Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

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Summary

Background We aimed to evaluate the use of baricitinib, a Janus kinase (JAK) 1–2 inhibitor, for the treatment of patients admitted to hospital with COVID-19.

Methods This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), is assessing multiple possible treatments in patients hospitalised with COVID-19 in the UK. Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus baricitinib 4 mg once daily by mouth for 10 days or until discharge if sooner (baricitinib group). The primary outcome was 28-day mortality assessed in the intention-to-treat population. A meta-analysis was done, which included the results from the RECOVERY trial and all previous randomised controlled trials of baricitinib or other JAK inhibitor in patients hospitalised with COVID-19. The RECOVERY trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936) and is ongoing.

Findings Between Feb 2 and Dec 29, 2021, from 10852 enrolled, 8156 patients were randomly allocated to receive usual care plus baricitinib versus usual care alone. At randomisation, 95% of patients were receiving corticosteroids and 23% were receiving tocilizumab (with planned use within the next 24 h recorded for a further 9%). Overall, 514 (12%) of 4148 patients allocated to baricitinib versus 546 (14%) of 4008 patients allocated to usual care died within 28 days (age-adjusted rate ratio 0·87; 95% CI 0·77–0·99; p=0·028). This 13% proportional reduction in mortality was somewhat smaller than that seen in a meta-analysis of eight previous trials of a JAK inhibitor (involving 3732 patients and 425 deaths), in which allocation to a JAK inhibitor was associated with a 43% proportional reduction in mortality (rate ratio 0·57; 95% CI 0·45–0·72). Including the results from RECOVERY in an updated meta-analysis of all nine completed trials (involving 11888 randomly assigned patients and 1485 deaths) allocation to baricitinib or another JAK inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0·80; 95% CI 0·72–0·89; p<0·0001). In RECOVERY, there was no significant excess in death or infection due to non-COVID-19 causes and no significant excess of thrombosis, or other safety outcomes.

Interpretation In patients hospitalised with COVID-19, baricitinib significantly reduced the risk of death but the size of benefit was somewhat smaller than that suggested by previous trials. The total randomised evidence to date suggests that JAK inhibitors (chiefly baricitinib) reduce mortality in patients hospitalised for COVID-19 by about one-fifth.

Funding UK Research and Innovation (Medical Research Council) and National Institute of Health Research.

Introduction

In patients admitted to hospital with severe COVID-19, the host immune response is thought to play a key role in driving an acute inflammatory process resulting in hypoxic respiratory failure that might require mechanical ventilator support or lead to death.[1,2] It has previously been shown that the use of dexamethasone and other corticosteroids reduces the risk of death in patients with severe hypoxic COVID-19 and that the addition of an interleukin-6 (IL-6) receptor blocker further reduces the risk of death in these patients.[3–6]

Baricitinib is an inhibitor of Janus kinase (JAK)1 and JAK2, which is licensed in the UK for the treatment of rheumatoid arthritis and atopic dermatitis. The JAKs are a

family of four transmembrane protein kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) that mediate intracellular signalling of a range of extracellular cytokines and interferons.[7] JAK inhibition prevents downstream phosphorylation and hence activation of signal transducers and activators of transcription (STAT). Since the JAK-STAT pathway mediates the effect of several cytokines, including IL-6, which are raised in severe COVID-19, JAK inhibitors have been proposed as a potential therapeutic option for severe COVID-19.[8,9] Baricitinib also has moderate inhibitory activity against TYK2 and genetic data support a causal link between high TYK2 expression and life-threatening COVID-19.[10] Baricitinib was also predicted, by use of artificial intelligence, to reduce

Research in context

Evidence before this study

We searched MEDLINE, Embase, MedRxiv and the WHO International Clinical Trials Registry Platform for trials published between Sept 1, 2019, and Feb 13, 2022, for randomised controlled trials evaluating the effect of baricitinib or another Janus kinase (JAK) inhibitor in patients hospitalised with COVID-19 using the search terms ("SARS-CoV-2.mp" OR "SARS-CoV2" OR "SARSCoV2.mp" OR "COVID.mp" OR "COVID-19.mp" OR "COVID19.mp" OR "2019-nCoV.mp" OR "Coronavirus.mp" or "Coronavirinae/") AND ("JAK inhibitor.mp or Janus kinase inhibitor/" OR "Janus kinase inhibitor.mp" OR "Baricitinib.mp or baricitinib/" OR terms for other specific JAK inhibitors (listed in the appendix p 28) and using validated filters to select for randomised controlled trials. No language restrictions were applied.

We identified eight relevant randomised trials with results available that assessed JAK inhibitors in patients hospitalised with COVID-19: three assessed baricitinib, three assessed ruxolitinib, and two assessed tofacitinib. Six of the trials had been fully published of which four were considered to have low risk of bias for the 28-day mortality outcome with two having some concerns (one because of lack of information about prespecified analyses and some imbalances between randomised groups of other interventions given during the trial; the other because of lack of information about the randomisation process, inconsistency in reporting of outcome endpoint timing, and lack of information about prespecified analyses). A meta-analysis of these eight trials, which included a total of 425 deaths among 3732 patients, suggested that allocation to a JAK inhibitor was associated with a 43% proportional reduction in 28-day mortality (rate ratio 0·57 [95% CI 0·45–0·72]).

Added value of this study

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is the largest randomised trial of the effect of a JAK inhibitor in patients hospitalised with COVID-19. We found that in 8156 patients admitted to hospital with COVID-19, baricitinib reduced 28-day mortality by 13%, increased the probability of discharge alive within 28 days, and, among patients who were not receiving invasive mechanical ventilation at randomisation, reduced the probability of progression to the composite outcome of invasive mechanical ventilation or death. The benefits were consistent in all subgroups of patients, including those receiving a systemic corticosteroid or an interleukin-6 (IL-6) receptor blocker.

Implications of all the available evidence

The randomised evidence from all nine completed JAK inhibitor trials to date suggest that treatment with baricitinib or an alternative JAK inhibitor reduces mortality by about one-fifth (rate ratio 0·80 [95% CI 0·72–0·89]) in patients hospitalised with COVID-19, including those already receiving a systemic corticosteroid or an IL-6 receptor blocker.

endocytosis of SARS-CoV-2 into lung cells by inhibiting AP2-associated protein kinase 1 and cyclin G associated kinase.[8]

Baricitinib was tested in combination with remdesivir in the Adaptive Covid-19 Treatment Trial-2 (ACTT-2) and was shown to improve time to recovery compared with remdesivir alone (rate ratio for recovery 1·16, 95% CI 1·01–1·32). There was also a suggestion that 28-day mortality might be reduced by baricitinib (hazard ratio 0·65, 95% CI 0·39–1·09).[11] As a consequence, the US Food and Drug Administration (FDA) issued an emergency use authorisation for the use of baricitinib for the treatment of COVID-19 in patients who are hospitalised and requiring oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[12] Since then, a further seven randomised trials of JAK inhibitors have reported (NCT04362137, NCT04377620 [13–17]), of which two have reported a significant reduction in mortality (NCT04377620[16]). Here we report the results of a large randomised controlled trial of baricitinib in patients hospitalised with severe COVID-19.

Methods

Study design and participants

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19. Details of the trial design and results for other possible treatments (dexamethasone, hydroxychloroquine, lopinavir–ritonavir, azithromycin, tocilizumab, convalescent plasma, colchicine, aspirin, and casirivimab plus imdevimab) have been published previously.[3,5,18–24] The trial is underway at 177 hospital organisations in the UK supported by the National Institute for Health Research Clinical Research Network (appendix pp 3–27). Of these, 159 UK hospitals enrolled participants in the evaluation of baricitinib. The trial is coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor. The trial is done in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (reference 20/EE/0101). The protocol and statistical analysis plan are available in the appendix (pp 68–145) with additional information available on the study website.

Patients aged at least 2 years admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if

they were to participate in the trial. Patients were ineligible for the comparison of baricitinib versus usual care if younger than 2 years, had estimated glomerular filtration rate (eGFR) of less than 15 mL/min per 1·73 m² or were on dialysis or haemofiltration, had a neutrophil count of less than 0·5×10⁹ per L, had evidence of active tuberculosis infection, or were pregnant or breastfeeding. Written informed consent was obtained from all patients, or a legal representative if patients were too unwell or unable to provide consent.

Randomisation and masking

Baseline data were collected by means of a web-based case report form that included demographics, amount of respiratory support, major comorbidities, suitability of the study treatment for a particular patient, SARS-CoV-2 vaccination status, and treatment availability at the study site (appendix pp 38–42).

Eligible and consenting patients were assigned in a 1:1 ratio to either usual standard of care plus baricitinib or usual standard of care alone, by means of web-based simple (unstratified) randomisation with allocation concealed until after randomisation (appendix pp 33–37). For some patients, baricitinib was unavailable at the hospital at the time of enrolment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. These patients were excluded from the randomised comparison between baricitinib versus usual care. Patients allocated to baricitinib were to receive baricitinib 4 mg daily for 10 days (or until discharge if sooner). The dose was to be reduced for patients with eGFR of less than 60 mL/min per 1·73 m² or receiving probenecid, and for children younger than 9 years (see appendix p 30 for dosing details). Previous or subsequent administration of tocilizumab was permitted at the discretion of the managing physician who was also responsible for considering the risk of infection and gastrointestinal perforation (particularly in the context of corticosteroid use).

As a platform trial, and in a factorial design, patients could be simultaneously randomised to other treatment groups: colchicine versus usual care, aspirin versus usual care, dimethyl fumarate versus usual care, casirivimab plus imdevimab versus usual care, and empagliflozin versus usual care. Further details of when these factorial randomisations were open are provided in the appendix (pp 38–39). Participants and local study staff were not masked to the allocated treatment. The Trial Steering Committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial.

Procedures

An online follow-up form was completed by site staff when patients were discharged, had died, or at 28 days after randomisation, whichever occurred first (appendix pp 45–50). Information was recorded on

	Baricitinib group (n=4148)	Usual care group (n=4008)
Age, years	58·5 (15·4)	57·7 (15·5)
<70	3142 (76%)	3086 (77%)
≥70 to <80	665 (16%)	655 (16%)
≥80	341 (8%)	267 (7%)
Sex		
Male	2740 (66%)	2638 (66%)
Female	1408 (34%)	1370 (34%)
Ethnicity		
White	3323 (80%)	3203 (80%)
Black, Asian, and minority ethnic	457 (11%)	469 (12%)
Unknown	368 (9%)	336 (8%)
Time since symptom onset, days	9 (6–12)	9 (6–11)
Time since admission to hospital, days	1 (1–3)	1 (1–3)
Respiratory support received		
None	228 (5%)	237 (6%)
Simple oxygen	2770 (67%)	2743 (68%)
Non-invasive ventilation	1016 (24%)	911 (23%)
Invasive mechanical ventilation	134 (3%)	117 (3%)
Laboratory measurements		
C-reactive protein, mg/L	84 (42–146)	87 (44–143)
Creatinine, μmol/L	76 (63–93)	77 (63–94)
Previous diseases		
Diabetes	961 (23%)	941 (23%)
Heart disease	782 (19%)	706 (18%)
Chronic lung disease	882 (21%)	783 (20%)
Tuberculosis	0	0
HIV	13 (<1%)	9 (<1%)
Severe liver disease*	33 (1%)	33 (1%)
Severe kidney impairment†	101 (2%)	79 (2%)
Any of the above	1957 (47%)	1834 (46%)
SARS-CoV-2 PCR test result		
Positive	3969 (96%)	3873 (97%)
Negative	43 (1%)	32 (1%)
Unknown	136 (3%)	103 (3%)
Received a COVID-19 vaccine	1755 (42%)	1665 (42%)
Use of other treatments		
Corticosteroids	3962 (96%)	3809 (95%)
Remdesivir	878 (21%)	789 (20%)
Tocilizumab	951 (23%)	921 (23%)
Plan to use tocilizumab within the next 24 h	391 (9%)	365 (9%)
Other randomly assigned treatments		
Colchicine	401 (10%)	401 (10%)
Aspirin	462 (11%)	453 (11%)
Casirivimab–imdevimab	440 (11%)	449 (11%)

Data are mean (SD), n (%), or median (IQR). 33 children and 4 post-partum women were randomly assigned. *Defined as requiring ongoing specialist care. †Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m².

***Table 1:* Baseline characteristics**

adherence to allocated trial treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, new cardiac arrhythmia, thrombosis, clinically significant bleeding, non-COVID-19 infection, and vital status (including cause of death). In addition, routinely collected health-care and registry data were obtained, including information on vital status at day 28 (with date and cause of death); discharge from hospital; and receipt of respiratory support or renal replacement therapy.

Outcomes

Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital, and, among patients not on invasive mechanical ventilation at randomisation, the composite outcome of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were use of invasive or non-invasive ventilation among patients not on any ventilation at randomisation, time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days), and use of renal dialysis or haemofiltration. Prespecified safety outcomes were cause-specific mortality, major cardiac arrhythmia, thrombotic and major bleeding events, and other infections. Information on suspected serious adverse reactions was collected in an expedited fashion to comply with regulatory requirements. Details of the methods used to ascertain and derive outcomes are provided in the appendix (pp 146–66).

Statistical analysis

For all outcomes, intention-to-treat analyses compared patients randomly assigned to baricitinib with patients randomly assigned to usual care. Through the play of chance in the unstratified randomisation, patients in the baricitinib group were slightly older than patients in the usual care group (table 1). In accordance with the prespecified statistical analysis plan for dealing with baseline imbalances in important prognostic factors (appendix p 130), estimates of the effect of allocation to baricitinib on major outcomes were adjusted for age in three groups (<70 years, ≥70 to <80 years, and ≥80 years). Sensitivity analyses were done without this adjustment and, separately, with further adjustment for other predefined subgroups of interest.

For the primary outcome of 28-day mortality, the hazard ratio from an age-adjusted Cox model was used to estimate the mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used the same method to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right-censored on day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the prespecified composite secondary outcome of progression to invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation), and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so a log-binomial regression model was used to estimate the age-adjusted risk ratio. Estimates of rate and risk ratios (both denoted RR) are shown with 95% CIs.

Prespecified analyses of the primary outcome were done in subgroups defined by six characteristics at the time of randomisation (age, sex, ethnicity, days since symptom onset, amount of respiratory support, and use of corticosteroids) with tests of heterogeneity or trend, as appropriate. The full database is held by the study team which collected the data from study sites and did the analyses at the Nuffield Department of Population Health, University of Oxford.

The independent data monitoring committee reviewed unmasked analyses of the study data and any other information considered relevant to the trial at intervals of around 2 to 4 weeks (depending on speed of enrolment) and was charged with establishing whether, in their view, the randomised comparisons in the study provided evidence on mortality that was strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies (appendix p 51).

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned. On the advice of the trial steering committee, recruitment to this comparison was closed on Dec 29, 2021 when over 8150 patients had been randomly assigned and the
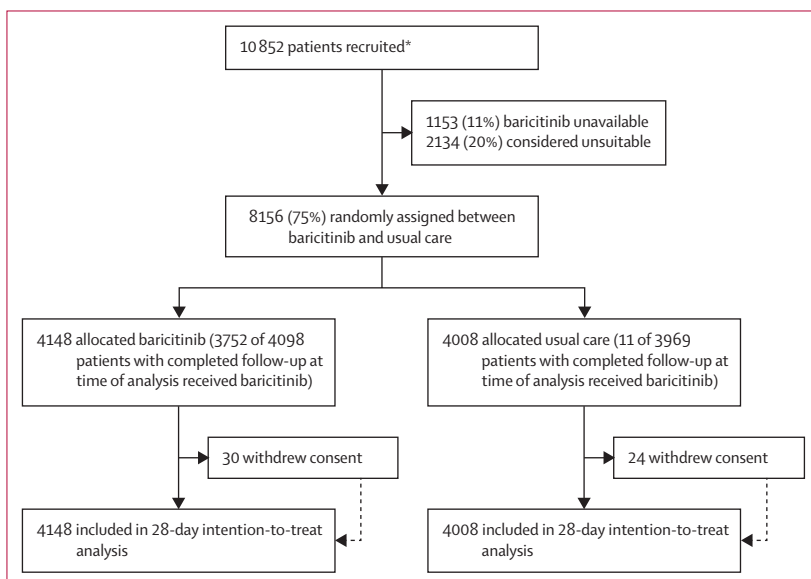

Figure 1: Trial profile
Baricitinib unavailable and baricitinib considered unsuitable are not mutually exclusive. *Number recruited overall during period that adult participants could be recruited into the baricitinib comparison.

masked 28-day mortality rate was 12·9% (suggesting there would be at least 1050 deaths), giving at least 90% power to detect a proportional risk reduction in the primary outcome of one-fifth at a two-sided significance level of 1%. The trial steering committee and all other individuals involved in the trial were masked to outcome data until after the close of recruitment.

For the primary outcome of 28-day mortality, the results from the RECOVERY trial were subsequently included in a meta-analysis of results from all previous randomised controlled trials of a JAK inhibitor for patients hospitalised with COVID-19. Details of the systematic search methods are provided in the appendix (pp 30–32). For each trial, we compared the observed number of deaths among patients allocated to the JAK inhibitor with the expected number if all patients were at equal risk (ie, we calculated the observed minus expected statistic [o–e], and its variance v). For RECOVERY, these were estimated from the age-adjusted mortality log rate ratio and its standard error but for other trials, where the exact timing of each death was not available, these were calculated from standard formulae for 2×2 contingency tables. We then combined trial results using the log of the mortality rate ratio calculated as the inverse-variance weighted average S/V with variance 1/V (and hence with 95% CI S/V ±1·96/√V), where S is the sum over all trials of (o–e) and V is the sum over all trials of v.[25] Such meta-analyses do not make any assumptions about the nature of any true heterogeneity in the log of the mortality rate ratio between different trials (in particular it does not assume that it is zero). Analyses were done by means of SAS version 9.4 and R version 4.0.3. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 2 and Dec 29, 2021, 8156 (75%) of 10 852 patients enrolled into the RECOVERY trial were eligible to be randomly allocated to baricitinib (ie, the treatment was available in the hospital at the time and the attending clinician was of the opinion that the patient had no known indication for or contraindication to it, figure 1). 4148 patients were randomly allocated to baricitinib and 4008 were randomly allocated to usual care. The mean age of study participants in this comparison was 58·1 years (SD 15·5) with a chance imbalance whereby patients randomly allocated to baricitinib were, on average, 0·8 years older than those allocated to the usual care group (table 1). At randomisation, 7771 (95%) patients were receiving corticosteroids and 1872 (23%) were receiving tocilizumab (with planned use within the next 24 h recorded for a further 756 [9%]; table 1, appendix p 53). About two-thirds

	Treatment allocation		RR (95% CI)	p value
	Baricitinib (n=4148)	Usual care (n=4008)		
Primary outcome				
28-day mortality	514 (12%)	546 (14%)	0·87 (0·77–0·99)	0·028
Secondary outcomes				
Time to being discharged alive, days	8 (5–17)	8 (5–20)	..	..
Discharged from hospital within 28 days	3338 (80%)	3136 (78%)	1·10 (1·04–1·15)	0·0002
Receipt of invasive mechanical ventilation or death*	633/4014 (16%)	678/3891 (17%)	0·89 (0·81–0·98)	0·016
Invasive mechanical ventilation	287/4014 (7%)	333/3891 (9%)	0·85 (0·73–0·99)	0·033
Death	475/4014 (12%)	502/3891 (13%)	0·89 (0·80–1·00)	0·049
Subsidiary clinical outcomes				
Receipt of ventilation†	595/2998 (20%)	638/2980 (21%)	0·93 (0·84–1·03)	0·16
Non-invasive ventilation	587/2998 (20%)	623/2980 (21%)	0·94 (0·85–1·04)	0·23
Invasive mechanical ventilation	131/2998 (4%)	149/2980 (5%)	0·89 (0·71–1·12)	0·32
Successful cessation of invasive mechanical ventilation‡	61/134 (46%)	43/117 (37%)	1·28 (0·87–1·90)	0·21
Use of haemodialysis or haemofiltration§	87/4139 (2%)	110/4003 (3%)	0·78 (0·59–1·03)	0·08

Data are n (%), n/N (%), or median (IQR). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. Estimates of the RR and its 95% CI are adjusted for age in three categories (<70 years, 70–79 years, and 80 years or older). *Analyses exclude those on invasive mechanical ventilation at randomisation. †Analyses exclude those on any form of ventilation at randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at randomisation. §Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Table 2: Effect of allocation to baricitinib on key study outcomes

were receiving simple oxygen and one-quarter were receiving non-invasive ventilation, with small numbers receiving invasive mechanical ventilation or no respiratory support at all. 3420 (42%) patients had received at least one dose of a SARS-CoV-2 vaccine.

The follow-up form was completed for 4098 (99%) patients in the baricitinib group and 3969 (99%) patients in the usual care group. Among patients with a completed follow-up form, 92% allocated to baricitinib were reported to have received the treatment compared with less than 1% allocated to usual care (figure 1, appendix p 54). Use of other treatments for COVID-19 was broadly similar among patients allocated to baricitinib and among those allocated to usual care, with nine-tenths receiving a corticosteroid, one-fifth receiving remdesivir, and one-tenth receiving casirivimab plus imdevimab, although use of tocilizumab during the follow-up period was slightly lower in the baricitinib group than in the usual care group (26% vs 29%; appendix p 54).

Primary and secondary outcome data are known for more than 99% of randomly assigned patients. Allocation to baricitinib was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone: 514 (12%) of 4148 patients in the baricitinib group died vs 546 (14%) of 4008 patients in the

usual care group (age-adjusted rate ratio 0·87; 95% CI 0·77–0·99; p=0·028; table 2, figure 2). Similar proportional risk reductions were seen in sensitivity analyses adjusted for all prespecified subgroups (as listed in figure 3) and

Figure 2: **Effect of allocation to baricitinib on 28-day mortality**

without adjustment for the 0·8-year age imbalance between randomised groups (appendix p 55), and when restricted to participants with a positive SARS-CoV-2 PCR test (age-adjusted rate ratio 0·90, 0·80–1·02).

The proportional effect of baricitinib on mortality was consistent across all six prespecified subgroups (all interaction p values >0·18; figure 3), including by amount of respiratory support received and use of dexamethasone at randomisation and, in five exploratory subgroups, including by use of tocilizumab or remdesivir at baseline (all interaction p values >0·10; appendix p 64). There was no evidence that the effect of baricitinib on mortality varied depending on concurrent randomised allocation to colchicine, aspirin, or casirivimab–imdevimab (all interaction p values >0·32).

Discharge alive within 28 days was more common among those allocated to baricitinib compared with usual care (80% vs 78%; age-adjusted rate ratio 1·10, 95% CI 1·04–1·15; median 8 days [IQR 5–17] vs 8 days [IQR 5–20]; table 2). Among patients not on invasive mechanical ventilation at baseline, allocation to baricitinib was associated with a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (16% vs 17%, age-adjusted risk ratio 0·89, 0·81–0·98; table 2 and appendix p 65). The proportional effects of
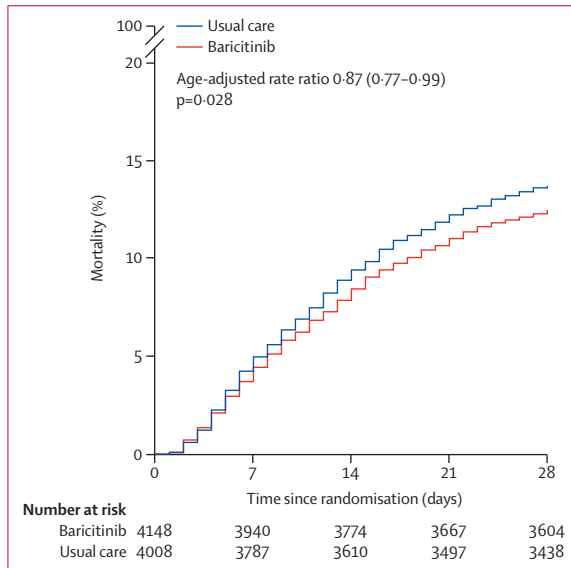

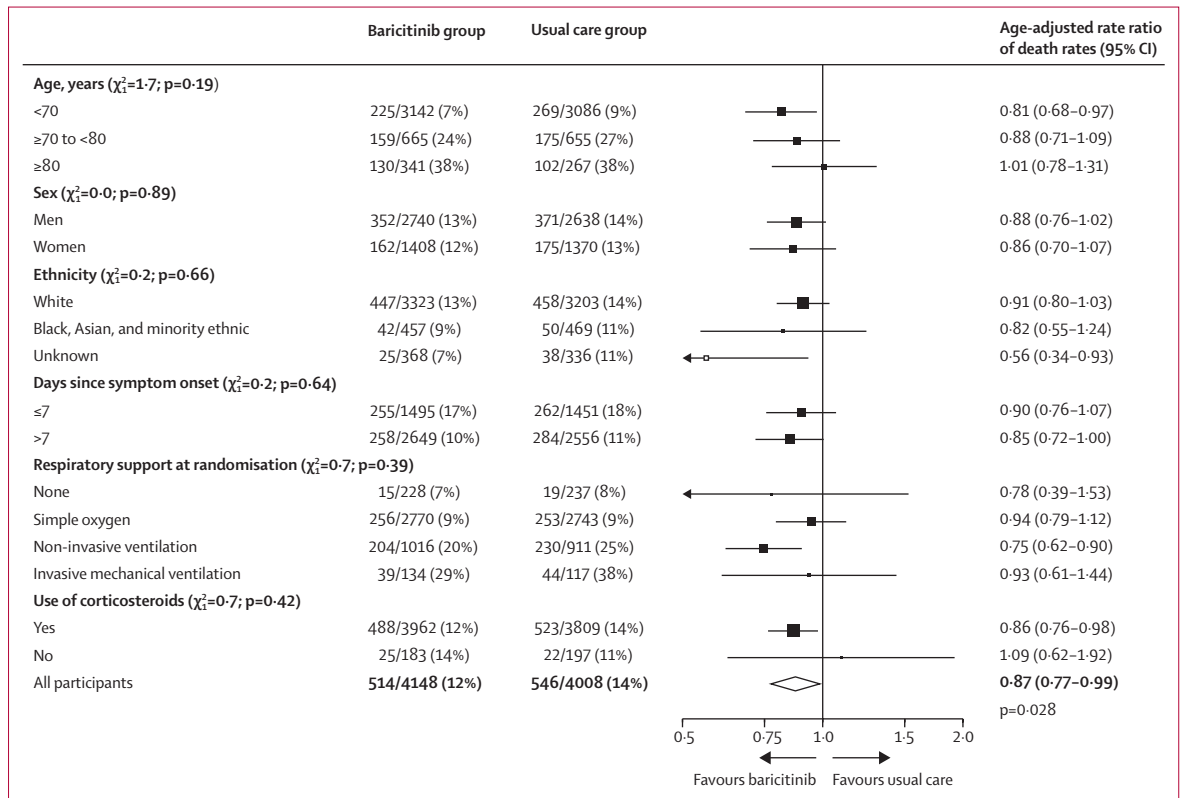|	Baricitinib group	Usual care group		Age-adjusted rate ratio of death rates (95% CI)
Age, years (χ^2_1=1·7; p=0·19)				
<70	225/3142 (7%)	269/3086 (9%)		0·81 (0·68–0·97)
≥70 to <80	159/665 (24%)	175/655 (27%)		0·88 (0·71–1·09)
≥80	130/341 (38%)	102/267 (38%)		1·01 (0·78–1·31)
Sex (χ^2_1=0·0; p=0·89)				
Men	352/2740 (13%)	371/2638 (14%)		0·88 (0·76–1·02)
Women	162/1408 (12%)	175/1370 (13%)		0·86 (0·70–1·07)
Ethnicity (χ^2_1=0·2; p=0·66)				
White	447/3323 (13%)	458/3203 (14%)		0·91 (0·80–1·03)
Black, Asian, and minority ethnic	42/457 (9%)	50/469 (11%)		0·82 (0·55–1·24)
Unknown	25/368 (7%)	38/336 (11%)		0·56 (0·34–0·93)
Days since symptom onset (χ^2_1=0·2; p=0·64)				
≤7	255/1495 (17%)	262/1451 (18%)		0·90 (0·76–1·07)
>7	258/2649 (10%)	284/2556 (11%)		0·85 (0·72–1·00)
Respiratory support at randomisation (χ^2_1=0·7; p=0·39)				
None	15/228 (7%)	19/237 (8%)		0·78 (0·39–1·53)
Simple oxygen	256/2770 (9%)	253/2743 (9%)		0·94 (0·79–1·12)
Non-invasive ventilation	204/1016 (20%)	230/911 (25%)		0·75 (0·62–0·90)
Invasive mechanical ventilation	39/134 (29%)	44/117 (38%)		0·93 (0·61–1·44)
Use of corticosteroids (χ^2_1=0·7; p=0·42)				
Yes	488/3962 (12%)	523/3809 (14%)		0·86 (0·76–0·98)
No	25/183 (14%)	22/197 (11%)		1·09 (0·62–1·92)
All participants	**514/4148 (12%)**	**546/4008 (14%)**		**0·87 (0·77–0·99)** p=0·028

Figure 3: **Effect of allocation to baricitinib on 28-day mortality by baseline characteristics**
Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. The days since onset and use of corticosteroids subgroups exclude those with missing data, but these patients are included in the overall summary diamond.
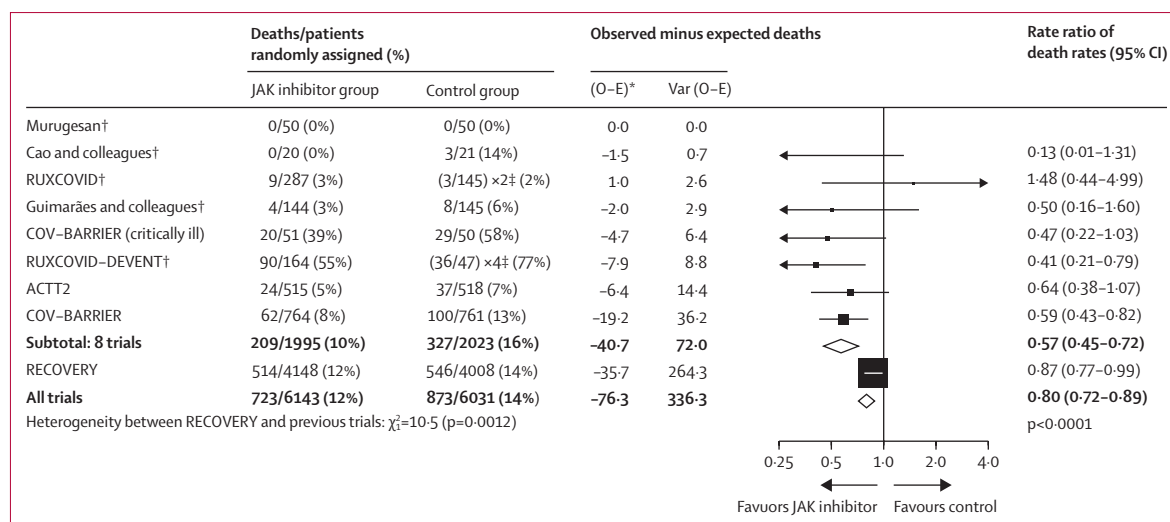
	Deaths/patients randomly assigned (%)		Observed minus expected deaths			Rate ratio of death rates (95% CI)
	JAK inhibitor group	Control group	(O–E)*	Var (O–E)		
Murugesan†	0/50 (0%)	0/50 (0%)	0·0	0·0		
Cao and colleagues†	0/20 (0%)	3/21 (14%)	–1·5	0·7		0·13 (0·01–1·31)
RUXCOVID†	9/287 (3%)	(3/145) ×2‡ (2%)	1·0	2·6		1·48 (0·44–4·99)
Guimarães and colleagues†	4/144 (3%)	8/145 (6%)	–2·0	2·9		0·50 (0·16–1·60)
COV–BARRIER (critically ill)	20/51 (39%)	29/50 (58%)	–4·7	6·4		0·47 (0·22–1·03)
RUXCOVID–DEVENT†	90/164 (55%)	(36/47) ×4‡ (77%)	–7·9	8·8		0·41 (0·21–0·79)
ACTT2	24/515 (5%)	37/518 (7%)	–6·4	14·4		0·64 (0·38–1·07)
COV–BARRIER	62/764 (8%)	100/761 (13%)	–19·2	36·2		0·59 (0·43–0·82)
Subtotal: 8 trials	**209/1995 (10%)**	**327/2023 (16%)**	**–40·7**	**72·0**		**0·57 (0·45–0·72)**
RECOVERY	514/4148 (12%)	546/4008 (14%)	–35·7	264·3		0·87 (0·77–0·99)
All trials	**723/6143 (12%)**	**873/6031 (14%)**	**–76·3**	**336·3**		**0·80 (0·72–0·89)**
Heterogeneity between RECOVERY and previous trials: χ^2_1=10·5 (p=0·0012)						p<0·0001

```
0·25    0·5    1·0    2·0    4·0
     Favours JAK inhibitor    Favours control
```

Figure 4: Meta-analysis of mortality in randomised controlled trials of a JAK inhibitor in patients hospitalised with COVID-19
JAK=Janus kinase. O–E=observed–expected. Var=variance. RR=mortality rate ratio. Details of the individual studies, including the use of placebo or other treatments in the control group are shown in the appendix (p 62). *For RECOVERY, the O–E and its variance are calculated from the age-adjusted log RR and its standard error. For the other trials, the O–E statistics and their variances are calculated from 2 × 2 tables. Rate ratio is calculated by taking ln rate ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Subtotals or totals of (O–E) and of V yield inverse-variance weighted averages of the ln rate ratio values. †These trials assessed a JAK inhibitor other than baricitinib. If the meta-analysis was restricted to RECOVERY plus the three other trials of baricitinib, the RR would be 0·81 (95% CI 0·73–0·91). ‡For balance, controls in the n:1 studies count n times in the control totals and subtotals, but only count once when calculating their O–E or V values.

baricitinib versus usual care on these secondary outcomes were similar across all prespecified subgroups (appendix pp 65–66). Results for the 33 children included in this comparison are shown in the appendix (p 56).

There were no significant differences in the prespecified subsidiary clinical outcomes of cause-specific mortality other than a reduction in death due to COVID-19 (appendix p 57) or in use of ventilation, successful cessation of invasive mechanical ventilation, or receipt of haemodialysis or haemofiltration (table 2). There were no significant differences in the rates of non-SARS-CoV-2 infection, thrombotic events, or clinically significant bleeding, but allocation to baricitinib was associated with a nominally significant reduction in new onset cardiac arrythmia (2·3% *vs* 3·2%, p=0·017; appendix p 58). In exploratory analyses, allocation to baricitinib versus usual care was not associated with any significant differences in non-COVID-19 causes of death or infection among those recorded as having been treated with tocilizumab at baseline (appendix pp 59–60). There were 12 reports of a serious adverse reaction believed to be related to treatment with baricitinib (appendix p 61), including four participants with a serious non-SARS-CoV-2 infection, three with a bowel perforation, and two with a pulmonary embolism. Our systematic search identified eight previous trials of a JAK inhibitor for the treatment of patients hospitalised with COVID-19, involving a total of 3732 randomly assigned patients and 425 deaths (figure 4, appendix p 62).[11,13–19] In these eight trials, allocation to a JAK inhibitor was associated with a significant 43% proportional reduction in mortality (rate ratio 0·57; 95% CI 0·45–0·72). This was significantly greater than the mortality risk

reduction seen in RECOVERY (test for heterogeneity, p=0·0012). After inclusion of the results from RECOVERY into this meta-analysis, the average mortality rate ratio from all nine trials, now involving 11 888 randomised patients and 1485 deaths, was 0·80 (0·72–0·89; p<0·0001).

Discussion

In this large, randomised trial, allocation to baricitinib significantly reduced 28-day mortality by about one-eighth. This is somewhat less than had been suggested by eight previous randomised controlled trials of a JAK inhibitor which, together, suggested that allocation to a JAK inhibitor in patients with COVID-19 reduces 28-day mortality by about two-fifths. RECOVERY was more than three times the size (in terms of statistical information) of these eight previous trials put together. When combined in an updated meta-analysis, allocation to baricitinib or another JAK inhibitor in these nine trials was associated with a significant reduction in 28-day mortality of one-fifth. Although not as large as perhaps previously thought, this still represents an important reduction in mortality risk for patients hospitalised because of COVID-19.

Strengths of the RECOVERY trial included that it was randomised, had a large sample size, had broad eligibility criteria, and more than 99% of patients were followed up for the primary outcome. The study has some limitations: this randomised trial is open label (ie, participants and local hospital staff are aware of the assigned treatment). However, the outcomes are unambiguous and were ascertained without bias through linkage to routine health records. Use of tocilizumab during the follow-up period

was slightly lower among those allocated to baricitinib compared with control (26% *vs* 29%). Based on what we already know about the effects of tocilizumab, this would, if anything, lead to a small underestimate of the effects of baricitinib. Furthermore, use of anti-viral or immuno-modulatory treatments known to reduce mortality in this setting was similar in those allocated to baricitinib and those allocated to usual care. Information on radiological, virological, or physiological outcomes was not collected. This evaluation of baricitinib was done only in the UK, with low rates of HIV among trial participants (<1%) and no participants with active tuberculosis, since active tuberculosis was a contraindication to inclusion in the baricitinib comparison. The effect of baricitinib on non-SARS-CoV-2 infections might be different in populations with a higher prevalence of tuberculosis or HIV.

The smaller effect size observed in RECOVERY compared with earlier trials of baricitinib might simply be a chance effect. However, several other factors could have contributed. The patient population in RECOVERY might have been broader than some of the other trials, which might have been enriched for patients more likely to benefit from immunomodulatory therapy. The use of concomitant therapies has varied between the trials. For example, the ACTT-2 trial[11] did not permit the use of dexamethasone as a treatment for COVID-19, and ACTT-2, COV-BARRIER,[16] RUXCOVID, and the study by Guimarães and colleagues[15] all excluded the use of an IL-6 receptor blocker (NCT04362137). Other factors that might be different between the trials include the prevalence of SARS-CoV-2 vaccination and the predominant circulating SARS-CoV-2 variant. However, there is no clear reason to believe that, among patients admitted to hospital with severe COVID-19 requiring oxygen or ventilatory support, the proportional risk reduction in mortality with baricitinib, a host-directed therapy, would differ by vaccination status or SARS-CoV-2 variant—and we found no evidence of this. Despite the heterogeneity of effect between RECOVERY and the previous eight trials combined, the overall result of the meta-analysis (which makes no assumptions about the nature of any true differences in treatment effects between the different populations studied) provides the best guide of the proportional benefits that might be expected from the use of baricitinib in clinical practice. The size of the RECOVERY trial allows exploration of the effects of treatment among different subgroups of patients. The benefits of baricitinib on 28-day mortality were consistent across all subgroups, including by age, sex, ethnicity, and amount of respiratory support received (although over 90% of participants were either on simple oxygen or receiving non-invasive mechanical ventilation). The benefits of baricitinib were also consistent regardless of concomitant treatment with remdesivir, a systemic corticosteroid or an IL-6 receptor blocker (tocilizumab or sarilumab), or previous receipt of a SARS-CoV-2 vaccine. Reassuringly, we found no

evidence that allocation to baricitinib was associated with excess rates of non-COVID-19 mortality, non-SARS-CoV-2 infection, or thrombosis by comparison with usual care.

On Nov 19, 2020, the FDA granted emergency use authorisation for baricitinib in combination with remdesivir, which was revised on July 28, 2021 to no longer require co-administration with remdesivir. On May 10, 2022 the FDA issued a new indication for the use of baricitinib in adults hospitalised with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.[12,26] US National Institutes of Health guidelines updated in February, 2022 recommend the use of baricitinib for patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation.[27] In January, 2022, the World Health Organization updated their COVID-19 therapeutics guidelines to include a strong recommendation for the use of baricitinib as an alternative to an IL-6 receptor blocker, in combination with corticosteroids, in patients with severe or critical COVID-19.[28] The results from the RECOVERY trial and our meta-analysis considerably strengthen the evidence that baricitinib can reduce mortality and other adverse clinical outcomes in patients hospitalised with COVID-19 and support the co-administration of baricitinib with dexamethasone or an IL-6 receptor blocker.

In summary, this large, randomised trial confirms evidence from previous smaller trials that treatment with baricitinib can reduce mortality in patients hospitalised with COVID-19, although the size of the benefit is about half that previously thought. The benefits appear to be consistent regardless of treatment with remdesivir, systemic corticosteroids, or an IL-6 receptor blocker such as tocilizumab. The results support the use of baricitinib in addition to other immunosuppressive therapies in patients hospitalised with COVID-19.

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