RECOVERY
Randomised Evaluation of COVID-19 Therapy

RECOVERY trial:

Tocilizumab in adults

Peter Horby on behalf of RECOVERY Collaborative Group

https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

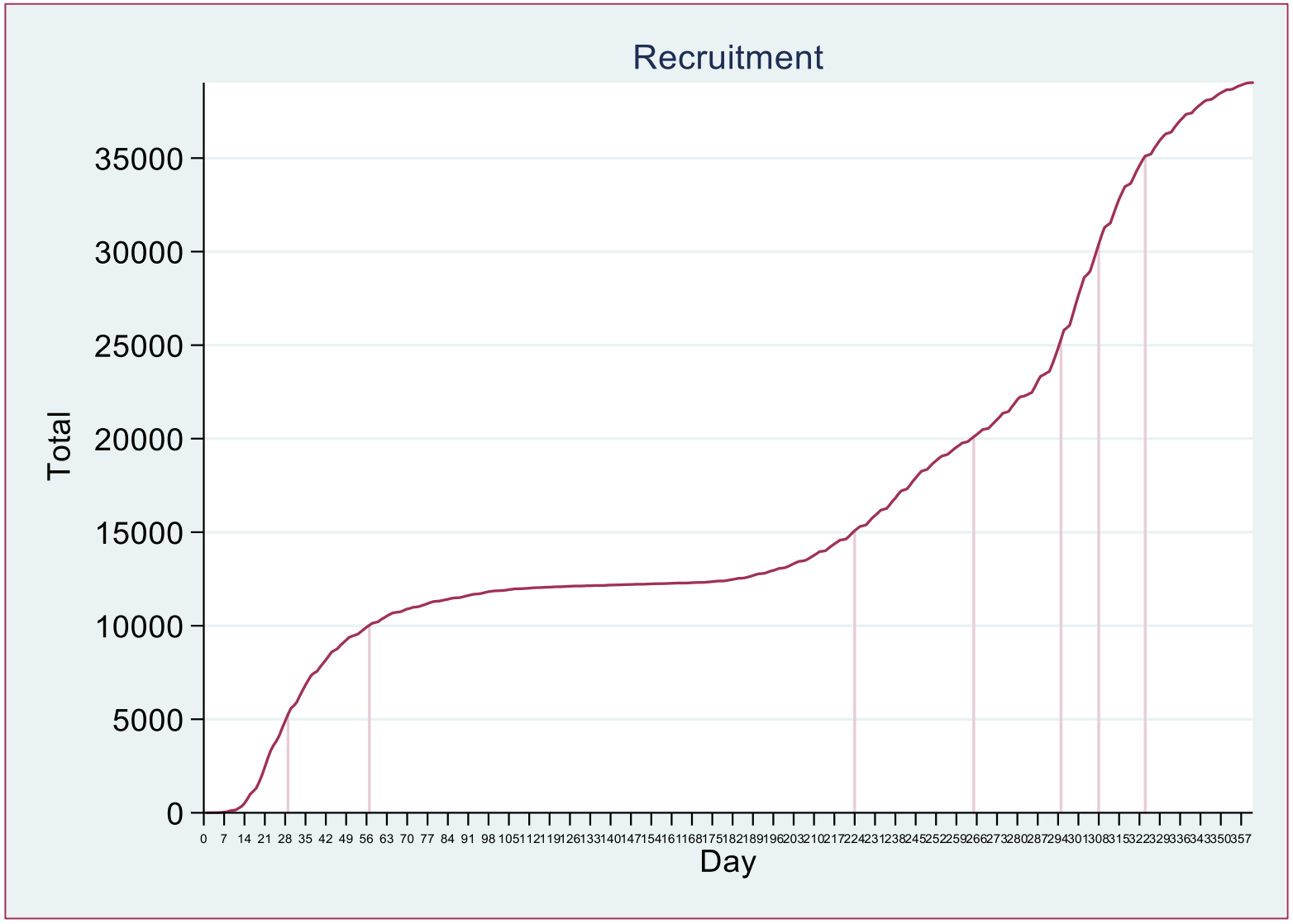
NIHR | Oxford Biomedical Research Centre

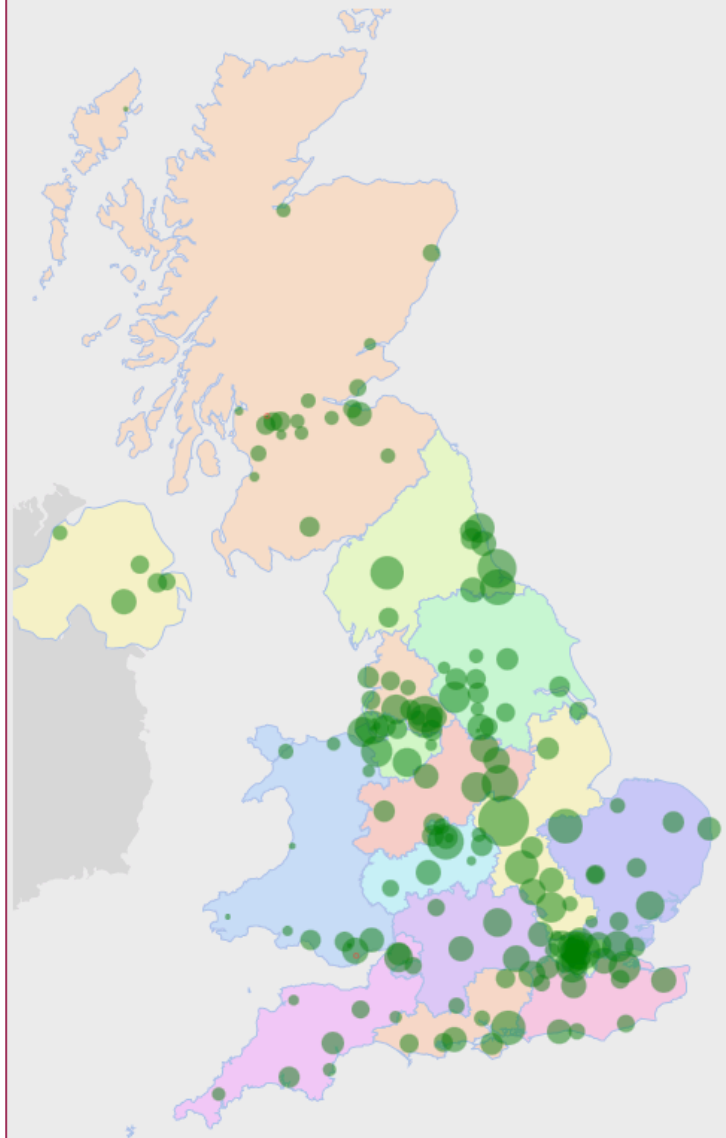
UKRI Medical Research Council

RECOVERY
– rapid & widespread recruitment

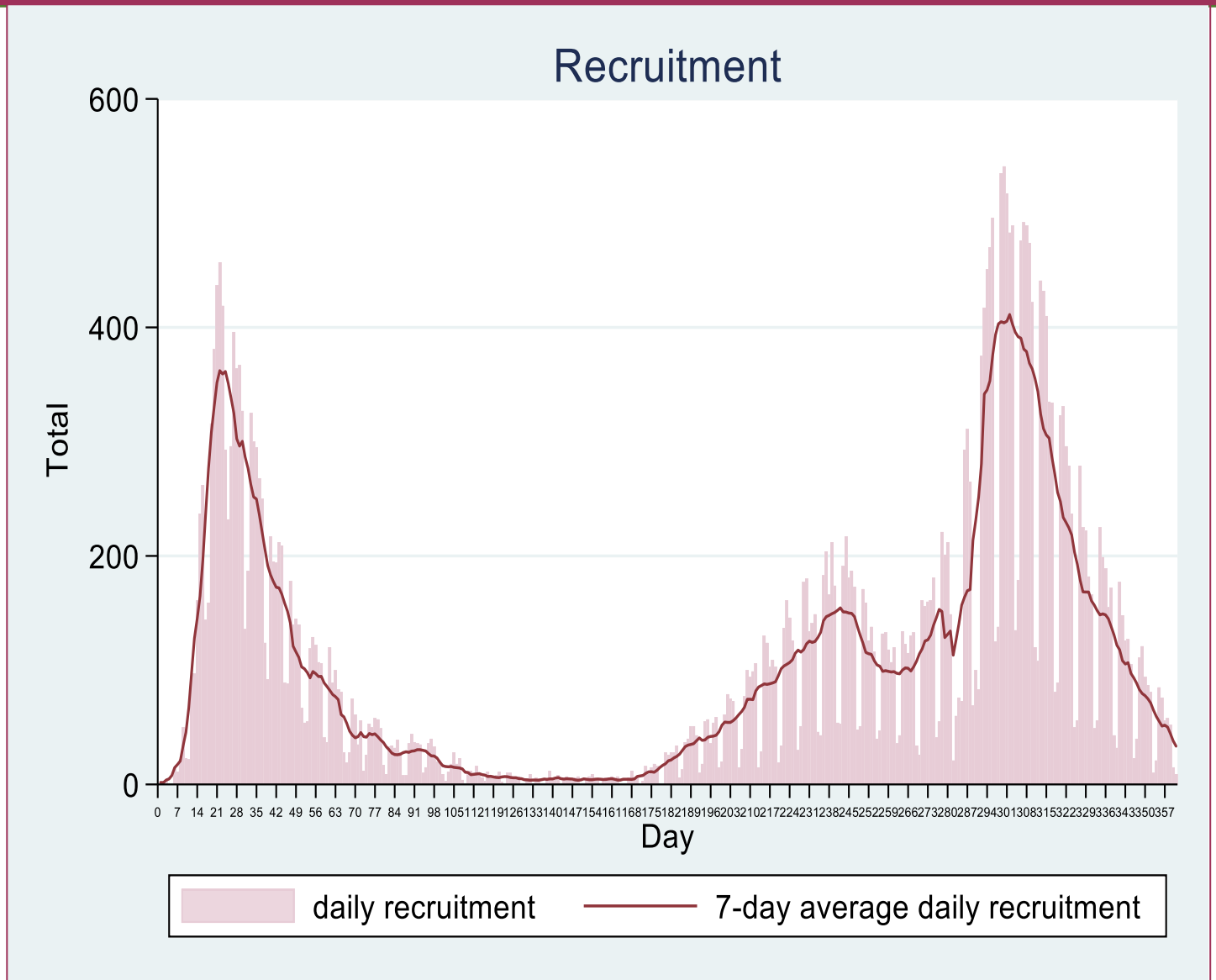
Active Sites	Recruiting Sites	Participants
180	178	39089

Phase 1 rands.	Phase 2 rands.	Phase 3 rands.	Phase 4 rands.	Phase 5 rands.
28600	4164	19350	14737	2724





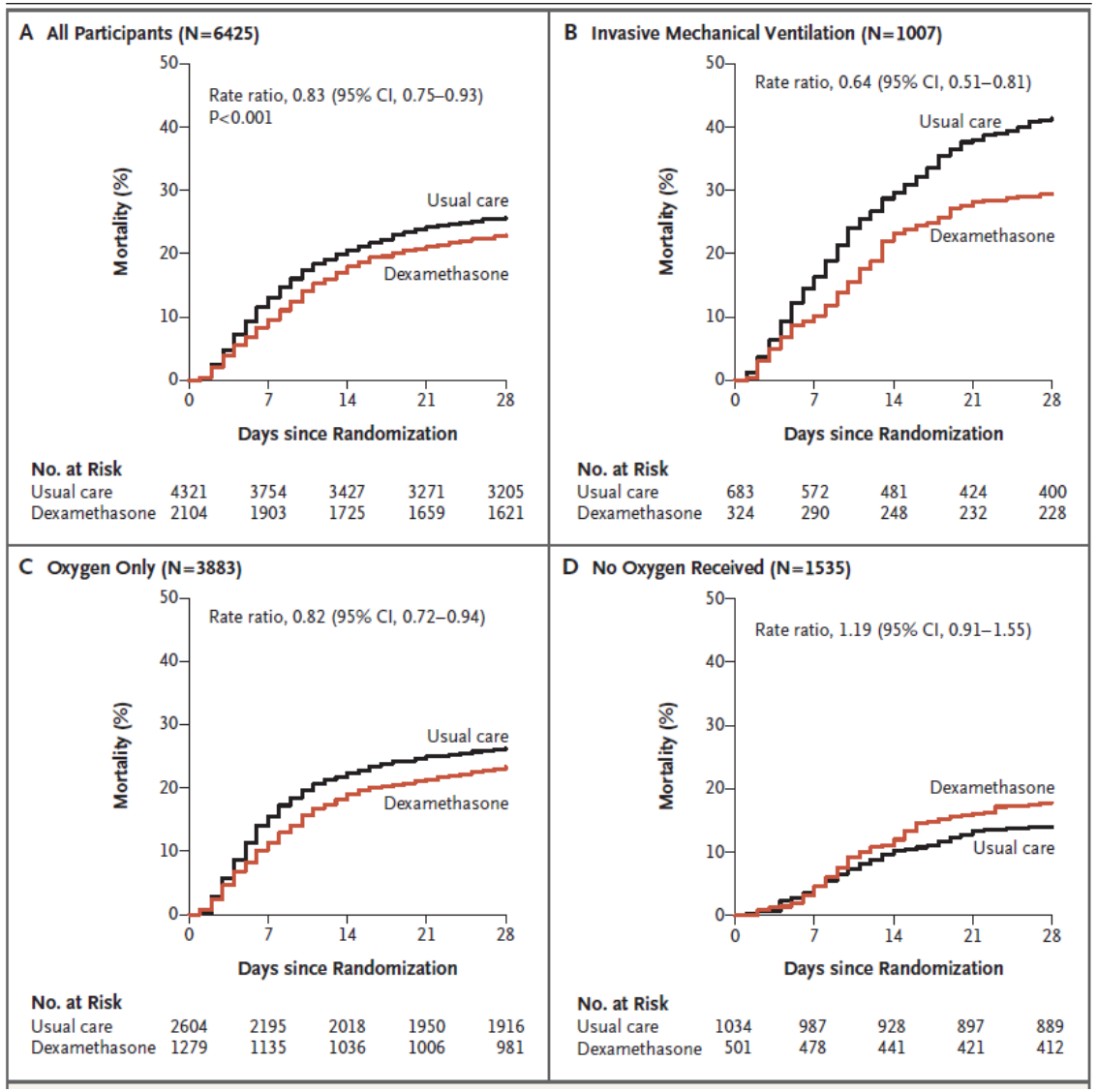
RECOVERY – daily recruitment

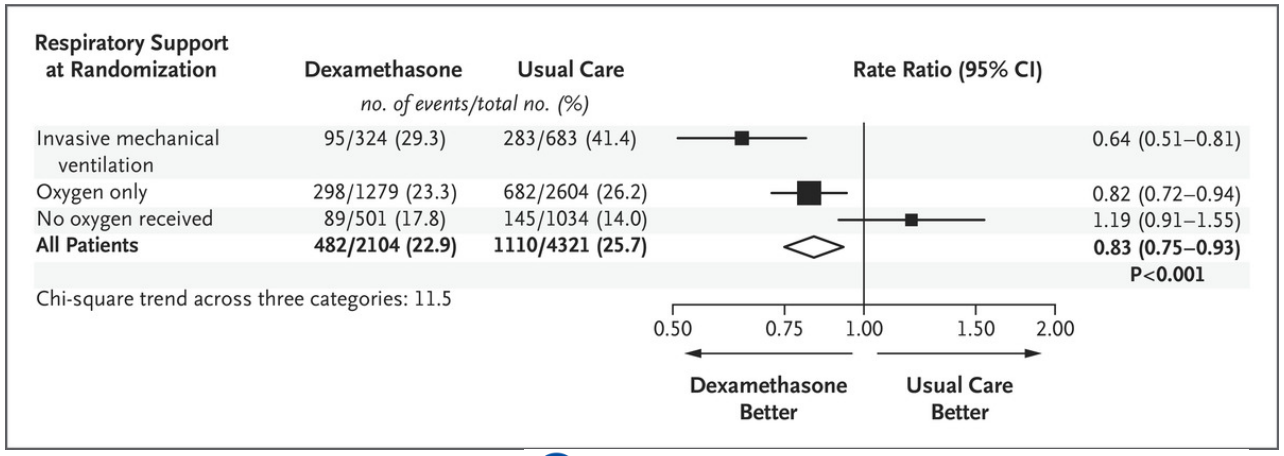


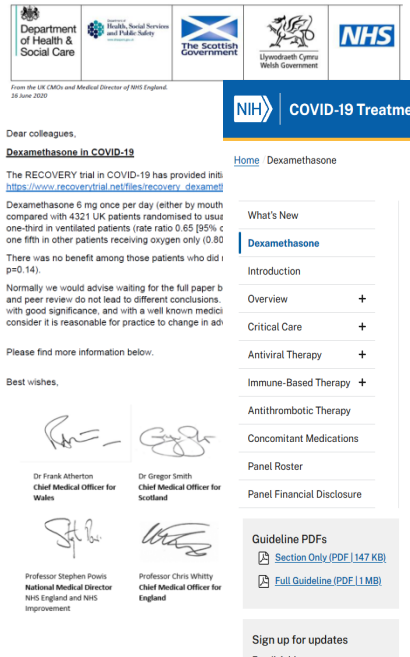
Dexamethasone:

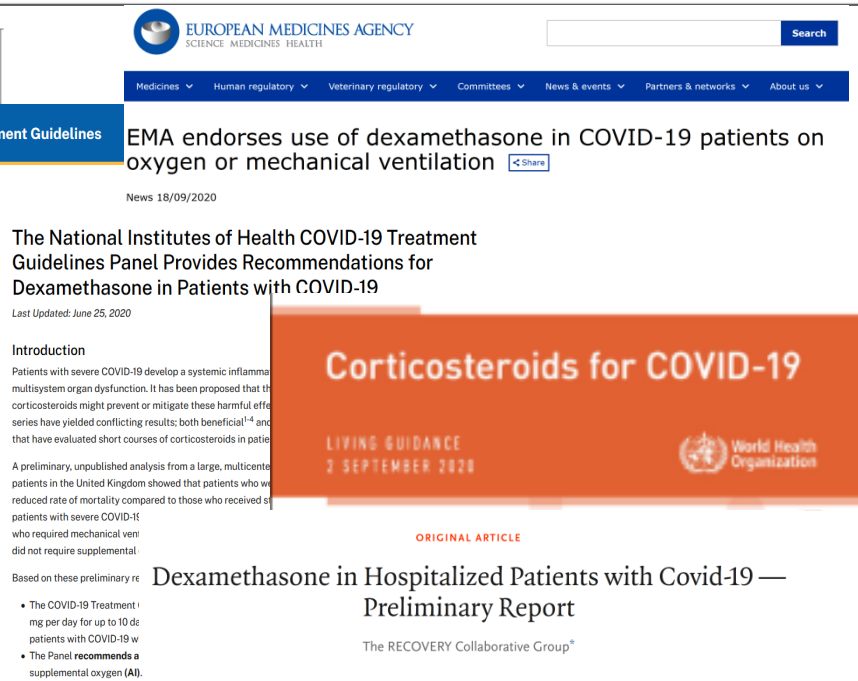
Reduces mortality in patients requiring oxygen or ventilation

DOI: 10.1056/NEJMoa2021436



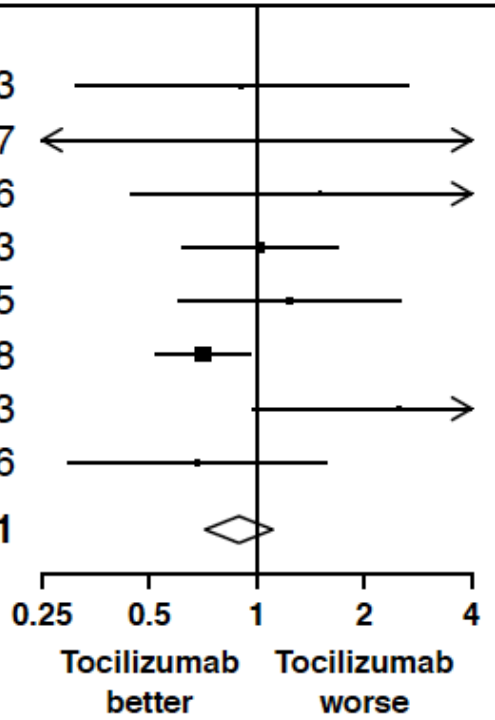






Effect of tocilizumab on 28-day mortality: evidence prior to RECOVERY

	Deaths / Patients randomised (%)		Observed–Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O–E)*	Var(O–E)	
COR–IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	–0.3	3.3	0.91 (0.31–2.65)
RCT–TCZ–COVID–19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22–21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44–5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62–1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60–2.52)
REMAP–CAP	98/353 (27.8)	142/402 (35.3)	–14.2	40.8	0.71 (0.52–0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97–6.50)
COVINTOC	11/91 (12.1)	15/89 (16.9)	–2.1	5.6	0.68 (0.30–1.56)
Subtotal: 8 trials	**225/1337 (16.8)**	**256/1396 (18.3)**	**–9.3**	**80.1**	**0.89 (0.72–1.11)**

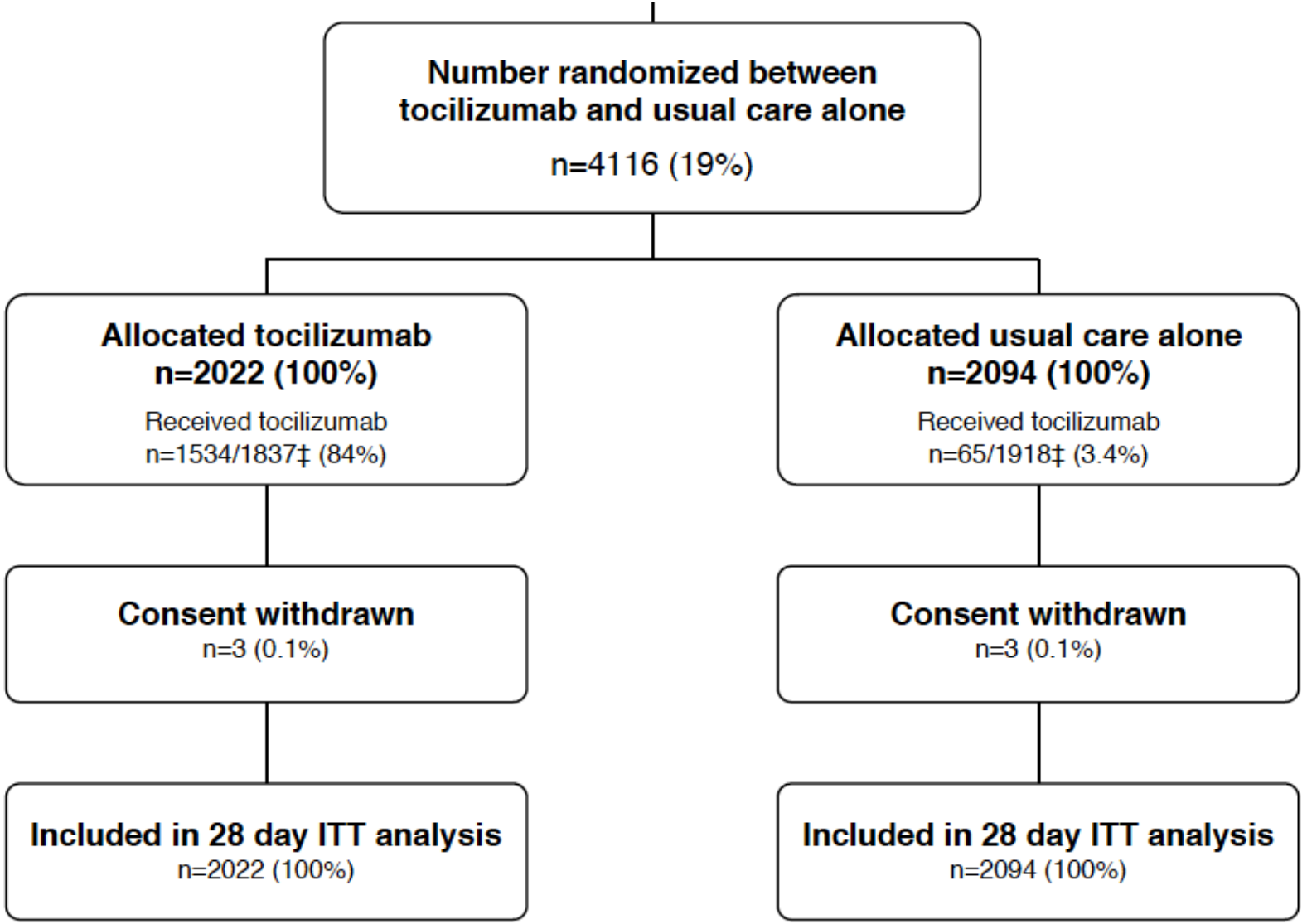


Tocilizumab - eligibility

- **Eligibility** (all of the following):
  - Hospitalised
  - SARS-CoV-2 infection (confirmed or clinically suspected)
  - Clinical evidence of progressive COVID-19:
    - Oxygen saturation <92% on room air or requiring oxygen therapy; and
    - C-reactive protein ≥75 mg/L

- Exclusions (any of the following):
  - Known hypersensitivity to tocilizumab
  - Evidence of active tuberculosis infection
  - Clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)
  - Any other contraindication (in the view of the attending clinician)

Randomisation



Tocilizumab – baseline characteristics

Age	≥18 <70	2686 (65%)
	≥70 <80	957 (23%)
	≥80	473 (12%)
Sex	Men	2772 (67%)
	Women	1344 (33%)
Ethnicity	White	2782 (68%)
	Black, Asian, & Minority Ethnic	698 (17%)
	Unknown	636 (15%)

Respiratory status	Oxygen only*	1868 (45%)
	Non-invasive ventilation	1686 (41%)
	Invasive mechanical ventilation	562 (14%)
Use of corticosteroids	Yes	3385 (82%)
	No	731 (18%)
Days since symptom onset		10 [7-14]
Days since hospital admission*		2 [1-5]
C-reactive protein*		143 [107-204]

Total: 4116

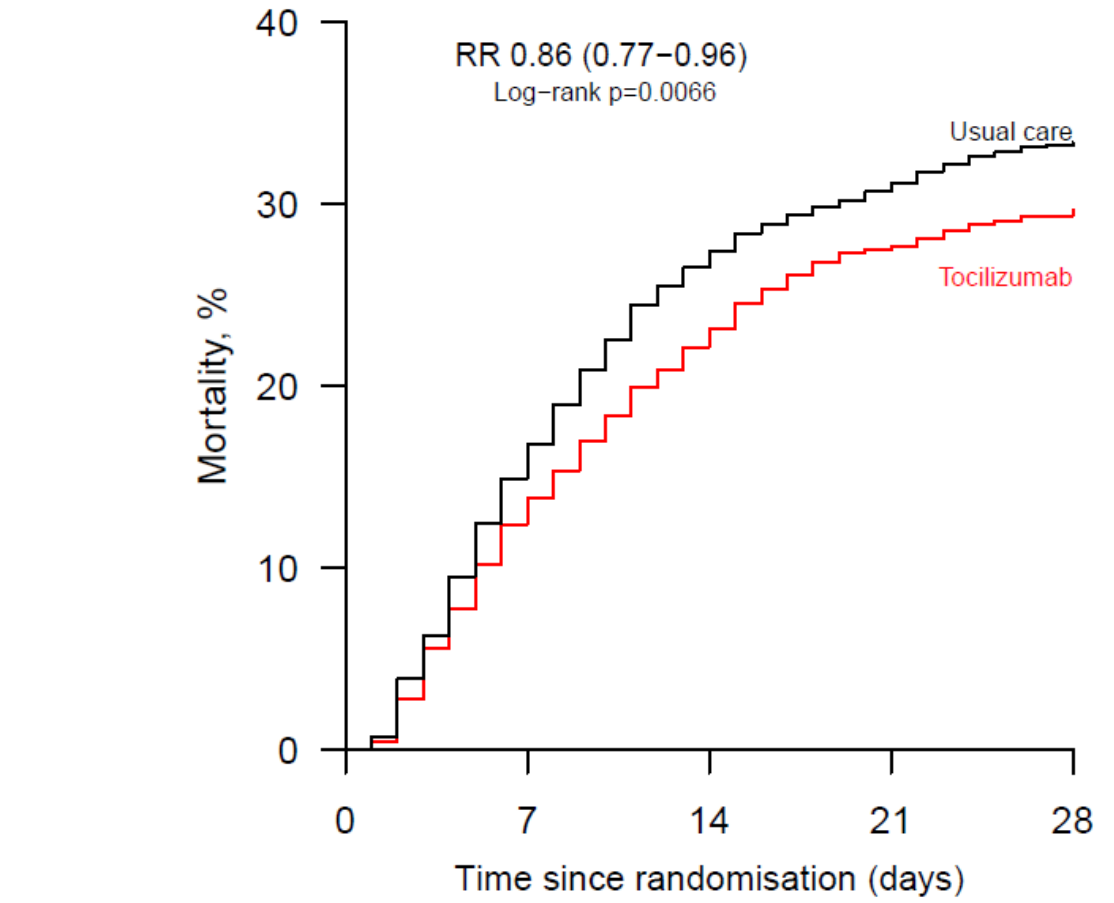
Recruitment closed 24 January 2021. Follow-up 92% complete.

* Includes 9 patients not receiving oxygen at randomisation

Effect of tocilizumab on 28-day mortality

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1



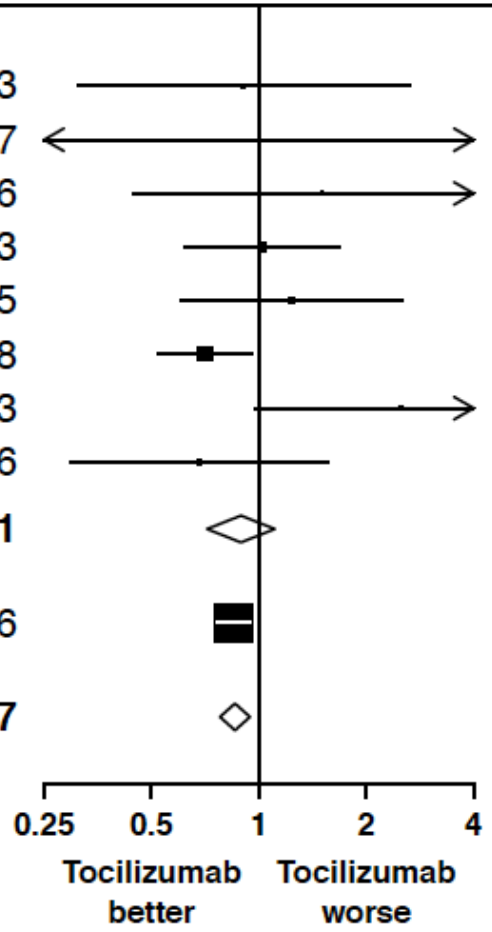
Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

Effect of tocilizumab on 28-day mortality: evidence after RECOVERY

	Deaths / Patients randomised (%)		Observed–Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O–E)*	Var(O–E)	
COR–IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	–0.3	3.3	0.91 (0.31–2.65)
RCT–TCZ–COVID–19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22–21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44–5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62–1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60–2.52)
REMAP–CAP	98/353 (27.8)	142/402 (35.3)	–14.2	40.8	0.71 (0.52–0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97–6.50)
COVINTOC	11/91 (12.1)	15/89 (16.9)	–2.1	5.6	0.68 (0.30–1.56)
Subtotal: 8 trials	**225/1337 (16.8)**	**256/1396 (18.3)**	**–9.3**	**80.1**	**0.89 (0.72–1.11)**
RECOVERY	621/2022 (30.7)	729/2094 (34.8)	–54.3	330.6	0.85 (0.76–0.95)
All trials	**846/3359 (25.2)**	**985/3490 (28.2)**	**–63.6**	**410.7**	**0.86 (0.78–0.94) p=0.002**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.1

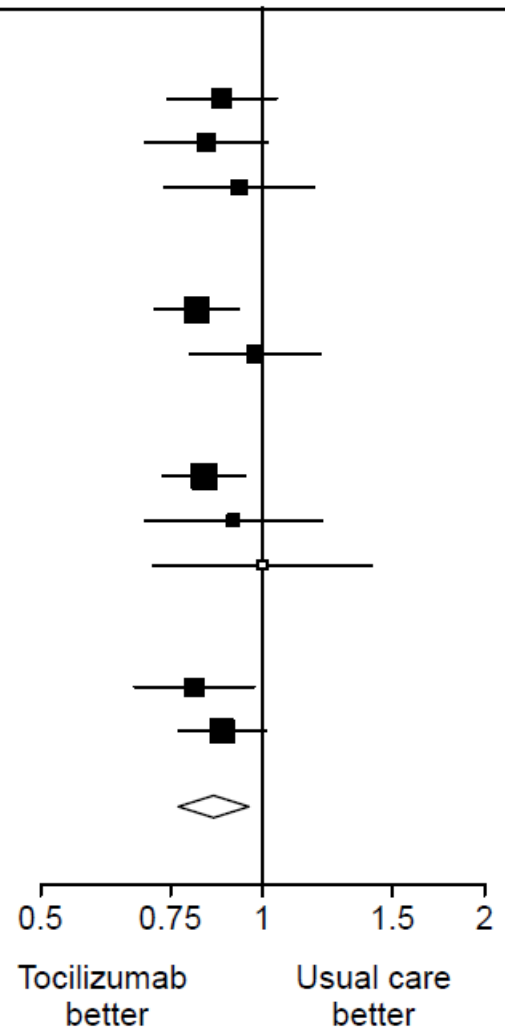


Effect of tocilizumab on 28-day mortality- by subgroup

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

	Tocilizumab	Usual care	RR (95% CI)
Age, years (χ^2_1=0.1; p=0.80)			
<70	256/1332 (19%)	289/1354 (21%)	0.88 (0.74−1.04)
≥70 <80	206/477 (43%)	234/480 (49%)	0.84 (0.69−1.01)
≥80	134/213 (63%)	171/260 (66%)	0.93 (0.74−1.17)
Sex (χ^2_1=2.2; p=0.14)			
Men	400/1335 (30%)	504/1437 (35%)	0.81 (0.71−0.93)
Women	196/687 (29%)	190/657 (29%)	0.98 (0.80−1.20)
Ethnicity (χ^2_1=0.3; p=0.56)			
White	429/1356 (32%)	519/1426 (36%)	0.83 (0.73−0.95)
Black, Asian, or Minority Ethnic	98/341 (29%)	110/357 (31%)	0.91 (0.69−1.20)
Unknown	69/325 (21%)	65/311 (21%)	1.00 (0.71−1.41)
Days since symptom onset (χ^2_1=0.6; p=0.46)			
≤7	210/668 (31%)	245/660 (37%)	0.81 (0.67−0.97)
>7	386/1354 (29%)	449/1433 (31%)	0.88 (0.77−1.01)
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77−0.96) p=0.0066**

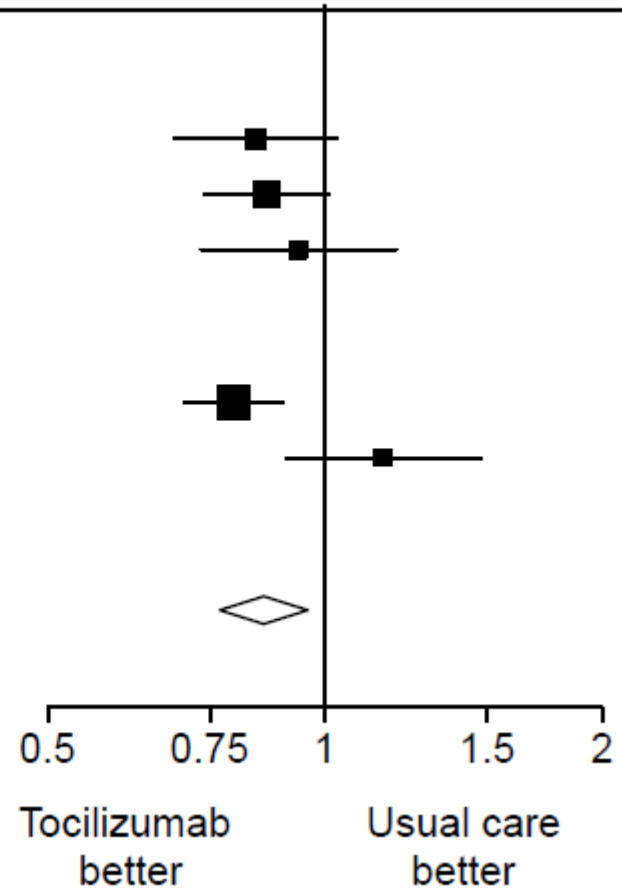


Effect of tocilizumab on 28-day mortality – by subgroup

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

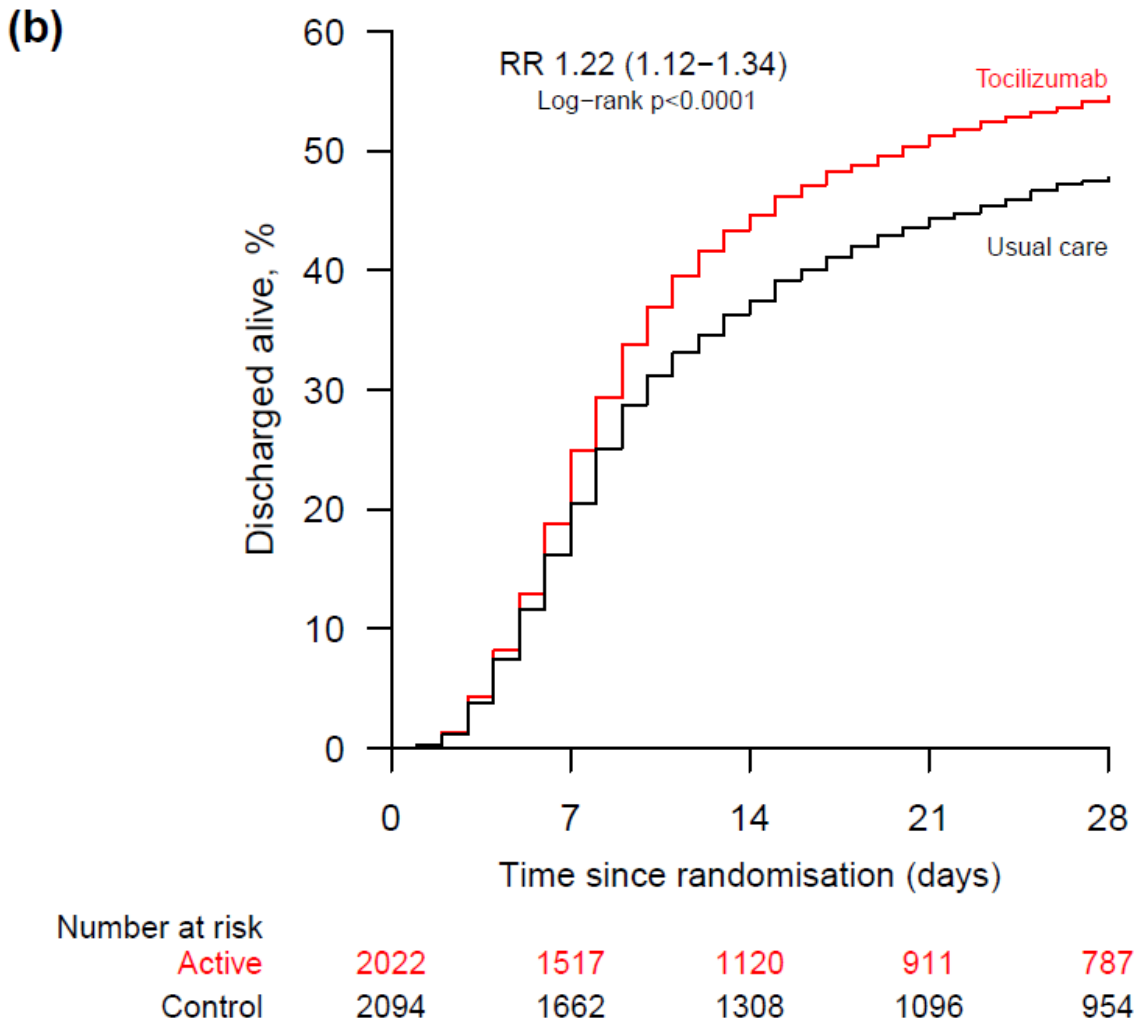
	Tocilizumab	Usual care	RR (95% CI)
Respiratory support at randomization (χ^2_1=0.4; p=0.52)			
No ventilator support*	175/935 (19%)	202/933 (22%)	0.84 (0.69–1.03)
Non–invasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74–1.01)
Invasive mechanical ventilation‡	125/268 (47%)	142/294 (48%)	0.94 (0.73–1.19)
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70–0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91–1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77–0.96) p=0.0066**



Secondary outcomes – discharge alive / IMV or death

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1



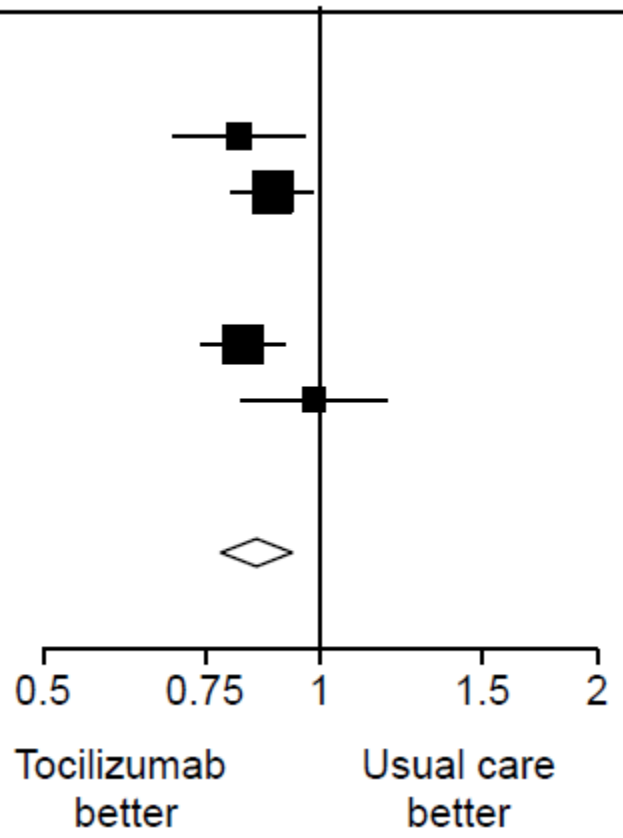
Outcome	TCZ	Usual care	RR (95% CI)	p
IMV	215	273	0.81 (0.68-0.95)	0.01
Death	471	552	0.88 (0.79-0.97)	0.01
IMV or death	571	687	0.85 (0.79-0.93)	0.0005

Effect of tocilizumab on need for invasive mechanical ventilation or death (among those not on IMV at baseline)

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

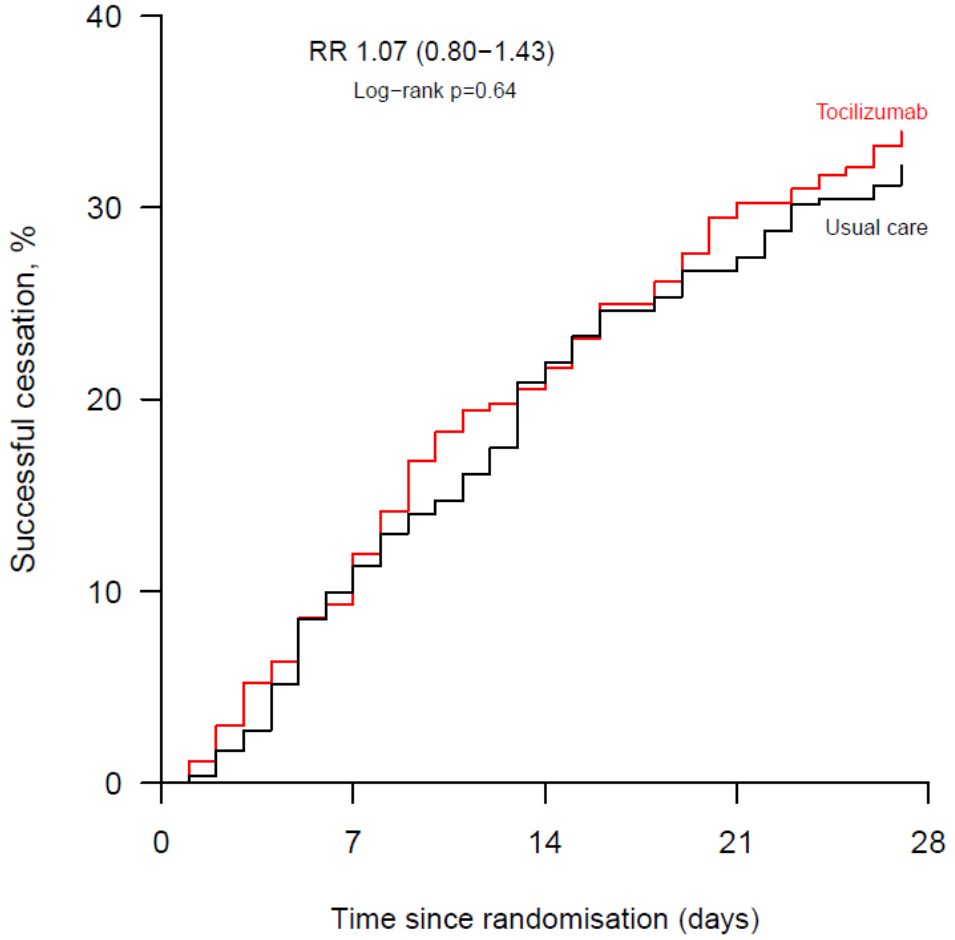
	Tocilizumab	Usual care	RR (95% CI)
Respiratory support at randomization (χ^2_1=0.7; p=0.40)			
No ventilator support*	198/935 (21%)	242/933 (26%)	0.82 (0.69–0.96)
Non–invasive ventilation†	373/819 (46%)	445/867 (51%)	0.89 (0.80–0.98)
Use of corticosteroids‡ (χ^2_1=2.9; p=0.09)			
Yes	447/1480 (30%)	550/1500 (37%)	0.82 (0.74–0.91)
No	124/273 (45%)	136/295 (46%)	0.99 (0.82–1.18)
Unknown	0/1 (0%)	1/5 (20%)	
All participants	**571/1754 (33%)**	**687/1800 (38%)**	**0.85 (0.78–0.93) p=0.0005**



Effect of tocilizumab on successful cessation of invasive mechanical ventilation

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1



Number at risk					
Active	268	236	210	187	177
Control	294	259	228	212	198

Effect of tocilizumab on main study outcomes

Preliminary data

www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

	Treatment allocation			
	Tocilizumab (n=2022)	Usual care (n=2094)	RR (95% CI)	p value
Primary outcome				
Total: 28-day mortality	596 (29%)	694 (33%)	0.86 (0.77-0.96)	0.0066
Secondary outcomes				
Median time to being discharged alive, days	20	>28		
Discharged alive from hospital within 28 days	1093 (54%)	990 (47%)	1.22 (1.12-1.34)	<0.0001
Receipt of invasive mechanical ventilation or death*	571/1754 (33%)	687/1800 (38%)	0.85 (0.78-0.93)	0.0005
Invasive mechanical ventilation	215/1754 (12%)	273/1800 (15%)	0.81 (0.68-0.95)	0.01
Death	471/1754 (27%)	552/1800 (31%)	0.88 (0.79-0.97)	0.01
Subsidiary clinical outcomes				
Receipt of ventilation†	233/935 (25%)	242/933 (26%)	0.96 (0.82-1.12)	0.61
Non-invasive ventilation	222/935 (24%)	223/933 (24%)	0.99 (0.84-1.17)	0.94
Invasive mechanical ventilation	45/935 (5%)	63/933 (7%)	0.71 (0.49-1.03)	0.07
Successful cessation of invasive mechanical ventilation‡	91/268 (34%)	94/294 (32%)	1.07 (0.80-1.43)	0.64
Use of haemodialysis or haemofiltration§	103/2003 (5%)	142/2075 (7%)	0.75 (0.59-0.96)	0.02

Safety

Webtable 2: Effect of allocation to tocilizumab on cause-specific 28-day mortality

	Treatment allocation		Absolute percent difference (95% CI)
	Tocilizumab (n=2022)	Usual care (n=2094)	
COVID	476 (23.5%)	539 (25.7%)	-2.20 (-4.83,0.43)
Other infection	3 (0.1%)	9 (0.4%)	-0.28 (-0.61,0.05)
Cardiac	1 (0.0%)	1 (0.0%)	0.00 (-0.13,0.14)
Stroke	0 (0.0%)	1 (0.0%)	-0.05 (-0.14,0.05)
Other vascular	1 (0.0%)	3 (0.1%)	-0.09 (-0.28,0.09)
Cancer	6 (0.3%)	3 (0.1%)	0.15 (-0.13,0.44)
Other medical	20 (1.0%)	18 (0.9%)	0.13 (-0.46,0.71)
External	0 (0.0%)	0 (0.0%)	0.00 (0.00,0.00)
Unknown cause*	89 (4.4%)	120 (5.7%)	-1.33 (-2.67,0.01)
All-cause	596 (29.5%)	694 (33.1%)	-3.67 (-6.50,-0.84)

* The cause of death for these participants will be known by the time of the final analyses.

Safety

Webtable 3: Effect of allocation to tocilizumab on cardiac arrhythmia

	Treatment allocation	
	Tocilizumab (n=2022)	**Usual care (n=2094)**
Number with follow-up form*	1569	1628
Atrial flutter or fibrillation	62 (4%)	74 (5%)
Other supraventricular tachycardia	11 (1%)	16 (1%)
Subtotal: Supraventricular tachycardia	72 (5%)	89 (5%)
Ventricular tachycardia	9 (1%)	10 (1%)
Ventricular fibrillation	1 (0%)	2 (0%)
Subtotal: Ventricular tachycardia or fibrillation	10 (1%)	10 (1%)
Atrioventricular block requiring intervention	5 (0%)	1 (0%)
Total: Any major cardiac arrhythmia	84 (5%)	99 (6%)

*Information on new cardiac arrhythmias was only collected on follow-up forms from 12 May 2020 onwards; percentages are of those with such a form completed.

Safety

- There were three reports of serious adverse reactions believed to be related to tocilizumab:
  - Otitis externa
  - Staphylococcus aureus bacteraemia
  - Lung abscess
- All resolved with standard treatment.

Summary - tocilizumab

Among patients hospitalised with COVID-19 with hypoxia & systemic inflammation:

- reduces mortality
- increases probability of hospital discharge alive within 28 days
- reduces probability of progressing to invasive mechanical ventilation or death

Benefits seen in all patient subgroups:

- age, sex, ethnicity, duration of symptoms, level of respiratory support

Benefits additional to those of corticosteroids

Acknowledgements

- UK Research & Innovation
- Wellcome Trust
- Department for International Development
- National Health Service in England, Wales, Scotland, and Northern Ireland
- National Institute for Health Research
- Bill & Melinda Gates Foundation
- Department of Health & Social Care

- NIHR Clinical Research Network
- NIHR Oxford Biomedical Research Centre
- NHS DigiTrials
- Medical Research Council Population Health Research Unit

with enormous thanks

to the very many doctors, nurses, & other healthcare & research staff at 177 NHS hospitals

and, most importantly

to the thousands of patients who participate

in this extraordinary project