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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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7 **Running title:** Baricitinib for COVID-19

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9 **RECOVERY Collaborative Group***

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12 *The Writing Committee and Trial Steering Committee are listed at the end of this

13 manuscript and a complete list of collaborators in the Randomised Evaluation of

14 COVID-19 Therapy (RECOVERY) trial is provided in the Supplementary Appendix.

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SUMMARY

Background: We evaluated the use of baricitinib, a Janus kinase (JAK) 1/2 inhibitor, for the treatment of patients admitted to hospital because of 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 for COVID-19. 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 conducted that 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).

Findings: Between 2 February 2021 and 29 December 2021, 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% receiving tocilizumab (with planned use within the next 24 hours recorded for a further 9%). Overall, 513 (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 0·77-0·98; p=0·026). This 13% proportional reduction in mortality was somewhat smaller than that seen in a meta-analysis of 8 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

46   from RECOVERY into an updated meta-analysis of all 9 completed trials (involving

47   11,888 randomised patients and 1484 deaths) allocation to baricitinib or other JAK

48   inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0.80;

49   95% CI 0.71-0.89; p<0.001). In RECOVERY, there was no significant excess in death or

50   infection due to non-COVID-19 causes and no excess of thrombosis, or other safety

51   outcomes.

52   **Interpretation:** In patients hospitalised for COVID-19, baricitinib significantly reduced the

53   risk of death but the size of benefit was somewhat smaller than that suggested by

54   previous trials. The total randomised evidence to date suggests that JAK inhibitors (chiefly

55   baricitinib) reduce mortality in patients hospitalised for COVID-19 by about one-fifth.

58   **Keywords:** COVID-19, baricitinib, clinical trial, meta-analysis.

59

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 may 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 that 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 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, that 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 tyrosine kinase 2 (TYK2) and genetic data support a causal link between high TYK2 expression and life-threatening COVID-19.[10] Baricitinib was also predicted, using artificial intelligence, to reduce endocytosis of SARs-CoV-2 into lung cells by inhibiting AP2-associated protein kinase 1 (AAK1) and cyclin G associated kinase (GAK).[8]

81 Baricitinib was tested in combination with remdesivir in the Adaptive Covid-19 Treatment

82 Trial-2 (ACTT-2) and was shown to improve time to recovery compared to remdesivir

83 alone (rate ratio for recovery 1.16, 95% CI 1.01-1.32). There was also a suggestion that

84 28-day mortality may be reduced by baricitinib (HR 0.65, 95% CI 0.39-1.09).[11] As a

85 consequence, the US Food and Drug Administration (US FDA) issued an emergency use

86 authorisation for the use of baricitinib in combination with remdesivir, for the treatment of

87 COVID-19 in hospitalised patients requiring oxygen, invasive mechanical ventilation or

88 extracorporeal membrane oxygenation (ECMO).[12] Since then, a further 7 randomised

89 trials of JAK inhibitors have reported,[13-19] of which two have reported a significant

90 reduction in mortality.[16,19] Here we report the results of a large randomised controlled trial

91 of baricitinib in patients hospitalised with severe COVID-19.

92

93 **METHODS**

94 **Study design and participants**

95 The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is an investigator-

96 initiated, individually randomised, controlled, open-label, platform trial to evaluate the

97 effects of potential treatments in patients hospitalised with COVID-19. Details of the trial

98 design and results for other possible treatments (dexamethasone, hydroxychloroquine,

99 lopinavir-ritonavir, azithromycin, tocilizumab, convalescent plasma, colchicine, aspirin,

100 and casirivimab plus imdevimab) have been published previously.[3,5,20-26] The trial is

101 underway at 177 hospital organisations in the United Kingdom supported by the National

102 Institute for Health Research Clinical Research Network (appendix pp 3-27). Of these,

103   159 UK hospitals took part in the evaluation of baricitinib. The trial is coordinated by the

104   Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the

105   trial sponsor. The trial is conducted in accordance with the principles of the International

106   Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK

107   Medicines and Healthcare products Regulatory Agency (MHRA) and the Cambridge East

108   Research Ethics Committee (ref: 20/EE/0101). The protocol and statistical analysis plan

109   are available in the appendix (pp 61-140) with additional information available on the

110   study website www.recoverytrial.net.

111   Patients aged at least 2 years admitted to hospital were eligible for the study if they had

112   clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history

113   that might, in the opinion of the attending clinician, put the patient at significant risk if they

114   were to participate in the trial. Patients were ineligible for the comparison of baricitinib vs.

115   usual care if aged <2 years, eGFR <15 mL/min/1.73m^2 or on dialysis or haemofiltration,

116   neutrophil count <0.5 x 10^9/L, had evidence of active TB infection, or were pregnant or

117   breastfeeding. Written informed consent was obtained from all patients, or a legal

118   representative if patients were too unwell or unable to provide consent.

119   **Randomisation and masking**

120   Baseline data were collected using a web-based case report form that included

121   demographics, level of respiratory support, major comorbidities, suitability of the study

122   treatment for a particular patient, and treatment availability at the study site (appendix pp

123   36-38). Data on SARS-CoV-2 vaccination status were collected from 22 December 2020.

124   Eligible and consenting patients were assigned in a 1:1 ratio to either usual standard of

125   care plus baricitinib or usual standard of care alone, using web-based simple (unstratified)

126   randomisation with allocation concealed until after randomisation (appendix pp 29-33).

127   For some patients, baricitinib was unavailable at the hospital at the time of enrolment or

128   was considered by the managing physician to be either definitely indicated or definitely

129   contraindicated. These patients were excluded from the randomised comparison between

130   baricitinib versus usual care. Patients allocated to baricitinib were to receive baricitinib 4

131   mg daily for 10 days (or until discharge if sooner). The dose was to be reduced for patients

132   with eGFR <60 mL/min/1.73m^2 or receiving probenecid, and for children aged <9 years

133   (see appendix p 28 for dosing details). Prior or subsequent administration of tocilizumab

134   was permitted at the discretion of the managing doctor who was also responsible for

135   considering the risk of infection and gastrointestinal perforation (particularly in the context

136   of corticosteroid use).

137   As a platform trial, and in a factorial design, patients could be simultaneously randomised

138   to other treatment groups: i) colchicine versus usual care, ii) aspirin versus usual care, iii)

139   dimethyl fumarate versus usual care, iv) casirivimab+imdevimab versus usual care, and

140   v) empagliflozin versus usual care. Further details of when these factorial randomisations

141   were open are provided in the supplementary appendix (pp 29-33). Participants and local

142   study staff were not masked to the allocated treatment. The Trial Steering Committee,

143   investigators, and all other individuals involved in the trial were masked to outcome data

144   during the trial.

145

146 **Procedures**

147 An online follow-up form was completed by site staff when patients were discharged, had

148 died, or at 28 days after randomisation, whichever occurred first (appendix pp 39-46).

149 Information was recorded on adherence to allocated trial treatment, receipt of other

150 COVID-19 treatments, duration of admission, receipt of respiratory or renal support, new

151 cardiac arrhythmia, thrombosis, clinically significant bleeding, non-COVID infection, and

152 vital status (including cause of death). In addition, routinely collected healthcare and

153 registry data were obtained, including information on vital status at day 28 (with date and

154 cause of death); discharge from hospital; and receipt of respiratory support or renal

155 replacement therapy.

156 **Outcomes**

157 Outcomes were assessed at 28 days after randomisation, with further analyses specified

158 at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes

159 were time to discharge from hospital, and, among patients not on invasive mechanical

160 ventilation at randomisation, the composite outcome of invasive mechanical ventilation

161 (including extra-corporeal membrane oxygenation) or death. Prespecified subsidiary

162 clinical outcomes were use of invasive or non-invasive ventilation among patients not on

163 any ventilation at randomisation, time to successful cessation of invasive mechanical

164 ventilation (defined as cessation of invasive mechanical ventilation within, and survival to,

165 28 days), and use of renal dialysis or haemofiltration. Prespecified safety outcomes were

166 cause-specific mortality, major cardiac arrhythmia, thrombotic and major bleeding events,

167 and other infections. Information on suspected serious adverse reactions was collected

168 in an expedited fashion to comply with regulatory requirements. Details of the methods

169 used to ascertain and derive outcomes are provided in the appendix (pp.141-161).

170

171 **Statistical Analysis**

172 For all outcomes, intention-to-treat analyses compared patients randomised to baricitinib

173 with patients randomised to usual care. Through the play of chance in the unstratified

174 randomisation, patients in the baricitinib group were slightly older than patients in the

175 usual care group (Table 1). In accordance with the prespecified statistical analysis plan

176 for dealing with baseline imbalances in important prognostic factors (appendix p 125),

177 estimates of the effect of allocation to baricitinib on major outcomes were adjusted for

178 age in three groups (<70 years, ≥70 to <80 years, and ≥80 years). (Exploratory analyses

179 were conducted without this adjustment and, separately, with further adjustment for other

180 predefined subgroups of interest.)

181 For the primary outcome of 28-day mortality, the hazard ratio from an age-adjusted Cox

182 model was used to estimate the mortality rate ratio. We constructed Kaplan-Meier survival

183 curves to display cumulative mortality over the 28-day period. We used the same method

184 to analyse time to hospital discharge and successful cessation of invasive mechanical

185 ventilation, with patients who died in hospital right-censored on day 29. Median time to

186 discharge was derived from Kaplan-Meier estimates. For the pre-specified composite

187 secondary outcome of progression to invasive mechanical ventilation or death within 28

188 days (among those not receiving invasive mechanical ventilation at randomisation), and

189 the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or

190 haemofiltration, the precise dates were not available and so a log-binomial regression

191 model was used to estimate the age-adjusted risk ratio. Estimates of rate and risk ratios

192 (both denoted RR) are shown with 95% confidence intervals.

193 Prespecified analyses of the primary outcome were done in subgroups defined by six

194 characteristics at the time of randomisation (age, sex, ethnicity, days since symptom

195 onset, level of respiratory support, and use of corticosteroids) with tests of heterogeneity

196 or trend, as appropriate. The full database is held by the study team which collected the

197 data from study sites and performed the analyses at the Nuffield Department of

198 Population Health, University of Oxford (Oxford, UK).

199 The independent Data Monitoring Committee reviewed unblinded analyses of the study

200 data and any other information considered relevant to the trial at intervals of around 2 to

201 4 weeks (depending on speed of enrolment) and was charged with determining if, in their

202 view, the randomised comparisons in the study provided evidence on mortality that was

203 strong enough (with a range of uncertainty around the results that was narrow enough)

204 to affect national and global treatment strategies (see appendix p 50).

205 As stated in the protocol, appropriate sample sizes could not be estimated when the trial

206 was being planned. On the advice of the Trial Steering Committee, recruitment to this

207 comparison was closed on 29 December 2021 when over 8150 patients had been

208 randomised and the blinded 28-day mortality rate was 12.9% (suggesting there would be

209 at least 1050 deaths), giving at least 90% power to detect a proportional risk reduction in

210 the primary outcome of one-fifth at 2P=0.01. The Trial Steering Committee and all other

211   individuals involved in the trial were masked to outcome data until after the close of

212   recruitment.

213   For the primary outcome of 28-day mortality, the results from the RECOVERY trial were

214   subsequently included in a meta-analysis of results from all previous randomised

215   controlled trials of a JAK inhibitor for patients hospitalised with COVID-19. Details of the

216   systematic search methods are provided in the appendix (p 28). For each trial, we

217   compared the observed number of deaths among patients allocated to the JAK inhibitor

218   with the expected number if all patients were at equal risk (i.e., we calculated the observed

219   minus expected statistic [o–e], and its variance v). For RECOVERY, these were estimated

220   from the age-adjusted mortality log rate ratio and its standard error but for other trials,

221   where the exact timing of each death was not available, these were calculated from

222   standard formulae for 2 × 2 contingency tables. We then combined trial results using the

223   log of the mortality rate ratio calculated as the inverse-variance-weighted average S/V

224   with variance 1/V (and hence with 95% CI S/V ±1·96/√V), where S is the sum over all

225   trials of (o–e) and V is the sum over all trials of v.[27] Such meta-analyses do not make any

226   assumptions about the nature of any true heterogeneity in the log RR between different

227   trials (in particular it does not assume that it is zero). Analyses were performed using SAS

228   version 9.4 and R version 4.0.3. The trial is registered with ISRCTN (50189673) and

229   clinicaltrials.gov (NCT04381936).

230   **Role of the funding source**

231   The funders of the study had no role in study design, data collection, data analysis, data

232   interpretation, or writing of the report. Baricitinib was provided from standard National

233   Health Service (NHS) stocks. The corresponding authors had full access to all the data

234   in the study and had final responsibility for the decision to submit for publication.

235

236   **RESULTS**

237   Between 2 February 2021 and 29 December 2021, 8156 (75%) of 10852 patients enrolled

238   into the RECOVERY trial at one of the 169 participating sites were eligible to be randomly

239   allocated to baricitinib (i.e. the treatment was available in the hospital at the time and the

240   attending clinician was of the opinion that the patient had no known indication for or

241   contraindication to it, figure 1). 4148 patients were randomly allocated to baricitinib and

242   4008 were randomly allocated to usual care. The mean age of study participants in this

243   comparison was 58.1 years (SD 15.5) with a chance imbalance whereby patients

244   randomly allocated to baricitinib were, on average, 0.8 years older than those allocated

245   usual care group (Table 1). At randomisation, 7771 (95%) patients were receiving

246   corticosteroids, 1872 (23%) were receiving tocilizumab (with planned use within the next

247   24 hours recorded for a further 756 [9%]) (Table 1, Webtable 1). About two-thirds were

248   receiving simple oxygen and one quarter were receiving non-invasive ventilation, with

249   small numbers receiving invasive mechanical ventilation or no respiratory support at all.

250   3420 (42%) patients had received at least one dose of a SARS-CoV-2 vaccine.

251   The follow-up form was completed for 4084 (98%) patients in the baricitinib group and

252   3950 (99%) patients in the usual care group. Among patients with a completed follow-up

253   form, 91% allocated to baricitinib were reported to have received the treatment compared

254   with <1% allocated to usual care (figure 1, webtable 2). Use of other treatments for

255   COVID-19 was broadly similar among patients allocated baricitinib and among those

256   allocated usual care, with nine-tenths receiving a corticosteroid, one-fifth receiving

257   remdesivir, and one-tenth receiving casirivimab+imdevimab, although use of tocilizumab

258   during the follow-up period was slightly lower in the baricitinib group than in the usual care

259   group (26% vs. 29%) (webtable 2).

260   Primary and secondary outcome data are known for >99% of randomly assigned patients.

261   Allocation to baricitinib was associated with a significant reduction in the primary outcome

262   of 28-day mortality compared with usual care alone: 513 (12%) of 4148 patients in the

263   baricitinib group died vs 546 (14%) of 4008 patients in the usual care group (age-adjusted

264   rate ratio 0·87; 95% CI 0·77–0·98; p=0·026; table 2, figure 2). Similar proportional risk

265   reductions were seen in sensitivity analyses adjusted for all pre-specified subgroups (as

266   listed in figure 3) and without adjustment for the 0.8 year age-imbalance between

267   randomised groups (webtable 3), and when restricted to participants with a positive

268   SARS-CoV-2 PCR test (age adjusted RR 0.90, 95% CI 0.79-1.02).

269   The proportional effect of baricitinib on mortality was consistent across all pre-specified

270   subgroups (Figure 3), including by level of respiratory support received (test for trend

271   p=0.33), use of dexamethasone at randomisation (test for heterogeneity p=0.41) and, in

272   exploratory analyses, by baseline CRP level (test for trend p=0.93) or by use of

273   tocilizumab or remdesivir at baseline (tests for heterogeneity p=0.53 and p=0.12,

274   respectively) (webfigure 1). There was no evidence that the effect of baricitinib on

275   mortality varied depending on concurrent randomised allocation to colchicine, aspirin or

276   casirivimab+imdevimab (all interaction p-values >0.32).

277   Discharge alive within 28 days was more common among those allocated to baricitinib

278   compared with usual care (80% vs. 78%; age-adjusted rate ratio 1·10, 95% CI 1·04 to

279   1·15; median 8 days [IQR 5 to 17] vs. 8 days [IQR 5 to 20]) (table 2 and webfigure 2).

280   Among patients not on invasive mechanical ventilation at baseline, allocation to baricitinib

281   was associated with a lower risk of progressing to the composite secondary outcome of

282   invasive mechanical ventilation or death (16% vs. 17%, age-adjusted risk ratio 0·90, 95%

283   CI 0·81 to 0·99) (table 2 and webfigure 3). The proportional effects of baricitinib versus

284   usual care on these secondary outcomes were also similar across all pre-specified

285   subgroups (webfigures 2 and 3).

286   There were no significant differences in the pre-specified subsidiary clinical outcomes of

287   cause-specific mortality other than that due to COVID-19 (Webtable 4) or in use of

288   ventilation, successful cessation of invasive mechanical ventilation, or receipt of

289   haemodialysis or haemofiltration (table 2). There were no significant differences in the

290   rates of non-coronavirus infection, thrombotic events, or clinically significant bleeding, but

291   allocation to baricitinib was associated with a nominally significant reduction in new onset

292   cardiac arrythmia (2.3% vs 3.1%, p=0.017) (webtable 5). There were 13 reports of a

293   serious adverse reaction believed to be related to treatment with baricitinib (webtable 6),

294   including 5 participants with a serious non-COVID infection, 3 with a bowel perforation

295   and 2 with a pulmonary embolism.

296   Our systematic search identified 8 previous trials of a JAK inhibitor for the treatment of

297   patients hospitalised with COVID-19, involving a total of 3732 randomised patients and

298   425 deaths (figure 4 and webtable 8). [11,13-19] In these 8 trials, allocation to a JAK inhibitor

299   was associated with a significant 43% proportional reduction in mortality (rate ratio 0.57;

300 95% CI 0.45-0.72). This was significantly greater than the mortality risk reduction seen in

301 RECOVERY (test for heterogeneity, p=0.001). After inclusion of the results from

302 RECOVERY into this meta-analysis, the average mortality rate ratio from all 9 trials, now

303 involving 11,888 randomised patients and 1484 deaths, was 0.80 (0.71-0.89; p<0.001).

304

305 **DISCUSSION**

306 In this large, randomised trial, allocation to baricitinib significantly reduced 28-day

307 mortality by about one-eighth. This is somewhat less than had been suggested by eight

308 previous randomised, controlled trials of a JAK inhibitor which, together, suggested that

309 allocation to a JAK inhibitor in COVID-19 patients reduces 28-day mortality by about two-

310 fifths. RECOVERY was more than three times the size (in terms of statistical information)

311 of these 8 previous trials put together. When combined in an updated meta-analysis,

312 allocation to baricitinib or another JAK inhibitor in these 9 trials was associated with a

313 significant reduction in 28-day mortality of one-fifth. Although not as large as perhaps

314 previously thought, this still represents an important reduction in mortality risk for patients

315 hospitalised because of COVID-19.

316 Strengths of the RECOVERY trial included that it was randomised, had a large sample

317 size, broad eligibility criteria and more than 99% of patients were followed up for the

318 primary outcome. The study has some limitations: this randomised trial is open label (i.e.,

319 participants and local hospital staff are aware of the assigned treatment), however, the

320 outcomes are unambiguous and were ascertained without bias through linkage to routine

321 health records. Use of tocilizumab during the follow-up period was slightly lower among

15

322   those allocated to baricitinib compared with control (26% vs. 29%). Based on what we

323   already know about the effects of tocilizumab, would, if anything, lead to a small

324   underestimate of the effects of baricitinib. Furthermore, use of anti-viral or

325   immunomodulatory treatments known to reduce mortality in this setting was similar in

326   those allocated baricitinib and those allocated usual care. Information on radiological,

327   virological or physiological outcomes was not collected.

328   The smaller effect size observed in RECOVERY compared to earlier trials of baricitinib

329   may simply be a chance effect. However, several other factors could have contributed.

330   The patient population in RECOVERY may have been broader than some of the other

331   trials, which may have been enriched for patients more likely to benefit from

332   immunomodulatory therapy. The use of concomitant therapies has varied between the

333   trials. For example, the ACTT-2 trial did not permit the use of dexamethasone as a

334   treatment for COVID-19, and ACTT-2, COV-BARRIER, RUXCOVID and the study by

335   Guimaraes and colleagues all excluded the use of an IL-6 receptor blocker.[11,15,16,18] Other

336   factors that may be different between the trials include the prevalence of SARS-CoV-2

337   vaccination and the predominant circulating SARS-CoV-2 variant. However, there is no

338   reason to believe that, among patients admitted to hospital with severe COVID-19

339   requiring oxygen or ventilatory support, the proportional risk reduction in mortality with

340   baricitinib, a host-directed therapy, would differ by vaccination status or SARS-CoV-2

341   variant. Despite the heterogeneity of effect between RECOVERY and the previous 8 trials

342   combined, the overall result of the meta-analysis (which makes no assumptions about the

343   nature of any true differences in treatment effects between the different populations

344 studied) provides the best guide of the proportional benefits that might be expected from

345 the use of baricitinib in clinical practice.

346 The size of the RECOVERY trial allows exploration of the effects of treatment among

347 different subgroups of patients. The benefits of baricitinib on 28-day mortality were

348 consistent across all subgroups, including by age, sex, ethnicity, C-reactive protein, and

349 level of respiratory support received (although over 90% participants were either on

350 simple oxygen or receiving non-invasive mechanical ventilation). The benefits of

351 baricitinib were also consistent regardless of concomitant treatment with remdesivir, a

352 systemic corticosteroid and/or an IL-6 receptor blocker (tocilizumab or sarilumab).

353 Reassuringly, we found no evidence that allocation to baricitinib was associated with

354 excess rates of non-COVID mortality, non-COVID infection or thrombosis by comparison

355 with usual care.

356 In November 2020, the US FDA granted Emergency Use Authorisation for baricitinib in

357 combination with remdesivir and it has yet to receive marketing approval for COVID-19.[12]

358 US National Institutes of Health guidelines updated in February 2022 recommend the use

359 of baricitinb for patients on dexamethasone who have rapidly increasing oxygen needs

360 and systemic inflammation.[28] In January 2022, the World Health Organization updated

361 their COVID-19 therapeutics guidelines to include a strong recommendation for the use

362 of baricitinib as an alternative to an IL-6 receptor blocker, in combination with

363 corticosteroids, in patients with severe or critical COVID-19.[29] The results from the

364 RECOVERY trial and our meta-analysis, considerably strengthen the evidence that

365 baricitinib can reduce mortality and other adverse clinical outcomes in patients

366   hospitalised with COVID-19 and support the co-administration of baricitinib with

367   dexamethasone and/or an IL-6 receptor blocker.

368   In summary, this large, randomised trial confirms evidence from previous smaller trials

369   that treatment with baricitinib can reduce mortality in patients hospitalised with COVID-

370   19, although the size of the benefit is about half that previously thought. The benefits

371   appear to be consistent regardless of treatment with remdesivir, systemic corticosteroids

372   and/or an IL-6 receptor blocker such as tocilizumab. The results support the use of

373   baricitinib in addition to other immunosuppressive therapies in patients hospitalised with

374   COVID-19.

375

376 **Research in context**

377 **Evidence before this study**

378 We searched Medline, Embase, MedRxiv, bioRxiv and the WHO International Clinical

379 Trials Registry Platform from Sept 1, 2019 to Feb 13, 2022, for randomised controlled

380 trials evaluating the effect of bariticinib or another Janus Kinase (JAK) inhibitor in

381 patients hospitalised with COVID-19 using the search terms ("SARS-CoV-2.mp" OR

382 "SARS-CoV2" OR "SARSCoV2.mp" OR "COVID.mp" OR "COVID-19.mp" OR

383 "COVID19.mp" OR "2019-nCoV.mp" OR "Coronavirus.mp" or "Coronavirinae/") AND

384 ("JAK inhibitor.mp or Janus kinase inhibitor/" OR "Janus kinase inhibitor.mp" OR

385 "Baricitinib.mp or baricitinib/" OR terms for other specific JAK inhibitors (listed in

386 appendix p 28) and using validated filters to select for randomised controlled trials. No

387 language restrictions were applied.

388 We identified eight relevant randomised trials with results available that assessed JAK

389 inhibitors in hospitalised patients with COVID-19: three assessed baricitinib, three

390 assessed ruxolitinib and two assessed tofacitinib. Six of the trials had been fully

391 published of which four were considered to be low risk of bias for the 28-day mortality

392 outcome with two having some concerns (one because of lack of information about pre-

393 specified analyses and some imbalances between randomised groups of other

394 interventions given during the trial; the other because of lack of information about the

395 randomisation process, inconsistency in reporting of outcome endpoint timing and lack

396 of information about pre-specified analyses). A meta-analysis of these eight trials, which

397 included a total of 425 deaths among 3732 patients, suggested that allocation to a JAK

398   inhibitor was associated with a 43% proportional reduction in 28-day mortality (OR 0.57

399   [95% confidence interval 0.45-0.72]).

400   **Added value of this study:**

401   The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is the largest

402   randomised trial of the effect of a JAK inhibitor in patients hospitalised with COVID-19.

403   We found that in 8156 patients admitted to hospital with COVID-19, baricitinib reduced

404   28-day mortality by 13%, increased the probability of discharge alive within 28 days,

405   and, amongst patients who were not receiving invasive mechanical ventilation at

406   randomisation, reduced the probability of progression to the composite outcome of

407   invasive mechanical ventilation or death. The benefits were consistent in all subgroups

408   of patients, including those receiving a systemic corticosteroid and/or an IL-6 receptor

409   blocker.

410   **Implications of all the available evidence:**

411   The randomised evidence from all 9 completed JAK inhibitor trials to date suggest that

412   treatment with baricitinib or an alternative JAK inhibitor reduces mortality by about one-

413   fifth in hospitalised COVID-19 patients, including those already receiving a systemic

414   corticosteroid and/or an IL-6 receptor blocker.

415

Contributors

This manuscript was initially drafted by the PWH and MJL, further developed by the Writing Committee, and approved by all members of the Trial Steering Committee. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. PWH, MM, JKB, MB, LCC, JD, SNF, TJ, EJ, KJ, WSL, AMo, AMu, KR, RH, and MJL designed the trial and study protocol. MM, LP, MC, G P-A, CL, DRC, CB, RS, PC, AA, CAG, BP, TF, AK, and the Data Linkage team at the RECOVERY Coordinating Centre, and the Health Records and Local Clinical Centre staff listed in the appendix collected the data. NS and JRE did the statistical analysis. All authors contributed to data interpretation and critical review and revision of the manuscript. PWH and MJL had access to the study data and had final responsibility for the decision to submit for publication.

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Declaration of interests

The authors have no conflict of interest or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to produce the manuscript. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The Nuffield Department of Population Health at the University of Oxford has a staff policy of not accepting honoraria or consultancy fees directly or indirectly from industry (see https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf).

Data sharing

The protocol, consent form, statistical analysis plan, definition & derivation of clinical characteristics & outcomes, training materials, regulatory documents, and other relevant study materials are available online at www.recoverytrial.net. As described in the protocol, the Trial Steering Committee will facilitate the use of the study data and approval will not be unreasonably withheld. Deidentified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the Steering Committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (e.g. relating to data protection and privacy). The Steering Committee will have the right to review and comment on any draft manuscripts prior to publication. Data will be made available in line with the policy and procedures described at: https://www.ndph.ox.ac.uk/data-access. Those wishing to request access should complete the form at https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx and e-mailed to: data.access@ndph.ox.ac.uk

Acknowledgements

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Table 1: Baseline characteristics by treatment allocation

	Treatment allocation	
	Baricitinib (n=4148)	**Usual care (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	3192 (77%)	3104 (77%)
Black, Asian, and minority ethnic	457 (11%)	455 (11%)
Unknown	499 (12%)	449 (11%)
Number of days since symptom onset	9 (6-12)	9 (6-11)
Number of days since admission to hospital	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		
CRP, mg/L	84 (42-146)	87 (44-143)
Creatinine, umol/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%)	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	3750 (90%)	3655 (91%)
Negative	50 (1%)	39 (<1%)
Unknown	348 (8%)	314 (8%)
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 hours	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 no pregnant women were randomised. 2 post-partum women were randomised to baricitinib *Defined as requiring ongoing specialist care. †Defined as estimated glomerular filtration rate <30 mL/min/1.73 m²

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

	Treatment allocation			
	Baricitinib (n=4148)	**Usual care (n=4008)**	**RR (95% CI)**	**p-value**
Primary outcome				
28-day mortality	513 (12%)	546 (14%)	0.87 (0.77-0.98)	0.026
Secondary outcomes				
Median (IQR) time to being discharged alive, days	8 (5 to 17)	8 (5 to 20)		
Discharged from hospital within 28 days	3337 (80%)	3137 (78%)	1.10 (1.04-1.15)	<0.001
Receipt of invasive mechanical ventilation or death*	631/4014 (16%)	670/3891 (17%)	0.90 (0.81-0.99)	0.026
Invasive mechanical ventilation	283/4014 (7%)	322/3891 (8%)	0.87 (0.74-1.01)	0.06
Death	475/4014 (12%)	502/3891 (13%)	0.89 (0.80-1.00)	0.049
Subsidiary clinical outcomes				
Receipt of ventilation †	595/2998 (20%)	637/2980 (21%)	0.93 (0.84-1.03)	0.17
Non-invasive ventilation	585/2998 (20%)	623/2980 (21%)	0.94 (0.85-1.04)	0.20
Invasive mechanical ventilation	131/2998 (4%)	148/2980 (5%)	0.90 (0.71-1.13)	0.35
Successful cessation of invasive mechanical ventilation ‡	61/134 (46%)	43/117 (37%)	1.28 (0.86-1.89)	0.22
Use of haemodialysis or haemofiltration §	85/4140 (2%)	109/4003 (3%)	0.77 (0.58-1.01)	0.06

Data are n (%) or n/N (%), unless otherwise indicated. 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. CI=confidence interval. 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.

Figure 1: Trial profile

Total recruited
n=10852

**Baricitinib unavailable (n=1153 [11%])
and/or considered unsuitable (n=2134 [20%])**

**Number randomised between
baricitinib and usual care**
n=8156 (75%)

4148 allocated baricitinib

3734 of 4084 patients with completed follow−up
at time of analysis received
baricitinib

4008 allocated usual care alone

11 of 3950 patients with completed follow−up
at time of analysis received
baricitinib

30 withdrew consent

24 withdrew consent

**4148 included in 28−day
ITT analysis**

**4008 included in 28−day
ITT analysis**
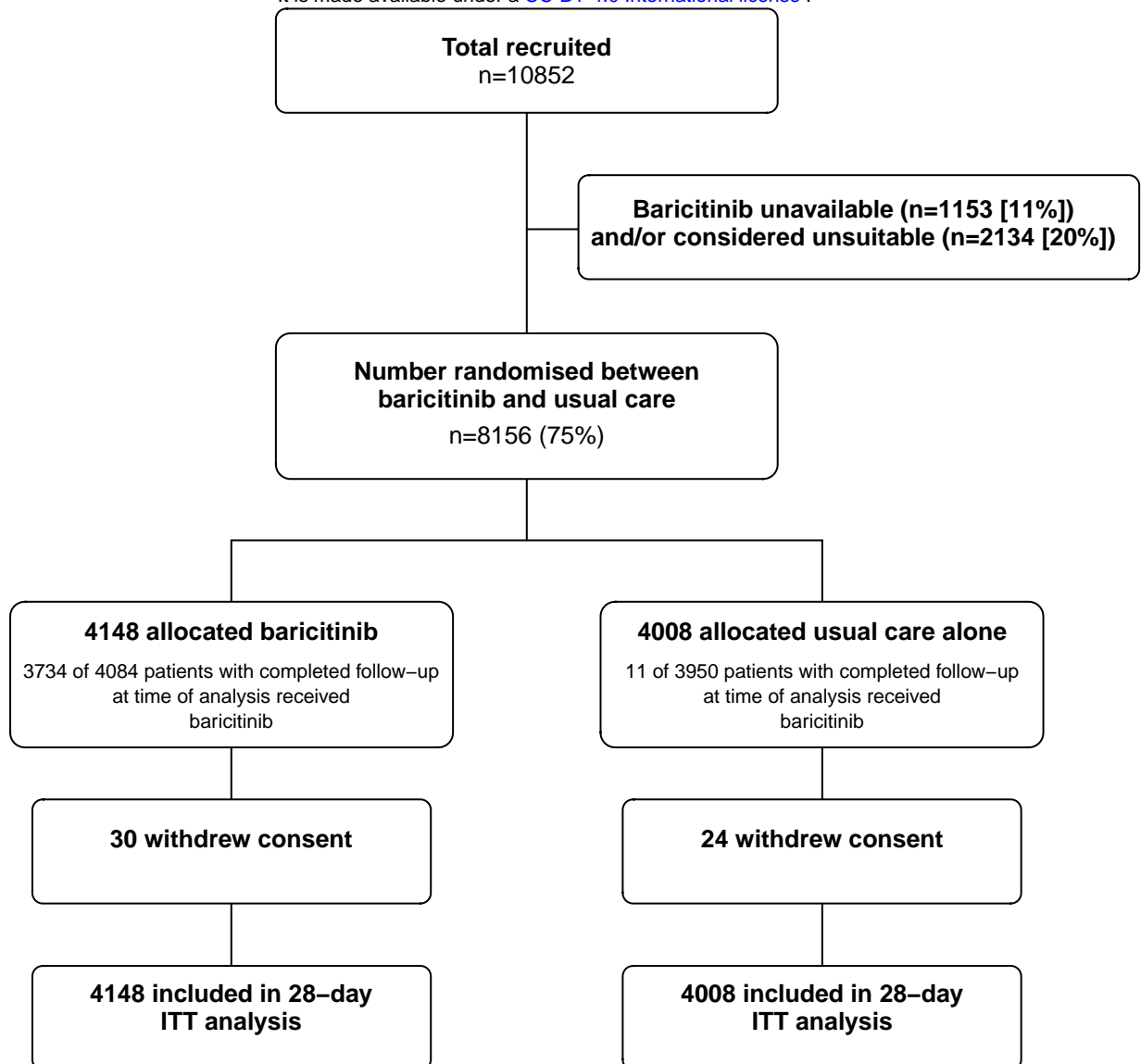
ITT=intention to treat. Baricitinib unavailable and baricitinib unsuitable groups are not mutually exclusive.
*Number recruited overall during the period that adult participants could be recruited into the baricitinib comparison.

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

RR=age−adjusted rate ratio

Figure 3: Effect of allocation to baricitinib on 28–day mortality by pre–specified baseline characteristics

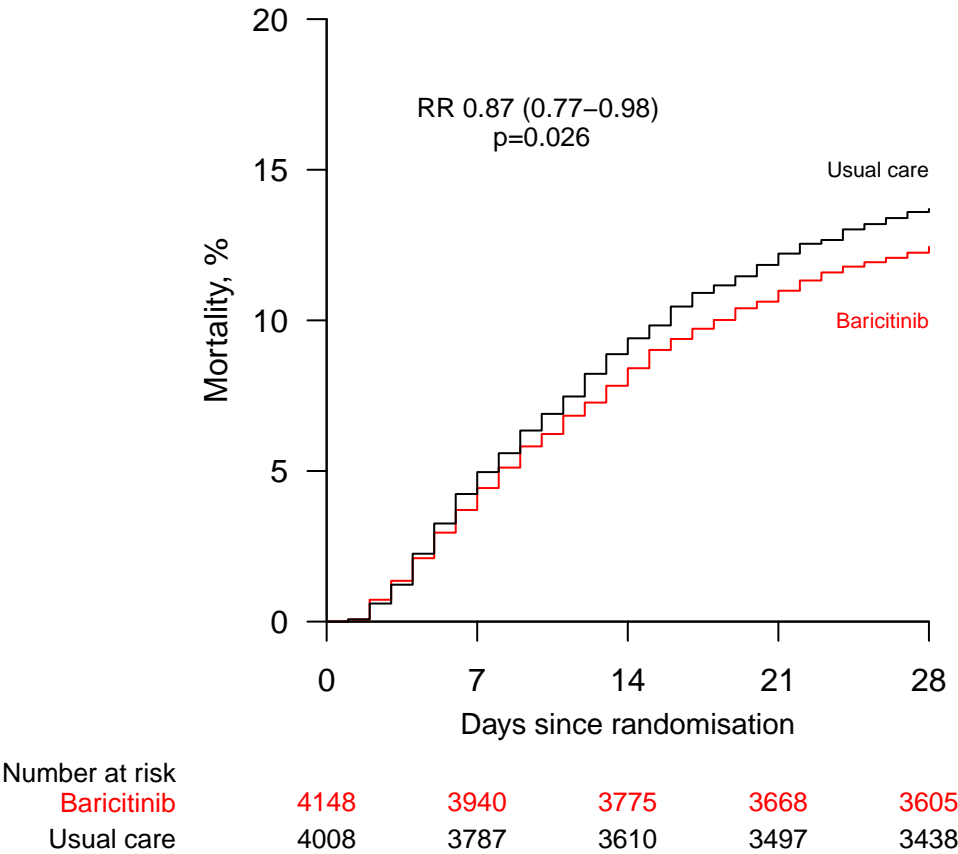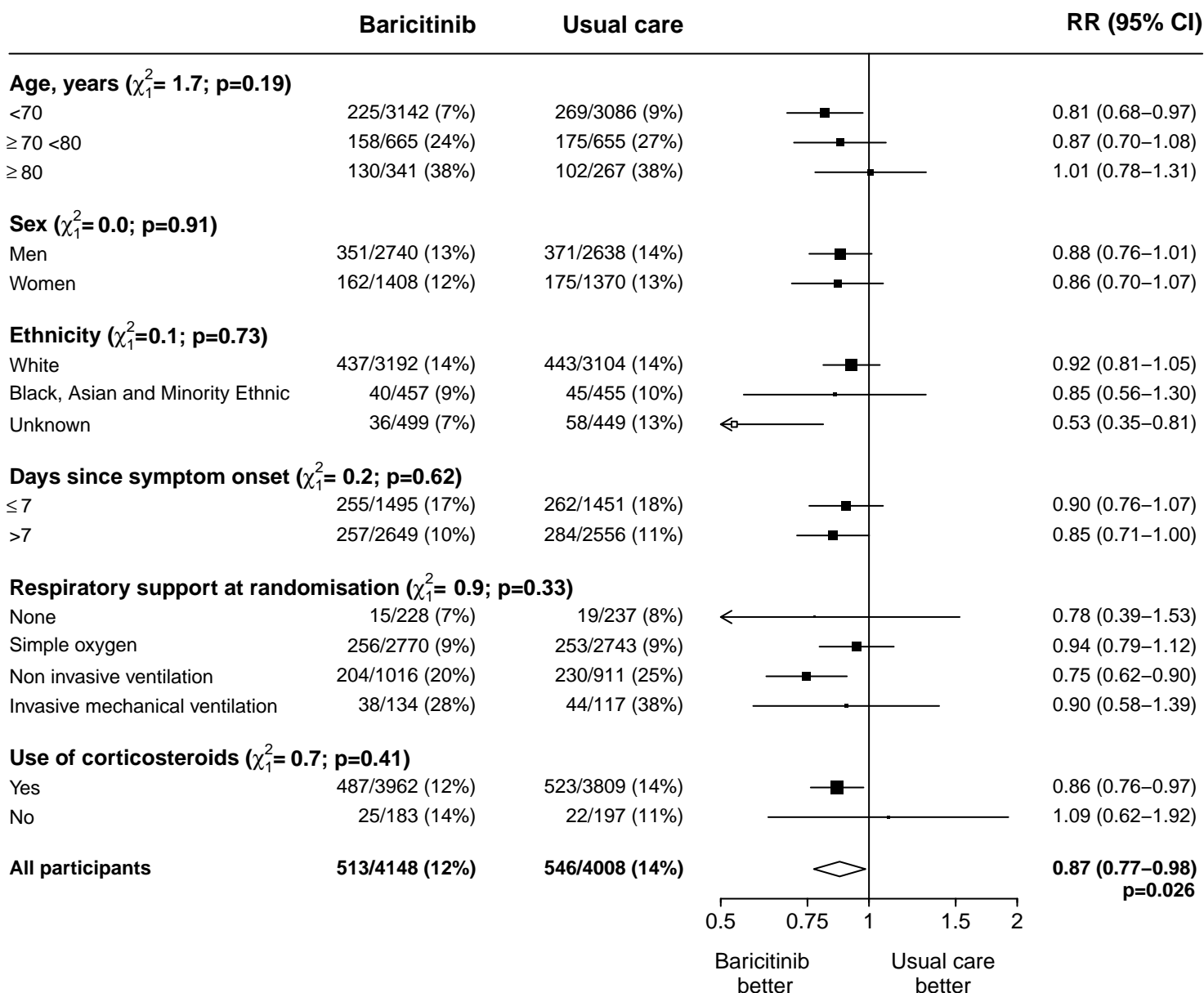|	Baricitinib	Usual care		RR (95% CI)
Age, years (χ^2_1= 1.7; p=0.19)				
<70	225/3142 (7%)	269/3086 (9%)		0.81 (0.68–0.97)
≥70 <80	158/665 (24%)	175/655 (27%)		0.87 (0.70–1.08)
≥80	130/341 (38%)	102/267 (38%)		1.01 (0.78–1.31)
Sex (χ^2_1= 0.0; p=0.91)				
Men	351/2740 (13%)	371/2638 (14%)		0.88 (0.76–1.01)
Women	162/1408 (12%)	175/1370 (13%)		0.86 (0.70–1.07)
Ethnicity (χ^2_1=0.1; p=0.73)				
White	437/3192 (14%)	443/3104 (14%)		0.92 (0.81–1.05)
Black, Asian and Minority Ethnic	40/457 (9%)	45/455 (10%)		0.85 (0.56–1.30)
Unknown	36/499 (7%)	58/449 (13%)		0.53 (0.35–0.81)
Days since symptom onset (χ^2_1= 0.2; p=0.62)				
≤7	255/1495 (17%)	262/1451 (18%)		0.90 (0.76–1.07)
>7	257/2649 (10%)	284/2556 (11%)		0.85 (0.71–1.00)
Respiratory support at randomisation (χ^2_1= 0.9; p=0.33)				
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	38/134 (28%)	44/117 (38%)		0.90 (0.58–1.39)
Use of corticosteroids (χ^2_1= 0.7; p=0.41)				
Yes	487/3962 (12%)	523/3809 (14%)		0.86 (0.76–0.97)
No	25/183 (14%)	22/197 (11%)		1.09 (0.62–1.92)
All participants	**513/4148 (12%)**	**546/4008 (14%)**		**0.87 (0.77–0.98)** **p=0.026**

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 95% CIs. The days since onset and use of corticosteroids subgroups exclude patients with missing data, but these patients are included in the overall summary diamond. RR=age adjusted rate ratio.

Figure 4: JAK inhibitor vs usual care in patients hospitalised with COVID – Meta–analysis of mortality in RECOVERY and other trials

	Deaths / Patients randomised (%)		Observed–Expected		Ratio of death rates, RR (95% CI)
	JAK inhibitor	**Control**	**(O–E)***	**Var(O–E)**	
Murugesan***	0/50 (0%)	0/50 (0%)	0.0	0.0	
Cao et al.***	0/20 (0%)	3/21 (14%)	−1.5	0.7	0.13 (0.01–1.31)
RUXCOVID***	9/287 (3%)	(3/145) x2** (2%)	1.0	2.6	1.48 (0.44–4.99)
Guimarães et al.***	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) x4** (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	513/4148 (12%)	546/4008 (14%)	−36.2	264.0	0.87 (0.77–0.98)
All trials	**722/6143 (12%)**	**873/6031 (14%)**	**−76.9**	**336.0**	**0.80 (0.71–0.89)** p<0.001

Heterogeneity between RECOVERY and previous trials: χ^2_1=10.3 (p=0.001)

```
0.25    0.5     1     2     4
JAK inhibitor          Control
  better                better
```

O–E=observed−expected. Var=variance. RR=Ratio of death rates. Details of the individual studies, including the use of placebo or other treatments in the control group are shown in Webtable 7.

* 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 2x2 tables. RR is calculated by taking ln RR to be (O–E)/V with Normal variance 1/V. Subtotals or totals of (O–E) and of V yield inverse–variance–weighted averages of the ln RR values without making any assumptions about the true heterogeneity in RRs between trials.

** For balance, controls in the n:1 studies count n times in the control totals and subtotals, but count only once when calculating their O–E and V values.

*** These trials did not assess baricitinib but assessed another JAK inhibitor. Restricting the meta–analysis to RECOVERY plus the 3 other baricitinib trials the RR would be 0.81 (95% CI 0.73–0.91).