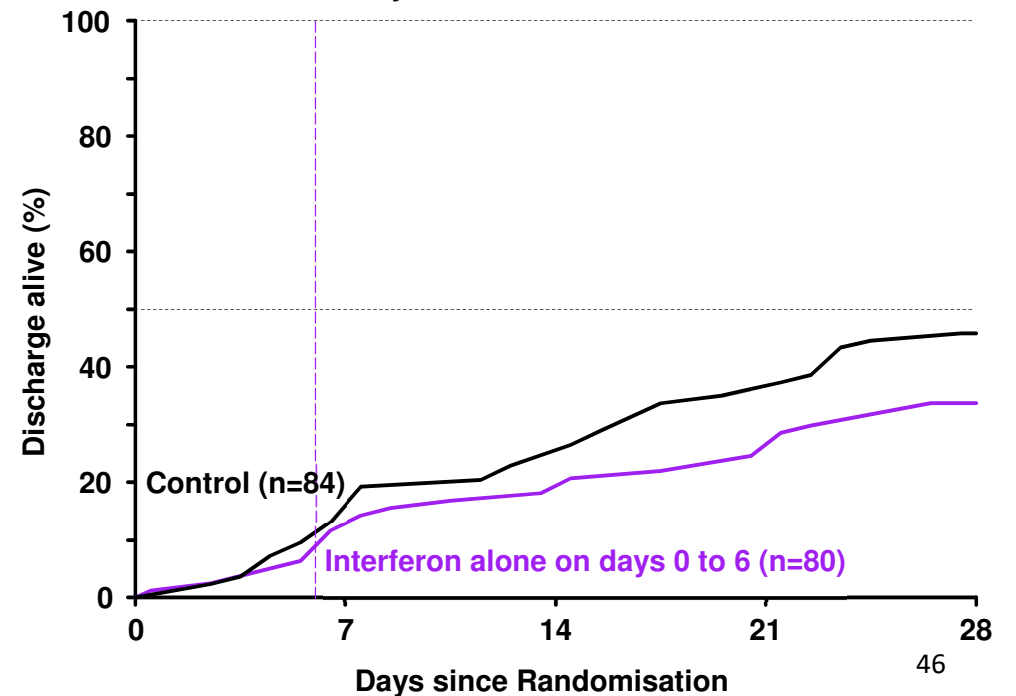
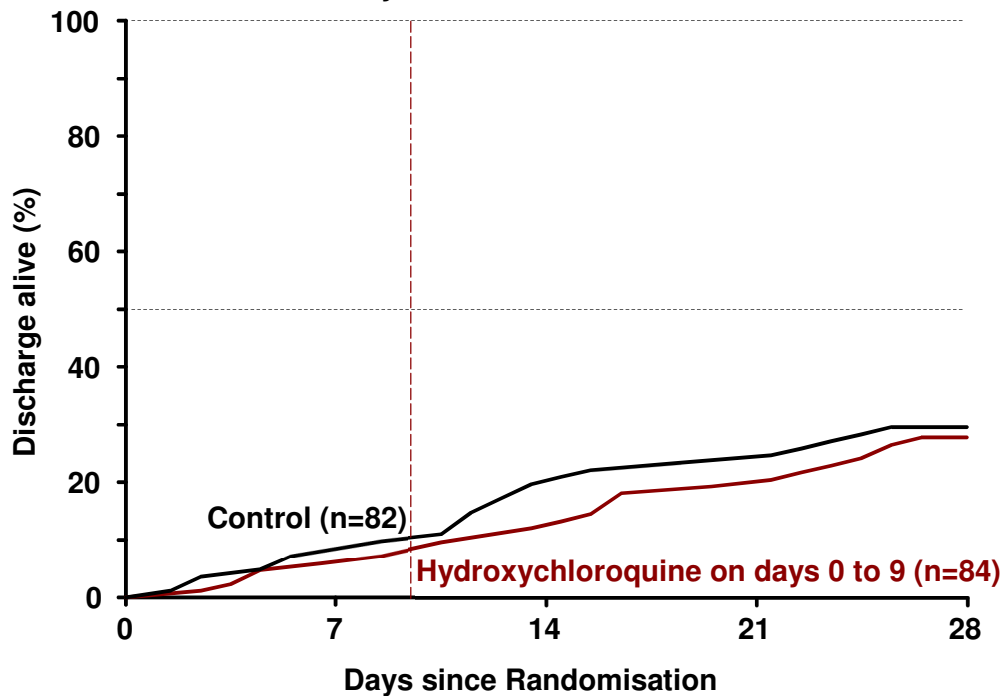
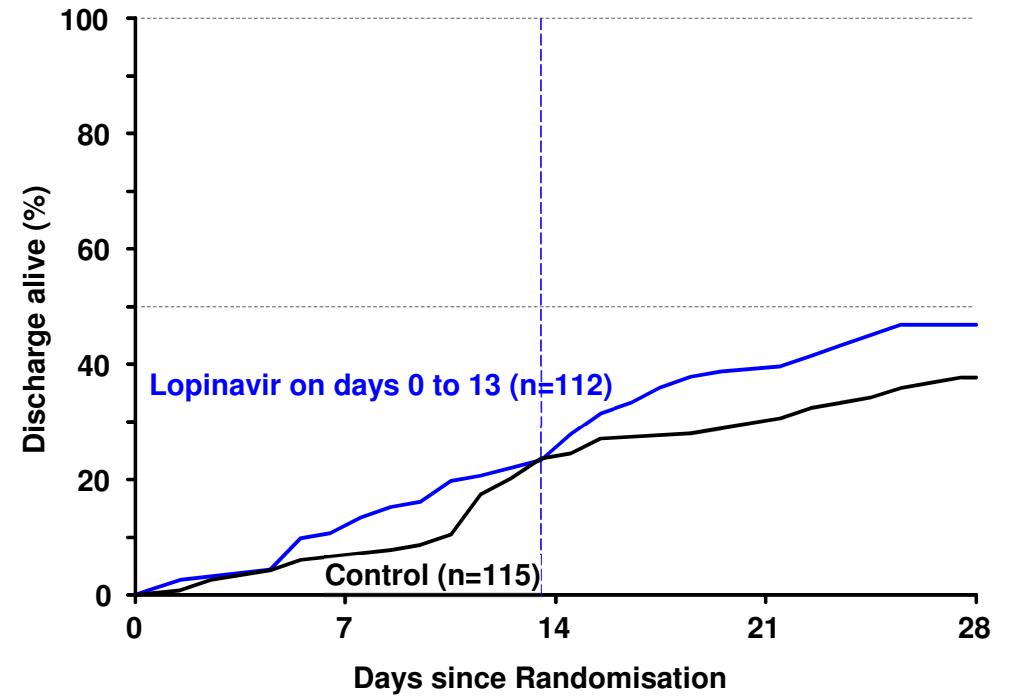
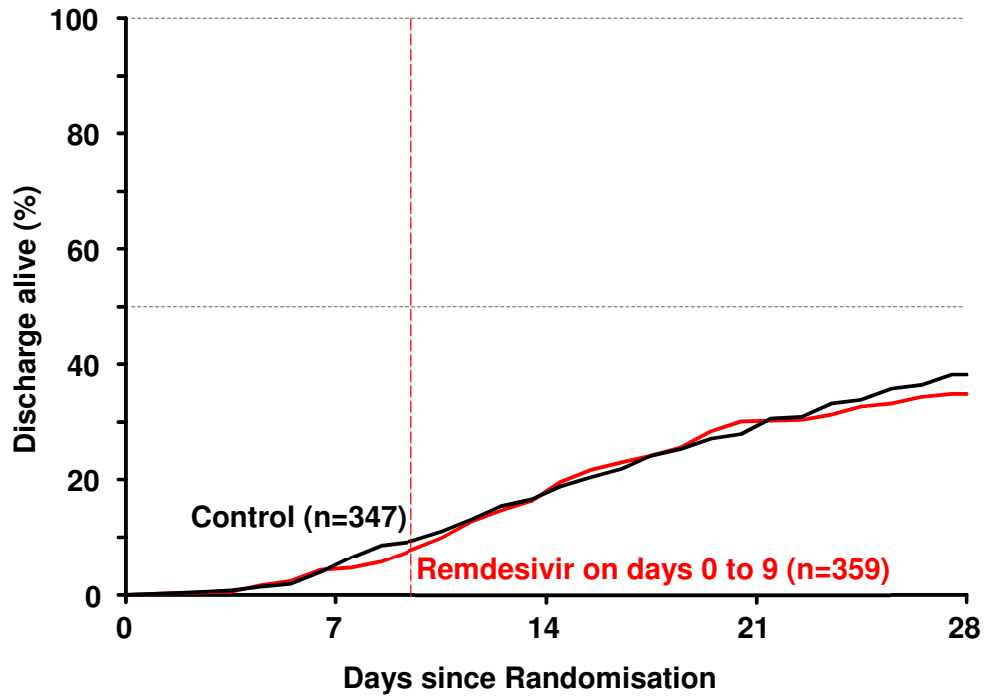


Figure S11A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients being given low-flow O₂ / high-flow O₂ at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

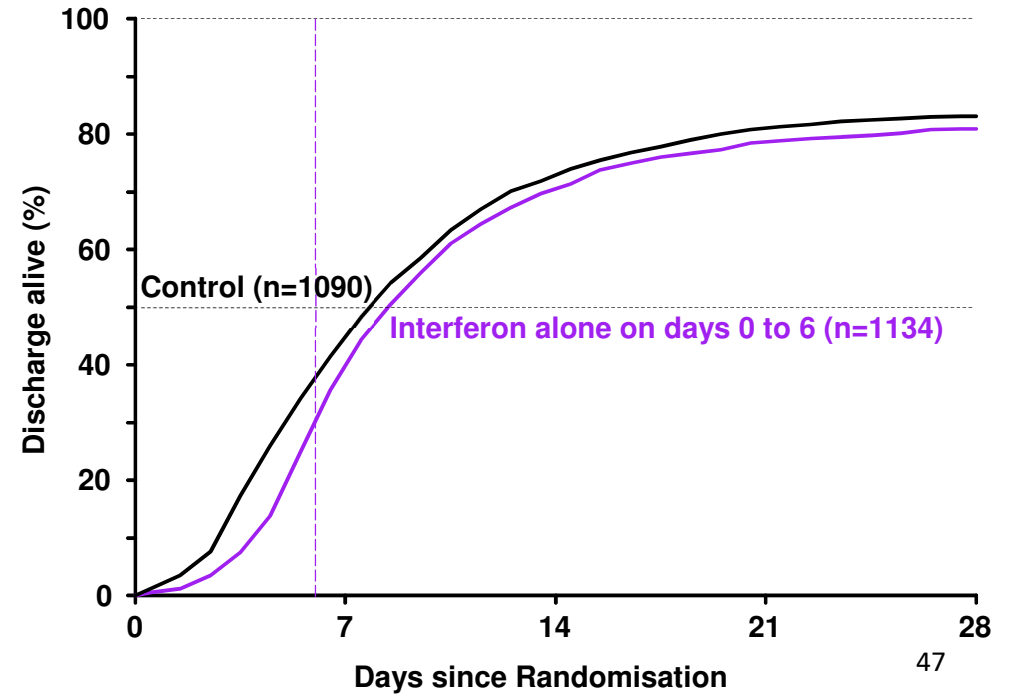
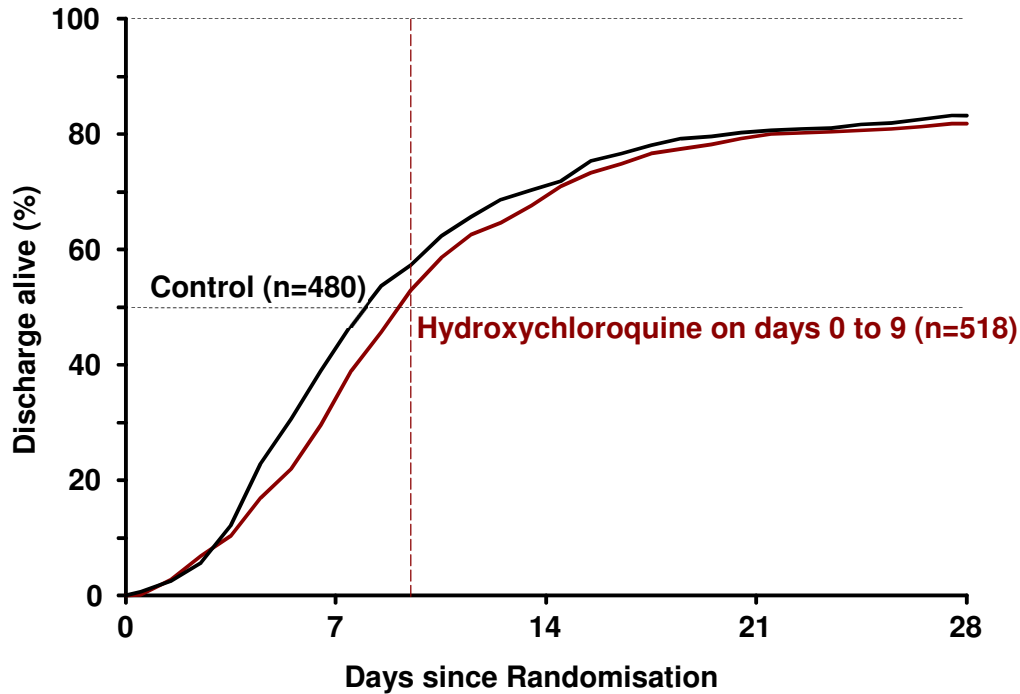
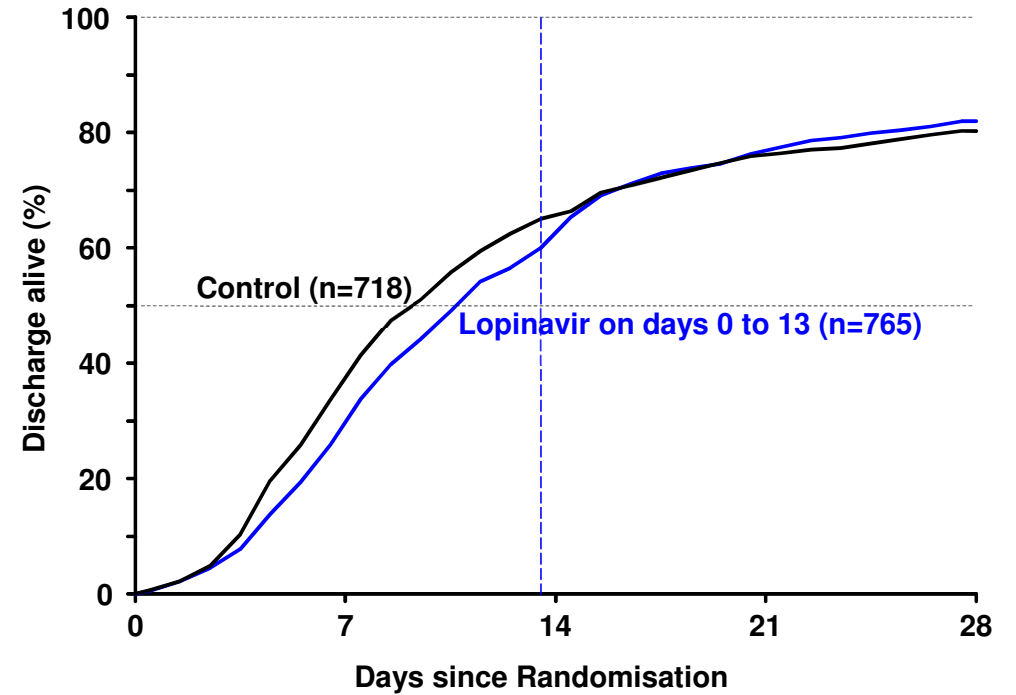
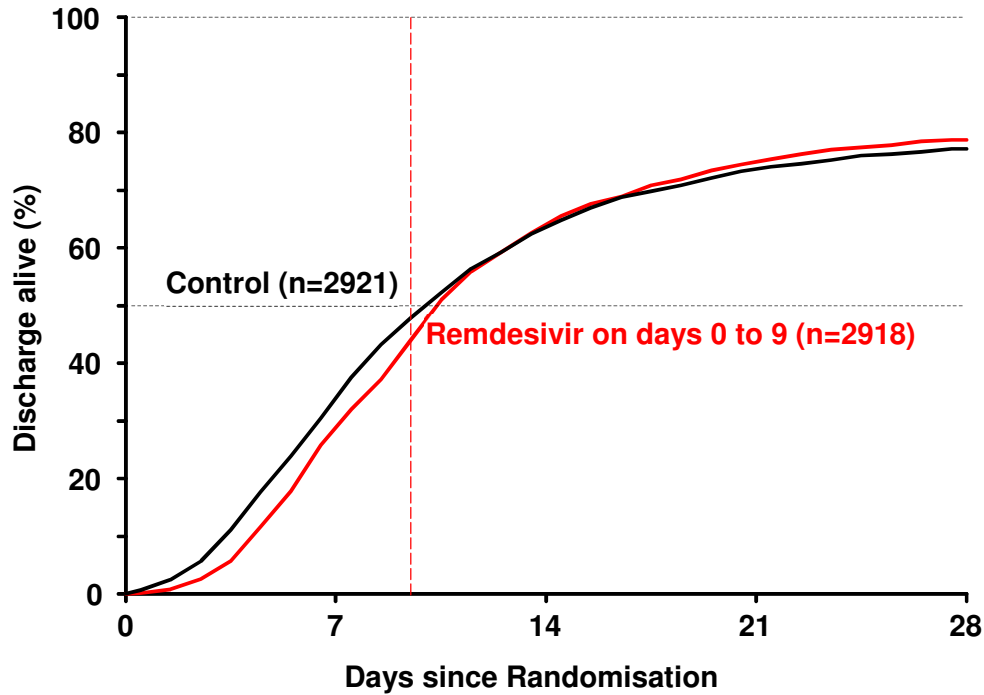


Figure S12A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients being given no O₂ at entry (Approximates "mild-to-moderate" in ACTT-1 & FDA reports.) Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

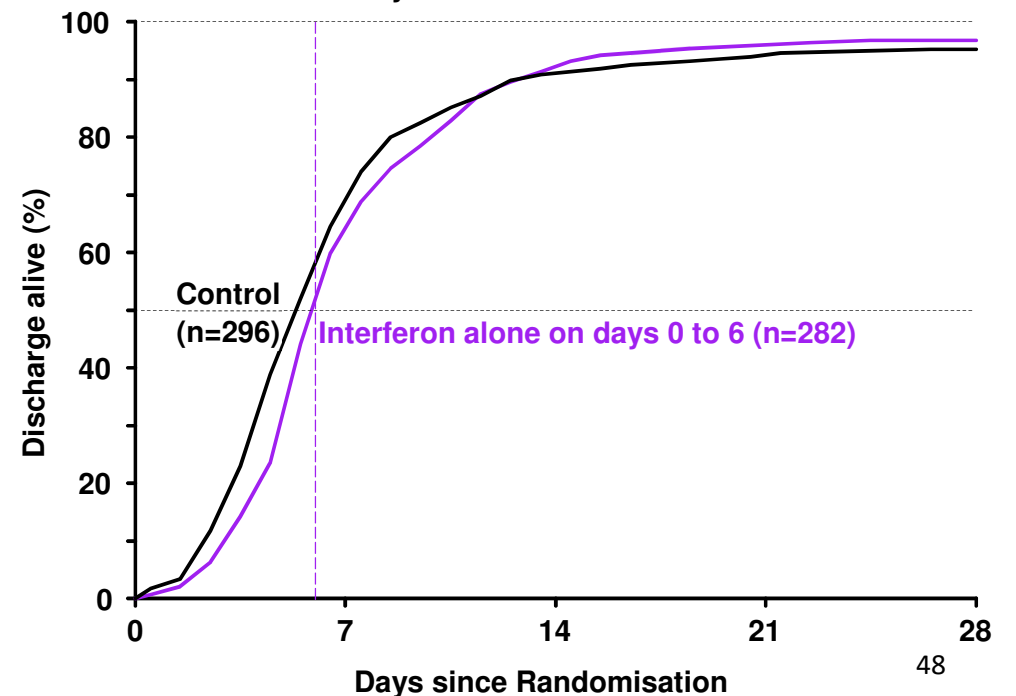
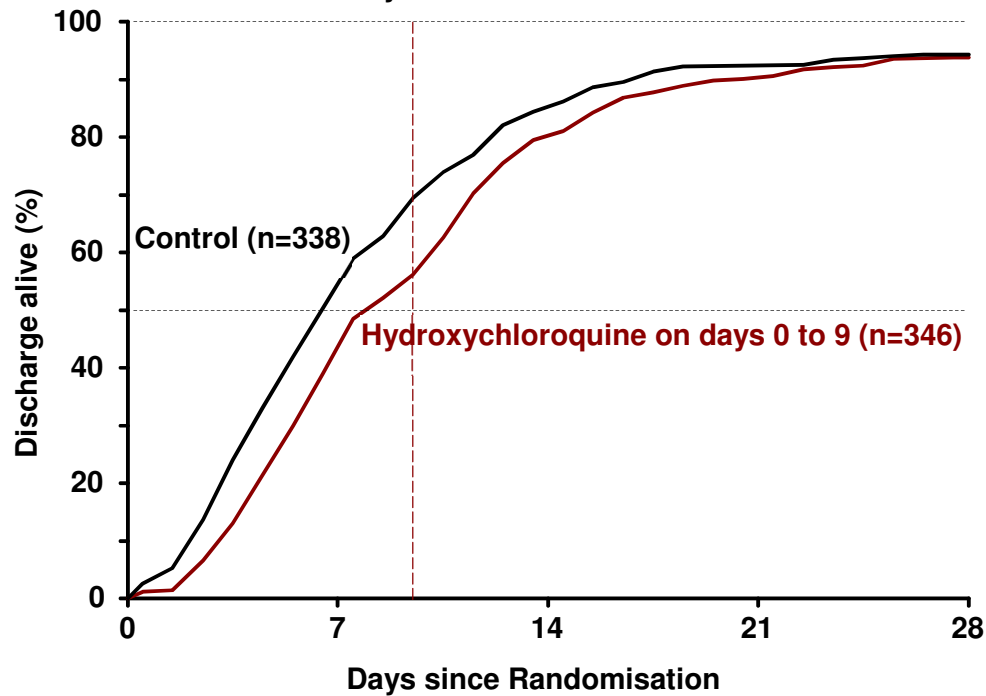
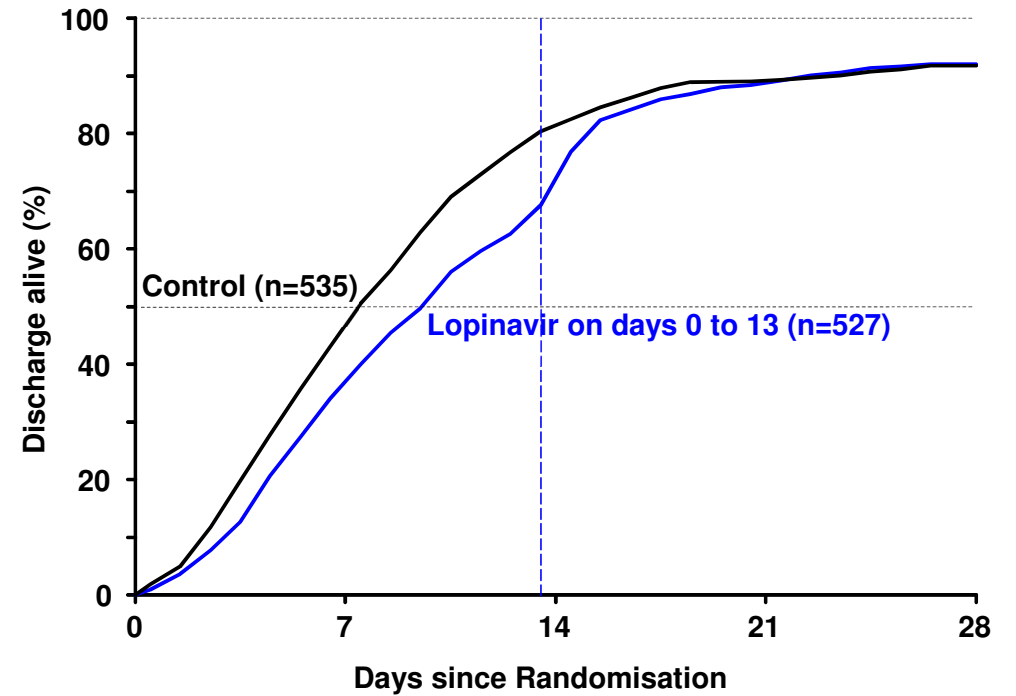
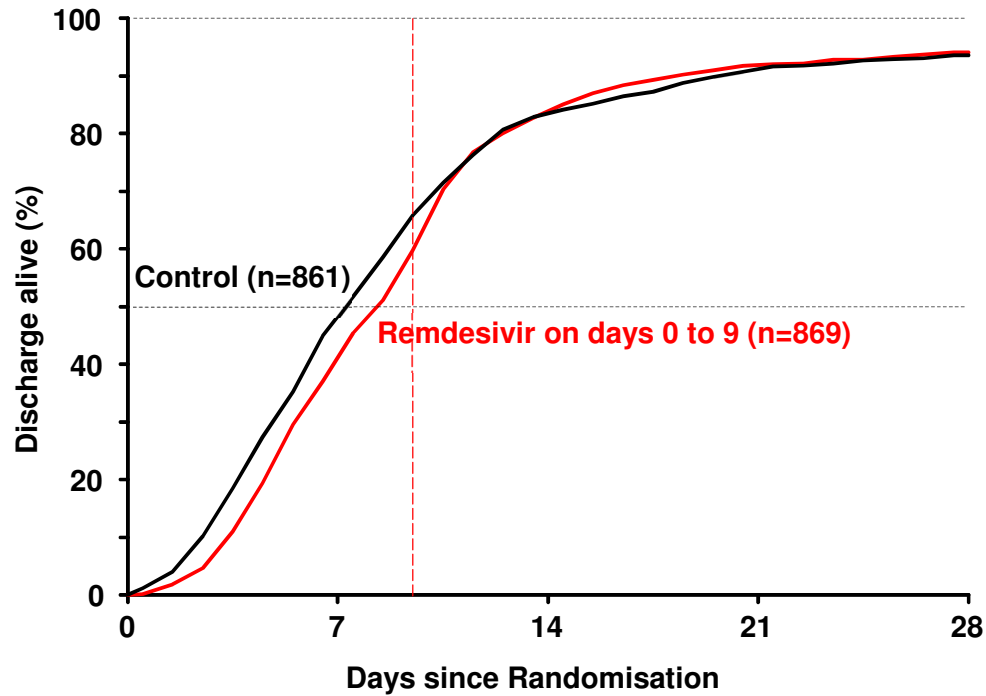


Figure S13A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients on low/high-flow O₂ or ventilated Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

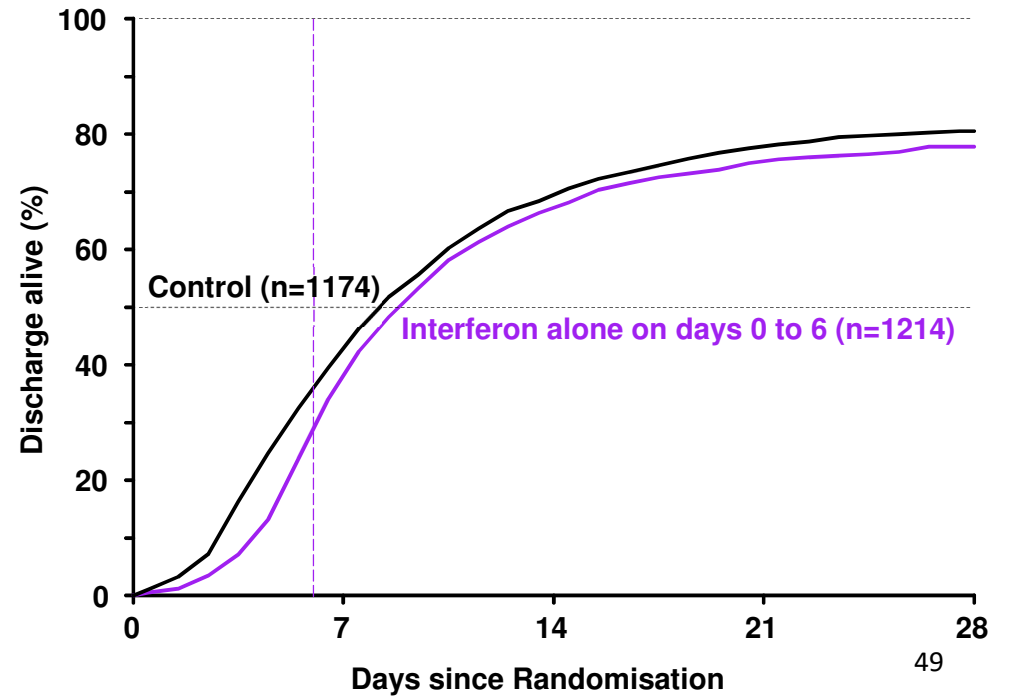
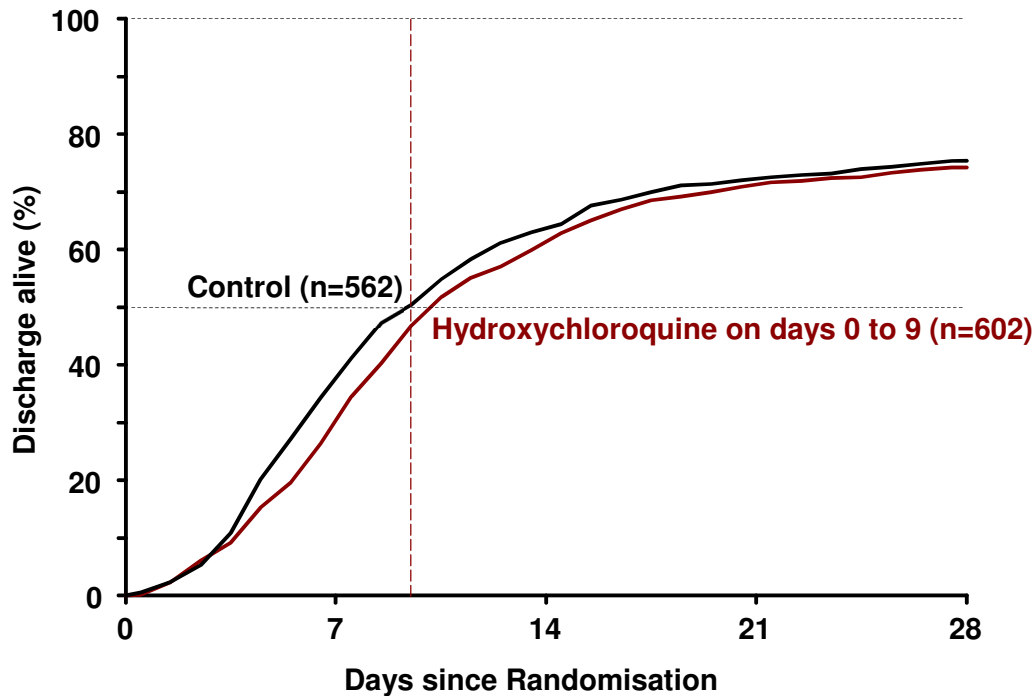
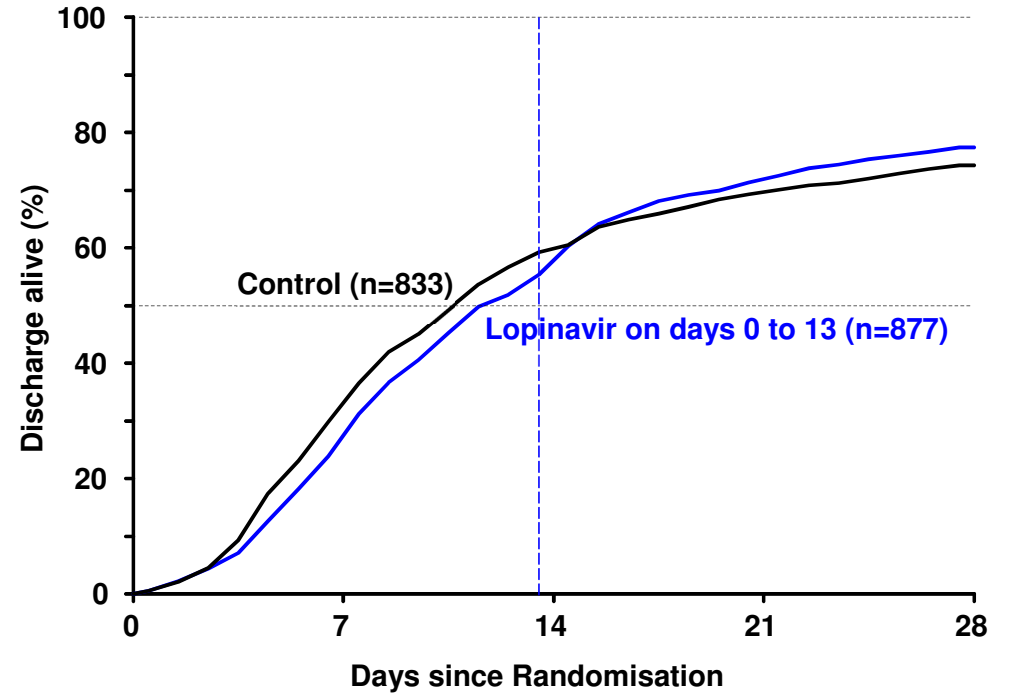
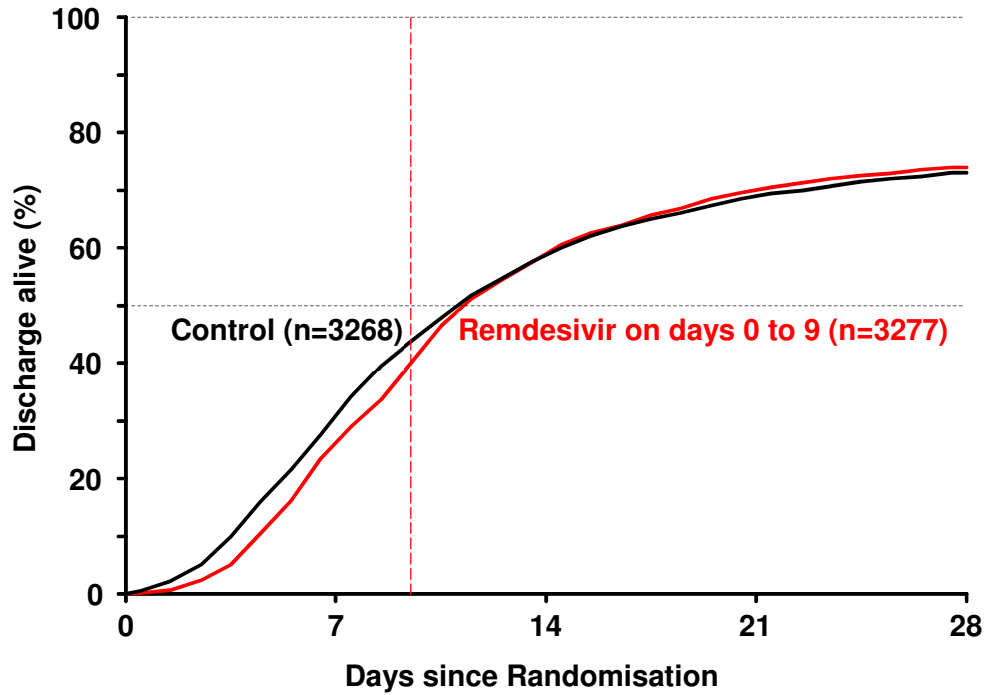


Figure S14A-D. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in all patients, regardless of respiratory support at entry Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

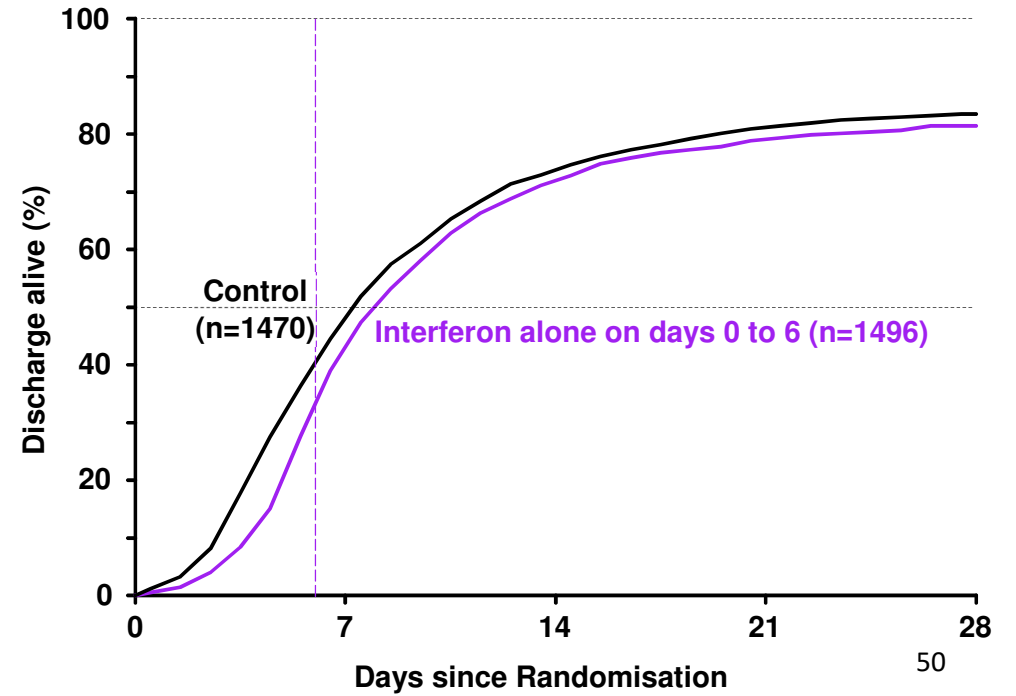
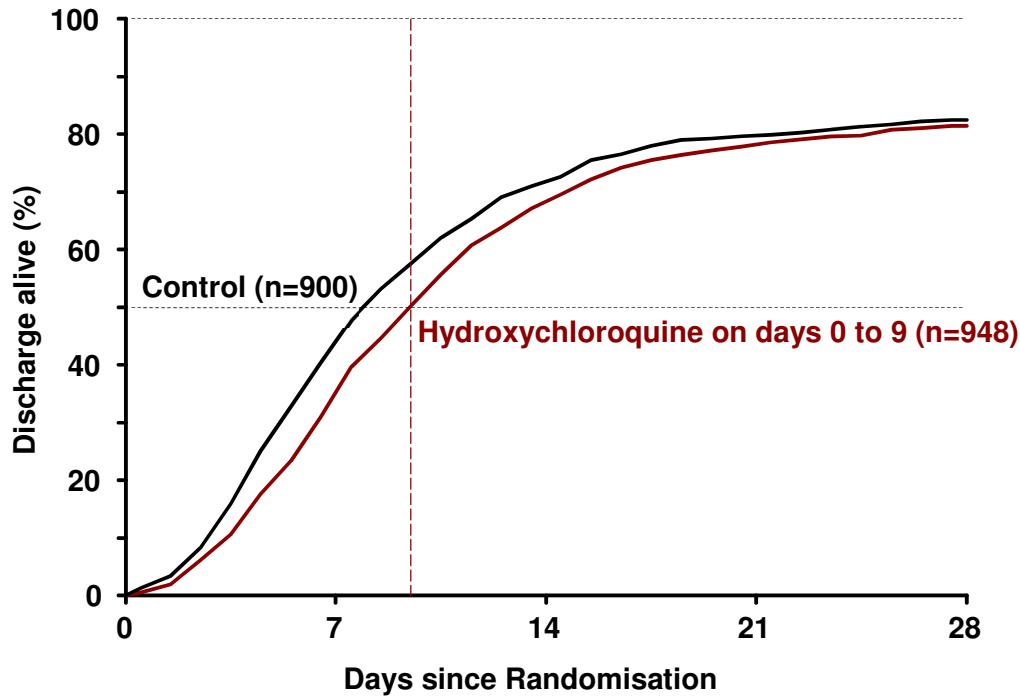
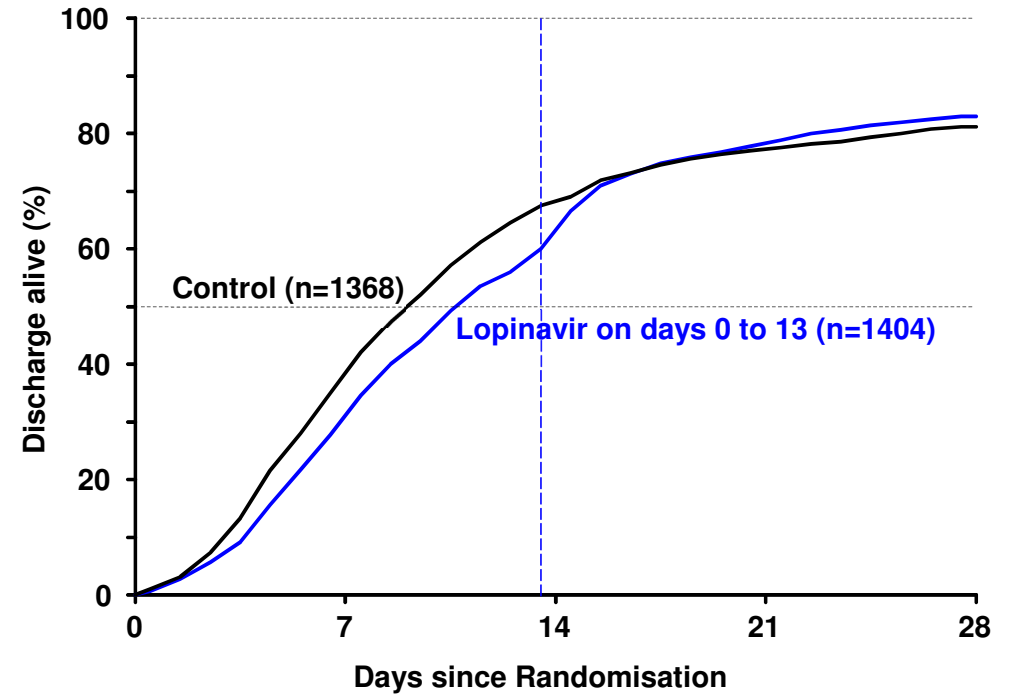
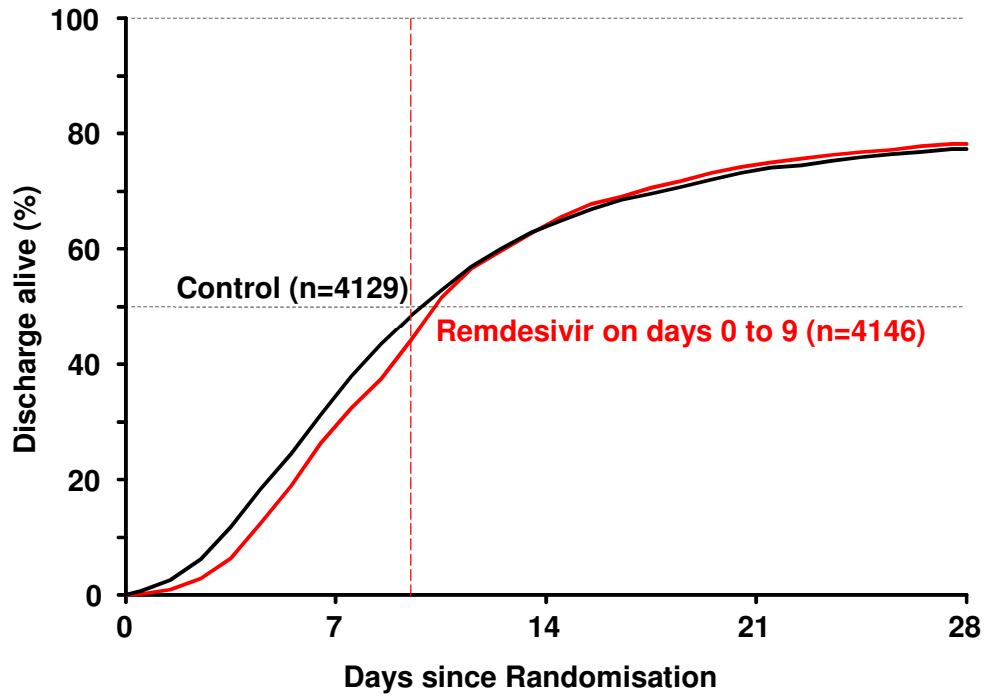


Figure S15A-D. Pairwise randomised comparisons between pairs of study drugs - effects on time to discharge alive, restricted to patients randomised where both of those two drugs were available Denominators: all who entered. Verticals: ends of scheduled treatment durations if still in hospital

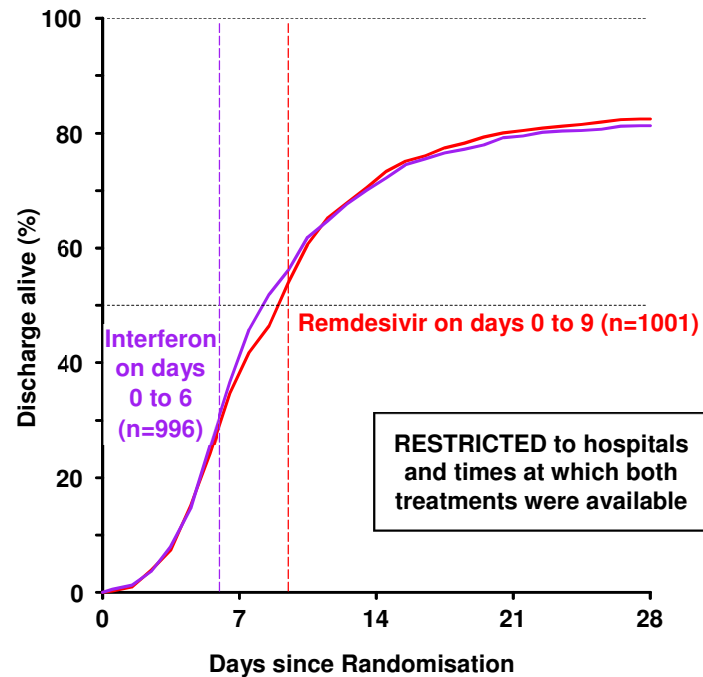
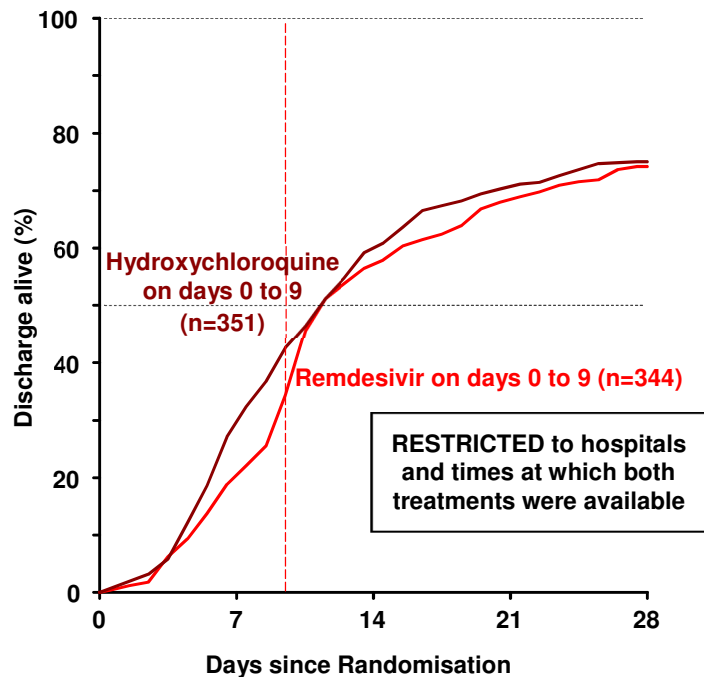
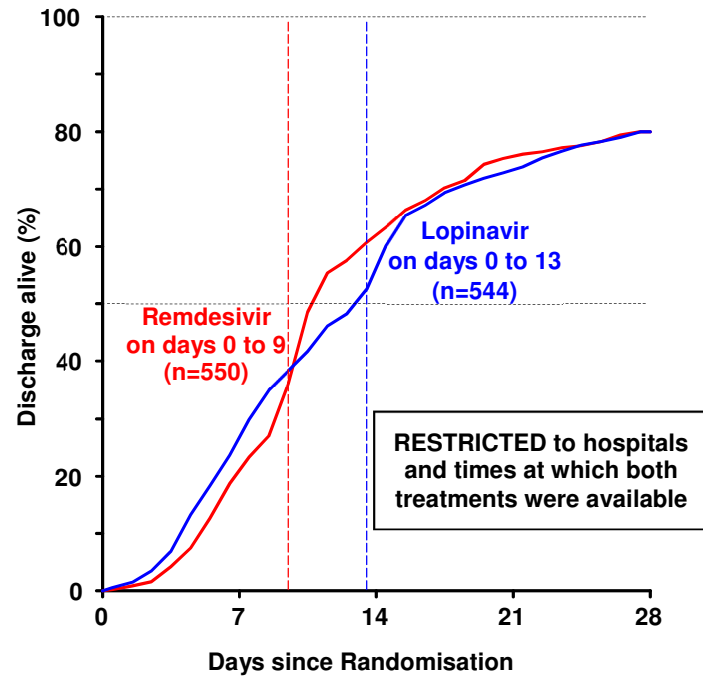
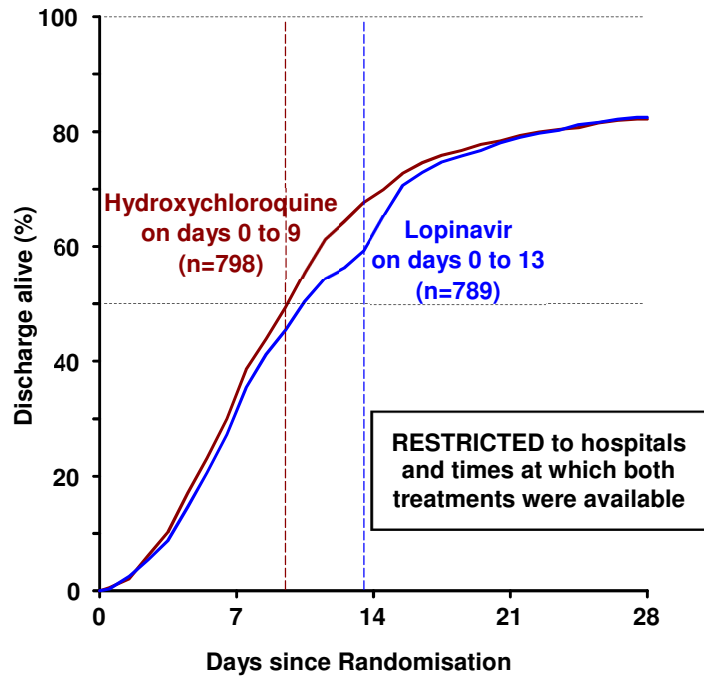
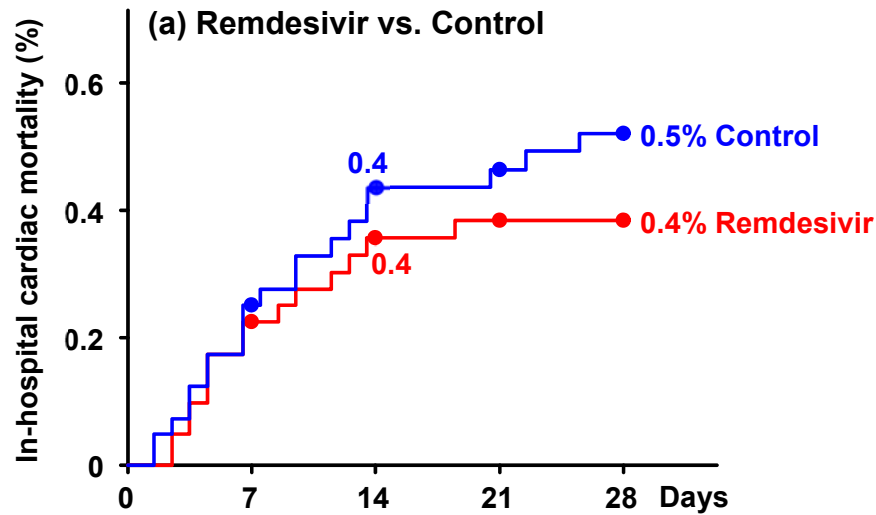
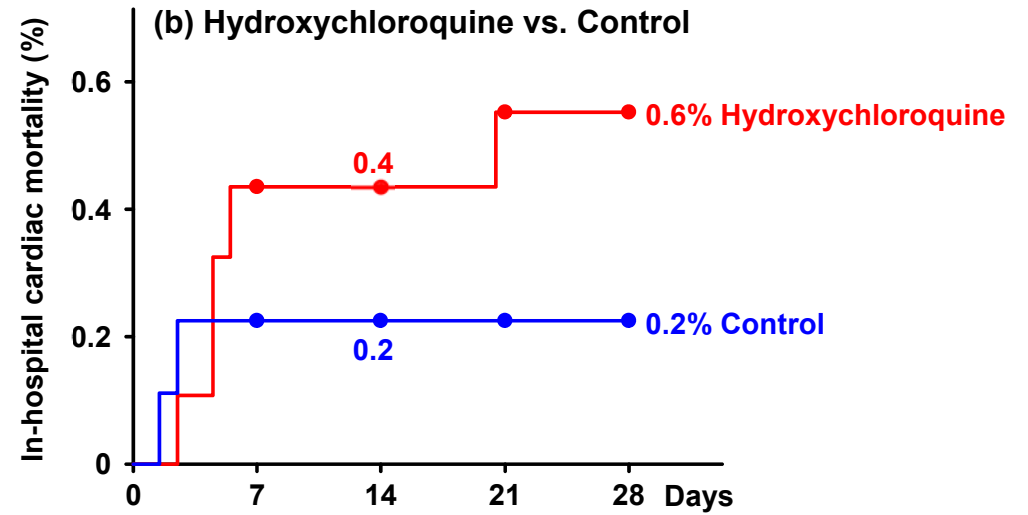


Figure S16A-D. Effects of (A) remdesivir, (B) hydroxychloroquine, (C) lopinavir, (D) interferon on cardiac death in hospital
(any death in hospital for which the trial's electronic death report included a cardiac cause)



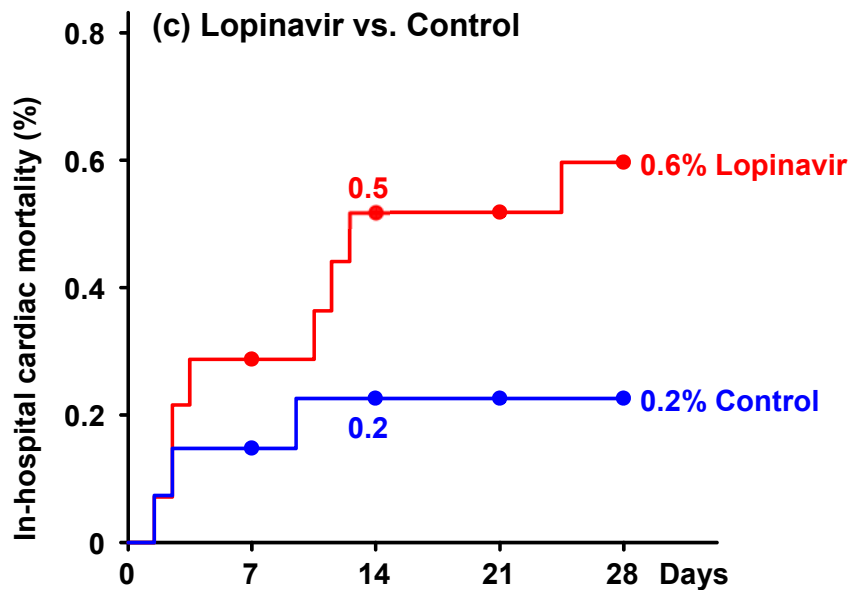
No. randomised, nos. dying, and denominators

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



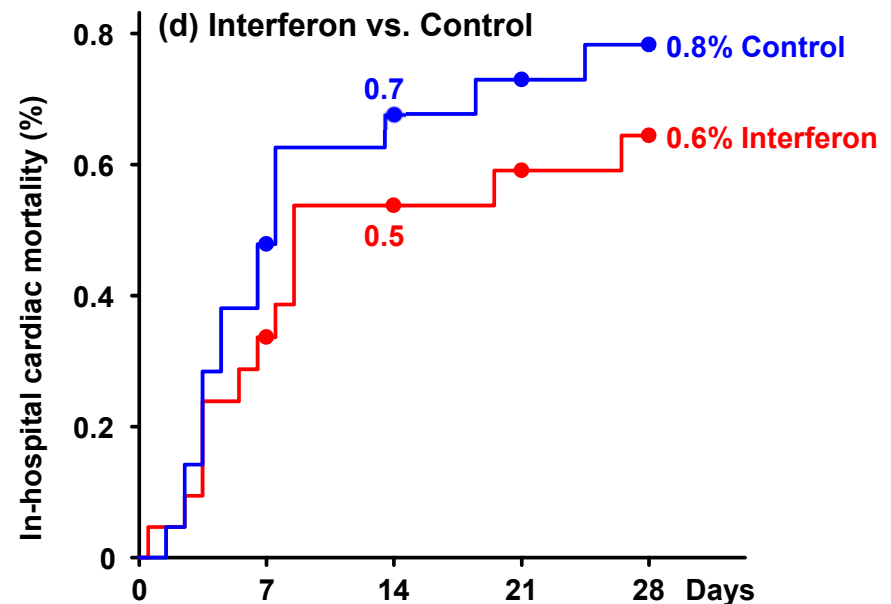
No. randomised, nos. dying, and denominators

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

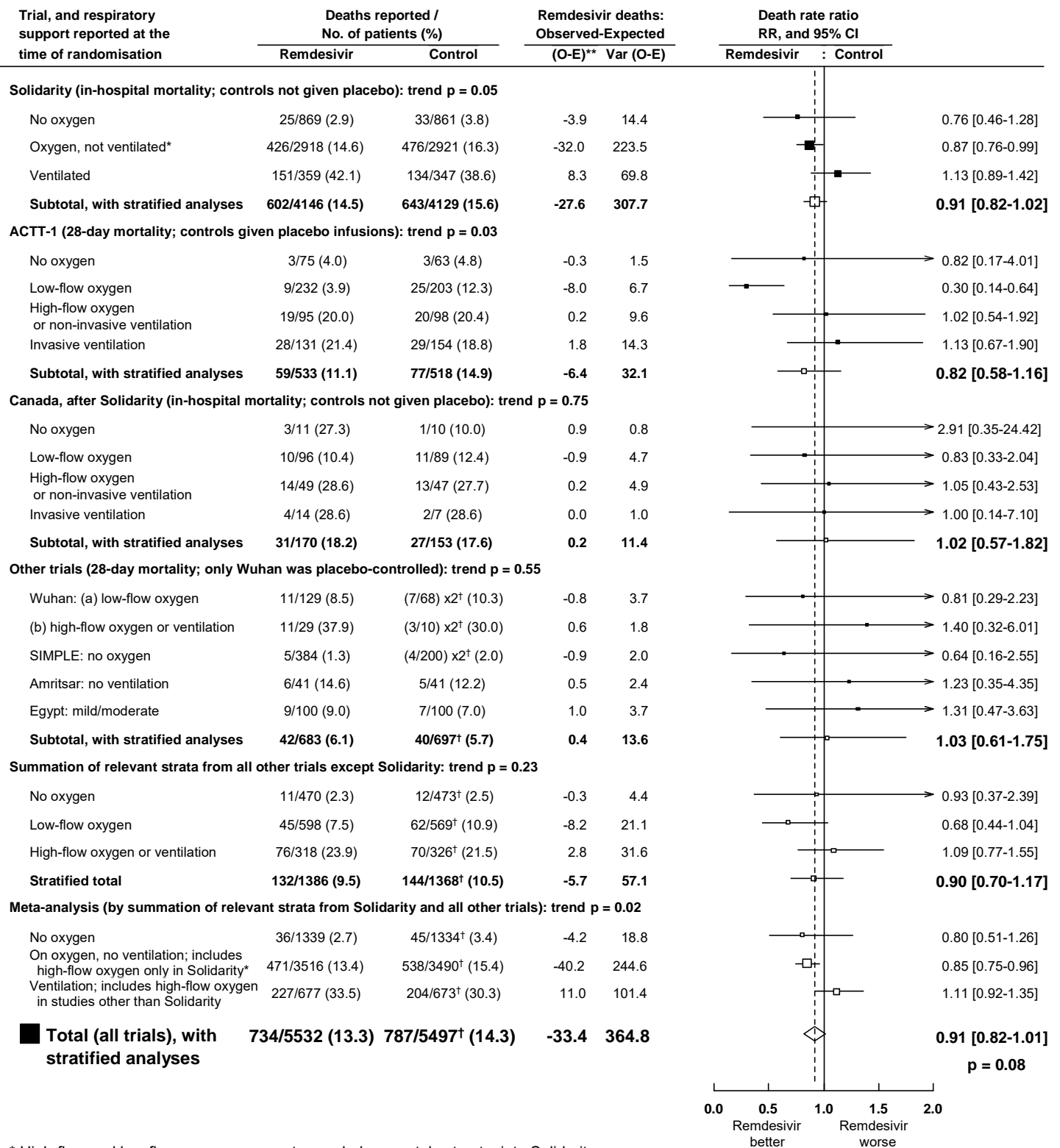


No. randomised, nos. dying, and denominators

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.



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

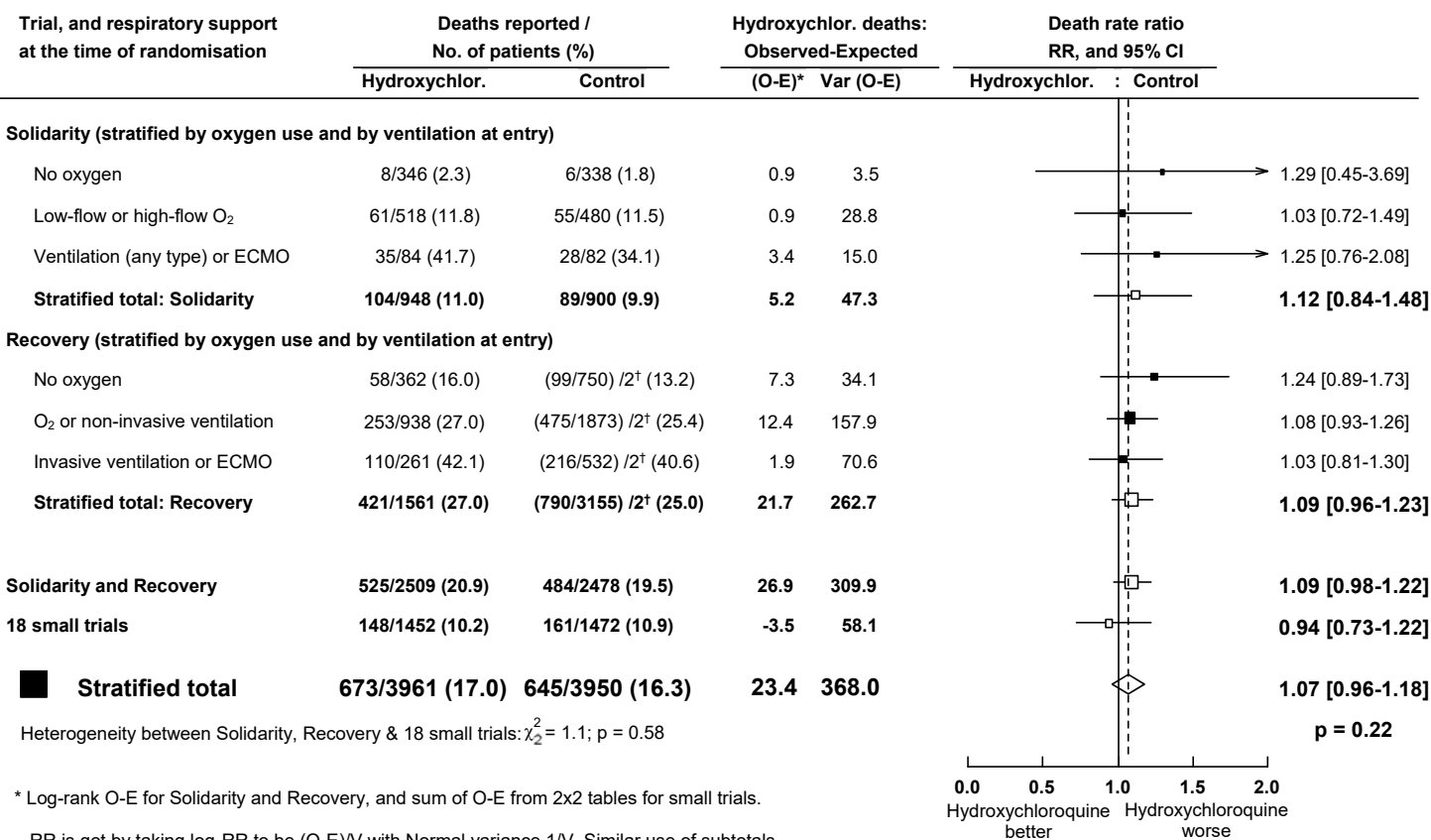
** Age-stratified log-rank O-E for Solidarity, O-E from 2x2 tables for small trials, and w.loge HR for ACTT-1 strata (with the weight w being the inverse of the variance of loge HR, obtained from the 95% CI for the Hazard Ratio). If V is the variance of the logrank statistic O-E then RR is got from taking loge 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 loge 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.



* 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.

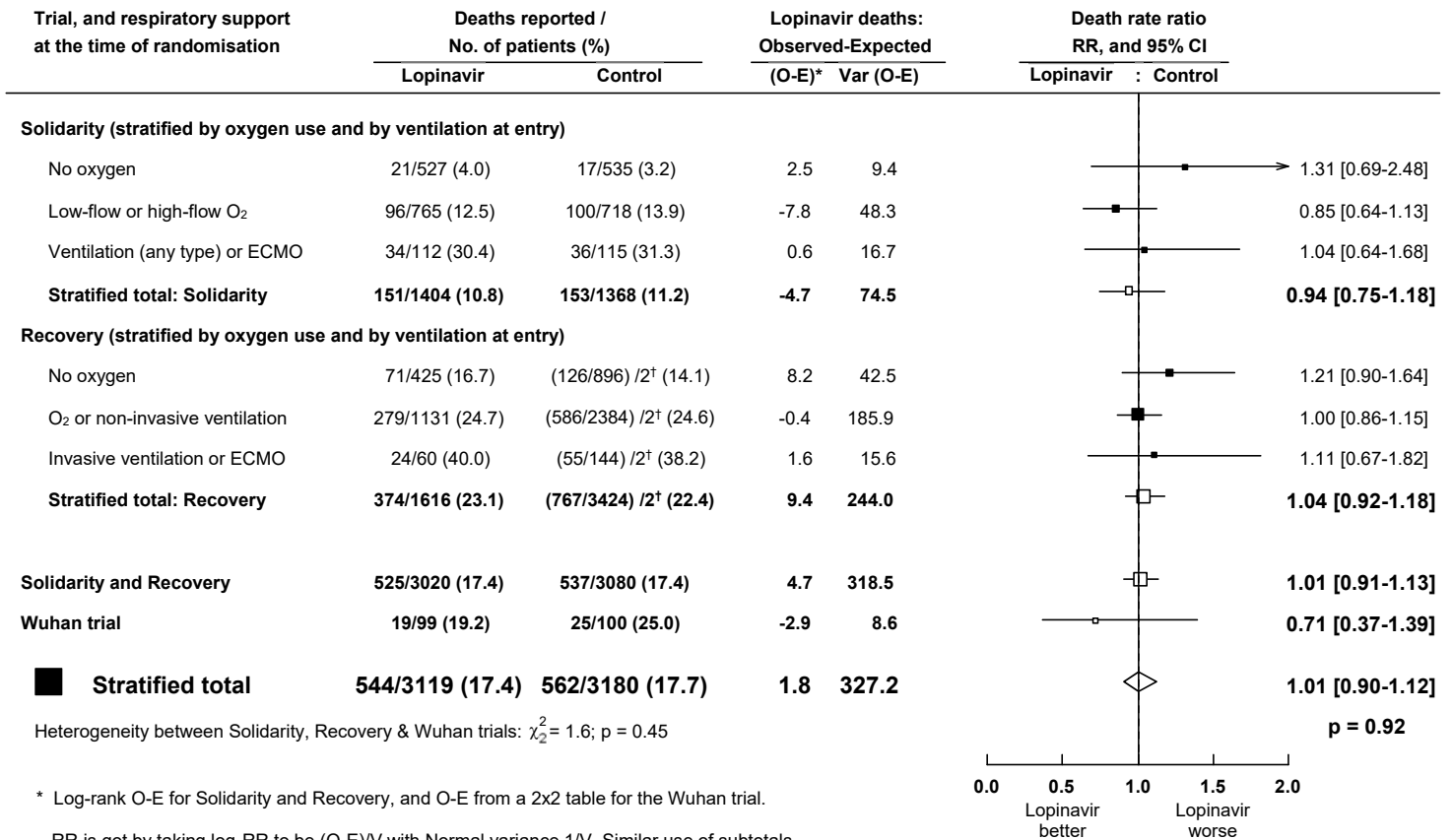
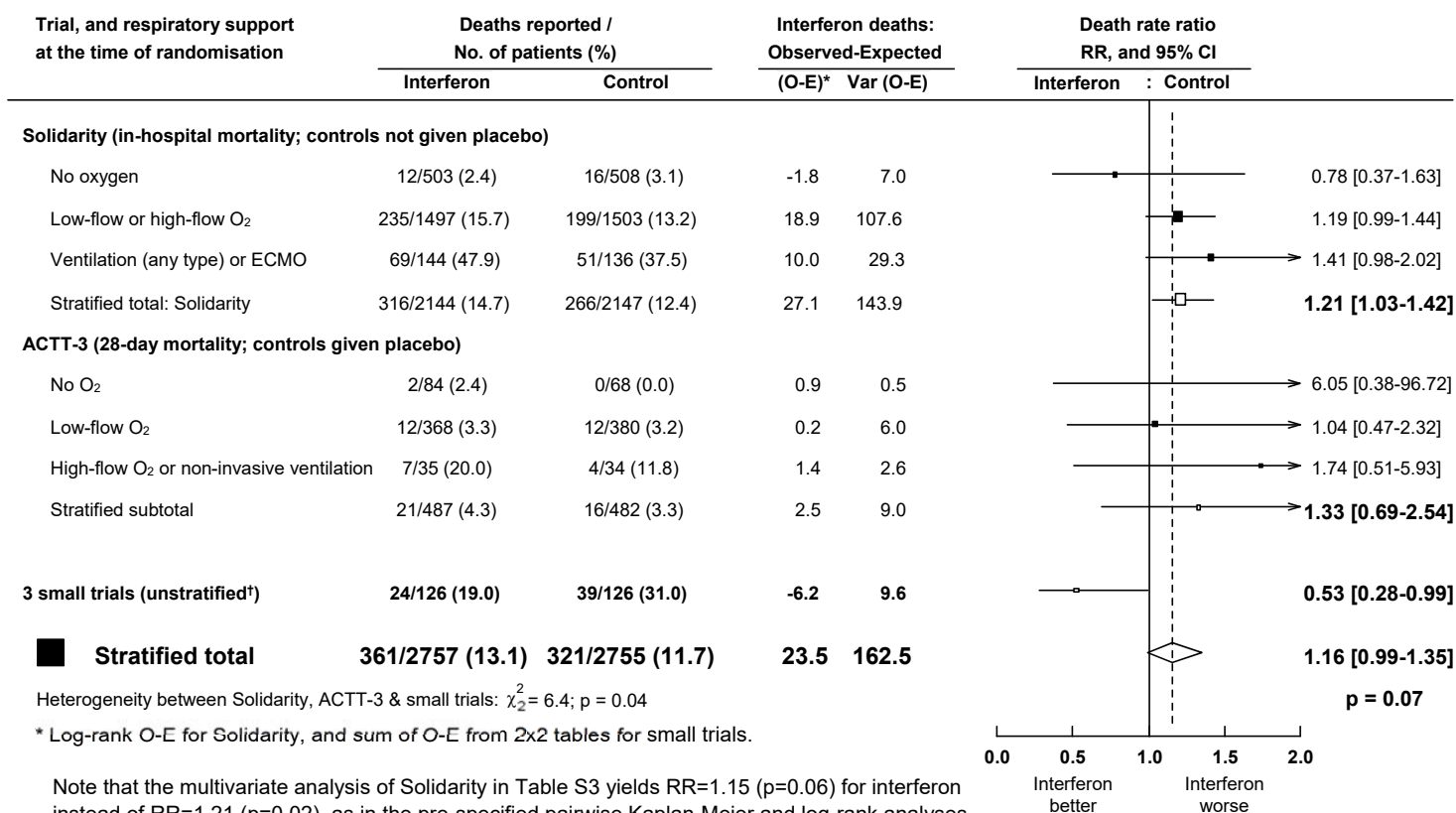


Figure S17D. Interferon-β vs its control in hospitalised COVID – Meta-analysis of mortality in Solidarity, ACTT-3, and the other RCTs with some deaths

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.



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

* 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 $\log_e RR$ to be $(O-E)/V$ with Normal variance $1/V$. Similar use of subtotals or of totals of $(O-E)$ and of V yields inverse-variance-weighted averages of the $\log_e RR$ 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.