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Drug interventions for prevention of COVID-19 progression to severe disease in outpatients: a systematic review with meta-analyses and trial sequential analyses (The LIVING Project)

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ABSTRACT

Objectives To assess the effects of interventions authorised by the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) for prevention of COVID-19 progression to severe disease in outpatients.

Setting Outpatient treatment.

Participants Participants with a diagnosis of COVID-19 and the associated SARS-CoV-2 virus irrespective of age, sex and comorbidities.

Interventions Drug interventions authorised by EMA or FDA.

Primary outcome measures Primary outcomes were all-cause mortality and serious adverse events.

Results We included 17 clinical trials randomising 16 257 participants to 8 different interventions authorised by EMA or FDA. 15/17 of the included trials (88.2%) were assessed at high risk of bias. Only molnupiravir and ritonavir-boosted nirmatrelvir seemed to improve both our primary outcomes. Meta-analyses showed that molnupiravir reduced the risk of death (relative risk (RR) 0.11, 95% CI 0.02 to 0.64; p=0.0145, 2 trials; very low certainty of evidence) and serious adverse events (RR 0.63, 95% CI 0.47 to 0.84; p=0.0018, 5 trials; very low certainty of evidence). Fisher's exact test showed that ritonavir-boosted nirmatrelvir reduced the risk of death (p=0.0002, 1 trial; very low certainty of evidence) and serious adverse events (p<0.0001, 1 trial; very low certainty of evidence) in 1 trial including 2246 patients, while another trial including 1140 patients reported 0 deaths in both groups.

Conclusions The certainty of the evidence was very low, but, from the results of this study, molnupiravir showed the most consistent benefit and ranked highest among the approved interventions for prevention of COVID-19 progression to severe disease in outpatients. The lack of certain evidence should be considered when treating patients with COVID-19 for prevention of disease progression.

PROSPERO registration number CRD42020178787.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our methodology has been predefined in detail reducing the risk of data-driven biased results and conclusions.

⇒ Risks of random errors and systematic errors are considered.

⇒ Our systematic review also has limitations as we only include drug interventions authorised by European Medicines Agency or US Food and Drug Administration.

INTRODUCTION

In December 2019, the emergence of a novel coronavirus, the SARS-CoV-2, caused an international outbreak of the respiratory illness COVID-19.[1] Since the initial outbreak in China, SARS-CoV-2 has spread globally and the WHO has labelled COVID-19 a public health emergency of global concern.[2] Today, the SARS-CoV-2 has mutated into several variants, including the alpha, beta, gamma, delta and omicron variants, which have complicated the pandemic further.[3 4] The clinical presentation of COVID-19 ranges from asymptomatic infection and mild respiratory tract illness to hospitalisation with severe pneumonia, multiorgan failure and death.[5]

Several vaccines have shown effectiveness in preventing the spread and progression of COVID-19.[6] However, some countries face vaccine hesitancy.[7 8] Also, the effectiveness of the vaccines may be compromised with the emergence of new variants of the virus.[7 8] In addition to this, only a few interventions for hospitalised patients with COVID-19 show significant beneficial effects and the effect

sizes are relatively small.[9 10] Therefore, there is a need for interventions preventing the progression of COVID-19 to severe disease—especially in patients with one or more risk factors.

For outpatient treatment of patients diagnosed with COVID-19, the European Medicines Agency (EMA) has authorised the use of sotrovimab (Xevudy), regdanvimab (Regkirona), remdesivir (Veklury), casirivimab/imdevimab (Ronapreve) and ritonavir-boosted nirmatrelvir (Paxlovid).[11] The US Food and Drug Administration (FDA) has authorised the use of molnupiravir (Lagevrio), bamlanivimab/etesevimab and bebtelovimab in addition to the drugs authorised by EMA but with the exception of regdanvimab.[12]

Sotrovimab, regdanvimab, casirivimab/imdevimab, bamlanivimab/etesevimab and bebtelovimab are monoclonal antibodies targeting parts of the spike protein of SARS-CoV-2.[13–18] Remdesivir and molnupiravir inhibit the RNA-dependent RNA polymerase in SARS-CoV-2.[17 19] Ritonavir-boosted nirmatrelvir targets the enzyme M^{pro} in SARS-CoV-2.[20]

Based on our LIVING protocol, a protocol for living systematic reviews assessing interventions for COVID-19,[21] this review aimed to assess the effects of interventions authorised by either EMA or FDA for prevention of the progression of COVID-19 to severe disease in outpatients.

Our hypothesis for dichotomous outcomes was that the included interventions would reduce the risk of all-cause mortality, serious adverse events, hospitalisations, mechanical ventilation, admission to intensive care unit, renal replacement therapy and non-serious adverse events with a relative risk reduction of 20%. Our hypothesis for continuous outcomes was that the included interventions would increase quality of life with a mean difference of the observed SD divided by 2.

METHODS

We report this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (online supplemental file 1).[22] The updated methodology used in this systematic review is conducted according to our protocol,[21] which was registered in the PROSPERO database (PROSPERO ID: CRD42020178787) prior to the initiation of the literature searches.

Search strategy and selection criteria
Electronic searches
An information specialist searched the Cochrane Central Register of Controlled Trials in The Cochrane Library, Medical Literature Analysis and Retrieval System Online (MEDLINE Ovid), Excerpta Medica database (Embase Ovid), Latin American and Caribbean Health Sciences Literature (LILACS; Bireme), CINAHL (EBSCO host), BIOSIS (Web of Science), Science Citation Index Expanded (SCI-EXPANDED; Web of Science), Chinese Biomedical Literature Database, Conference Proceedings Citation Index—Science (Web of Science), China Network Knowledge Information, Chinese Science Journal Database (VIP) and Wanfang Database to identify relevant trials. We searched all databases from their inception to 19 April 2022. For all detailed search strategies, see online supplemental file 2.

Searching other resources
The reference lists of relevant trial publications were checked for any unidentified randomised clinical trials. To identify unpublished trials, we searched clinical trial registries (eg, ClinicalTrials.gov; clinicaltrialregister.eu; who.int/ictrp; chictr.org.cn) of Europe, the USA and China and websites of pharmaceutical companies, FDA and EMA. We also searched the COVID-19 Study Registry and the real-time dashboard of randomised trials.[23 24]

We included unpublished and grey literature trials. We assessed relevant retraction statements and errata for included trials. We searched preprint servers (bioRxiv, medRxiv) for unpublished trials, and all corresponding authors were contacted to obtain individual patient data.

Inclusion and exclusion criteria
We only included trials assessing interventions authorised by EMA or FDA in outpatients, irrespective of publication status, year and language. We did not include quasirandomised studies or observational studies. We included participants of all ages with a diagnosis of COVID-19 and the associated SARS-CoV-2 virus confirmed by laboratory tests (such as reverse transcription PCR). Participants were included irrespective of sex and comorbidities.

Data extraction
Two authors independently screened relevant trials. Five authors working in pairs (JJP, CKJ, PF, FS and ATK) independently extracted data using a standardised data extraction sheet. Discrepancies were resolved through discussion or, if required, through discussion with the last author (JCJ). We contacted corresponding authors if relevant data were unclear or missing for data extraction.

Risk-of-bias assessment
Risk of bias was assessed with the Cochrane risk-of-bias tool V.2 (RoB 2).[25 26] Five authors working in pairs (JJP, CKJ, PF, FS and ATK) independently assessed risk of bias. Discrepancies were resolved through discussion or, if required, through discussion with the last author (JCJ). Bias was assessed with the following domains: bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of outcomes and bias arising from selective reporting of results.[25 26] We contacted corresponding authors of trials in case of unclear or missing data for the risk-of-bias assessment.

Outcomes and subgroup analyses
Primary and secondary outcomes were predefined in our protocol.[21] Primary outcomes were all-cause mortality and serious adverse events (as defined by the International

Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines).[21 27] Secondary outcomes were admissions to intensive care (as defined by trialists), initiation of invasive or non-invasive mechanical ventilation (as defined by trialists), renal replacement therapy (as defined by trialists), quality of life and non-serious adverse events. We classified non-serious adverse events as any adverse event not classified as serious according to the ICH-GCP definition.

We chose to add hospitalisations as a post hoc outcome. We planned several subgroup analyses, which were described in detail in our protocol.[21] We chose to add drug dose and trial population (low risk, high risk, mixed risk or unclear risk as defined by trialists) as post hoc subgroup analyses. For all outcomes, we used the results reported at maximum follow-up.

Assessment of statistical and clinical significance

Aggregate data meta-analyses were performed according to Cochrane,[25] Keus *et al*[28] and the eight-step assessment by Jakobsen *et al*[29] for better validation of meta-analytic results in systematic reviews. We report the effect sizes using relative risk (RR) for dichotomous outcomes. We assessed a total of two primary outcomes per comparison and therefore adjusted our threshold for significance.[29] A p value of 0.033 or less was used as the threshold for statistical significance.[21 29] Because we primarily considered results of secondary outcomes as hypothesis generating, we did not adjust the p value threshold for secondary outcomes. We conducted both random effects (inverse variance and DerSimonian-Laird) and fixed-effect (Mantel-Haenszel) meta-analyses for all analyses and chose the most conservative result as our primary result and the less conservative result as a sensitivity analysis.[25 29 30] We used trial sequential analysis (TSA) to control for random errors.[31–39] TSA estimates the diversity-adjusted required information size (DARIS), which is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect. Statistical heterogeneity was quantified by calculating heterogeneity ($\tau2$) for traditional meta-analyses and diversity (D2) for TSA. We used Grading Recommendations Assessment Development Evaluation (GRADE) to assess the certainty of evidence (risk of bias, inconsistency, indirectness, imprecision and publication bias). These assessments were based on the recommendations in the GRADE Handbook.[40] We downgraded imprecision in GRADE by two levels if the accrued number of participants was below 50% of the DARIS and one level if the number was between 50% and 100% of DARIS.[29] We did not downgrade if the boundary for benefit, harm, futility or DARIS was crossed. Publication bias was assessed based on visual inspection of a funnel plot if 10 or more trials were included. In addition to this, publication bias was assessed regarding the study design (only including randomised clinical trials), study size (small and large studies), lag bias and search strategy as recommended in the GRADE Handbook.[40] We used Fisher's exact test to calculate p values for all single trial results. Stata V.17

(StataCorp LLC, College Station, Texas, USA) was used for all statistical analyses.[41]

Patient and public involvement
None.

RESULTS
Study characteristics
On 19 April 2022, our literature searches identified 435 515 records after duplicates were removed. We included a total of 17 clinical trials[13–20 42–50] randomising 16 257 participants to 8 different experimental drug interventions versus placebo or no intervention (figure 1 and online supplemental table S1 and figure S1). For a detailed overview of excluded trials, see online supplemental table S2.

The characteristics of included trials and the trial results can be found in online supplemental table S1. Most trials were at high risk of bias (online supplemental table S3). The maximum follow-up time ranged from 14[48 49] to 85 days[18] after randomisation. For several of our outcomes, it was not possible to conduct meta-analysis due to insufficient data. Specifically, no trials reported data on renal replacement therapy and quality of life. It was not possible to perform any sensitivity analyses to assess the potential impact of missing data due to unclear reporting in most of the included trials. See table 1 for a visual overview of all results with assessment of certainty.

Molnupiravir versus control
We identified 6 trials randomising 4393 participants to molnupiravir versus standard care (with or without placebo).[17 43–45 49 50]

All-cause mortality
Six trials reported data on all-cause mortality.[17 43–45 49 50] Four of these trials reported no deaths in either of the compared groups.[17 43 49 50] These four trials were not included in the meta-analysis. Meta-analysis of the remaining two trials showed evidence of a beneficial effect of molnupiravir versus control on all-cause mortality (RR 0.11, 95% CI 0.02 to 0.64; τ^2=0.0, I²=0.0%; p=0.0145) (online supplemental figure S1). Visual inspection of the forest plot and measures to quantify heterogeneity (τ^2=0.0, I²=0.0%) indicated no heterogeneity. TSA showed that we did not have enough information to confirm or reject that molnupiravir versus control reduced the risk of all-cause mortality with a relative risk reduction of 20% (no graph produced). The time points of assessment were 14,[49] 28,[17 50] 29[43–45] or 31 days[17 43] after randomisation. This outcome result was assessed at high risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S4).

It was not possible to perform any predefined subgroup analyses due to lack of relevant data

Serious adverse events
Six trials reported data on serious adverse events.[17 43–45 49 50] One of these trials reported no serious adverse events

Identification

Records identified through database searching
(n = 3,151,980)

CENTRAL	=	408,575
MEDLINE	=	414,721
EMBASE	=	608,928
LILACS	=	432,518
CINAHL	=	891,331
BIOSIS	=	117,712
SCIsearch	=	273,977

Additional records identified through other sources
(n = 57)

Screening

Records after duplicates removed
(n = 435,515)

Records screened
(n = 435,515)

Records excluded
(n = 379,791)

Eligibility

Full-text records assessed for eligibility
(n = 112)

Articles excluded after full-text
(n = 95)

Non-randomised (n = 42)

Wrong intervention (n = 30)

Wrong population (n = 23)

Trials included in qualitative synthesis
(n=17)

Included

Trials included in quantitative synthesis (meta-analysis)
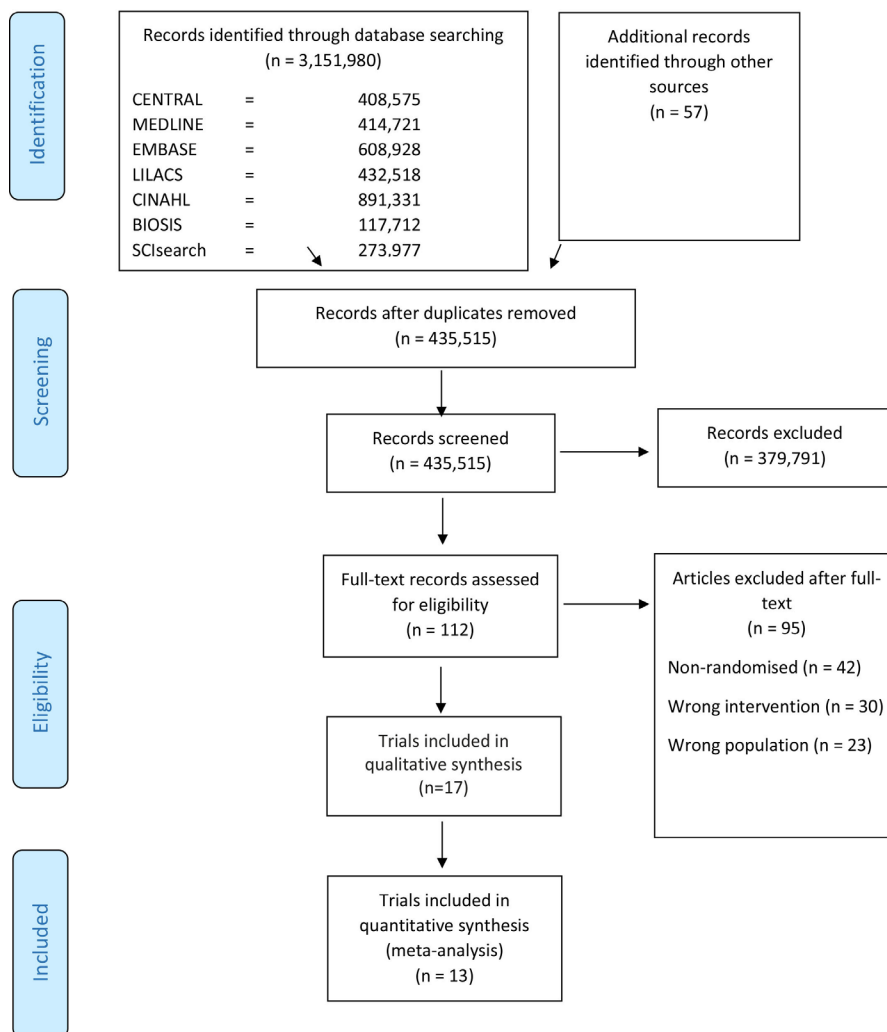(n = 13)

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

Table 1 Visual overview of results with assessments of certainty

	ACM	SAE	HOS	MV	ICU	RRT	NSAE	QoL
Molnupiravir	Very low	Very low					*	
Ritonavir-boosted nirmatrelvir	Very low†	Very low†					†	
Bamlanivimab/etesevimab	Very low†	Very low†	†				†	
Sotrovimab	Very low†	Very low†	†	†	†		†	
Casirivimab/imdevimab	Very low †	Very low*		†	†		†	
Remdesivir	Very low†	Very low†	†				†	
Regdanvimab	Very low	Very low†	†	†	†			
Bebtelovimab	Very low†	Very low†					†	
No evidence of a difference								
Evidence of a beneficial effect								
Meta-analysis not possible due to no events								

*TSA shows that the required information size has been reached.
†Results based on a single trial.
ACM, all-cause mortality; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HOS, hospitalisations; ICU, intensive care unit; MV, mechanical ventilation; NSAE, non-serious adverse events; QoL, quality of life; RRT, renal replacement therapy; SAE, serious adverse events; TSA, trial sequential analysis.

in either of the compared groups.[43] This trial was not included in the meta-analysis. Meta-analysis of the remaining five trials showed evidence of a beneficial effect of molnupiravir versus control on serious adverse events (RR 0.63, 95% CI 0.47 to 0.84; τ^2=0.0, I^2=0.0%; p=0.0018) (online supplemental figure S2). Visual inspection of the forest plot and measures to quantify heterogeneity (τ^2=0.0, I^2=0.0%) indicated no heterogeneity. TSA showed that we did not have enough information to confirm or reject that molnupiravir versus control reduced the risk of serious adverse events with a relative risk reduction of 20% (online supplemental figure S3). The time points of assessment were 14,[49] 28,[17 50] 29[43–45] or 31 days[17 43] after randomisation. This outcome result was assessed at high risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S4).

None of the subgroup analyses comparing the effects in different trial populations (p=0.188), comparators (p=0.101) or drug dose (p=0.840) showed evidence of a difference (online supplemental figures S4–S6). It was not possible to perform the remaining predefined subgroup analyses due to lack of relevant data.

Hospitalisations

Four trials reported data on hospitalisations.[43 44 49 50] One of these trials reported no hospitalisations in either of the compared groups.[43] This trial was not included in the meta-analysis. Meta-analysis of the remaining three trials showed evidence of a beneficial effect of molnupiravir versus control on hospitalisations (RR 0.44, 95% CI 0.26 to 0.74; τ^2=0.0, I^2=0.0%; p=0.0019) (online supplemental figure S7). Visual inspection of the forest plot and measures to quantify heterogeneity (τ^2=0.0, I^2=0.0%) indicated no heterogeneity. TSA showed that we did not have enough information to confirm or reject that molnupiravir versus control reduced the risk of hospitalisations with a relative risk reduction of 20% (online supplemental figure S8). The time points of assessment were 14,[49] 28,[50] 29[43–45] or 31 days[43] after randomisation. This outcome result was assessed at high risk of bias (online supplemental table S3).

Ritonavir-boosted nirmatrelvir versus placebo

We identified 2 trials randomising 3386 participants to ritonavir-boosted nirmatrelvir versus placebo.[20 42] Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR) randomised patients with standard risk of COVID-19 progression to severe disease.[42] Standard risk of COVID-19 was defined as unvaccinated adults who were at low risk of hospitalisation or death and vaccinated adults with one or more risk factors for progression to severe disease.[42] Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) randomised patients with high risk of COVID-19 progression to severe disease.[20]

All-cause mortality

Two trials reported data on all-cause mortality.[20 42] It was not possible to perform meta-analysis on ritonavir-boosted nirmatrelvir versus placebo on all-cause mortality due to insufficient data. In EPIC-HR, 0 out of 1039 participants (0.0%) died in the ritonavir-boosted nirmatrelvir group versus 13 out of 1046 participants (1.2%) in the placebo group (Fisher's exact test: p=0.0002).[20] The time point of assessment was 34 days after randomisation.[20] This outcome result was assessed at high risk of bias (online supplemental table S3). In EPIC-SR, 0 out of 428 participants (0.0%) died in the ritonavir-boosted nirmatrelvir group versus 0 out of 426 participants (0.0%) in the placebo group.[42] The time point of assessment was unclear.[42] This outcome result was assessed at high risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S5).

It was not possible to perform any predefined subgroup analyses due to lack of relevant data.

Serious adverse events

Two trials reported data on serious adverse events.[20 42] It was not possible to perform meta-analysis on ritonavir-boosted nirmatrelvir versus placebo on serious adverse events due to insufficient data. In EPIC-HR, 18 out of 1109 participants (1.6%) had a serious adverse event in the ritonavir-boosted nirmatrelvir group versus 74 out of 1115 participants (6.6%) in the placebo group (Fisher's exact test: p<0.0001).[20] The time point of assessment was 34 days after randomisation.[20] This outcome result was assessed at high risk of bias (online supplemental table S3). In EPIC-SR, 1.4% had a serious adverse event in the ritonavir-boosted nirmatrelvir group versus 1.9% in the placebo group.[42] The time point of assessment and the number of participants analysed were unclear.[42] This outcome result was assessed at high risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S5).

It was not possible to perform any predefined subgroup analyses due to lack of relevant data.

Hospitalisations

Meta-analysis showed evidence of a beneficial effect of ritonavir-boosted nirmatrelvir versus placebo on hospitalisations (RR 0.16, 95% CI 0.07 to 0.36; τ^2=0.11, I^2=28.2%; p<0.0001) (online supplemental figure S9). Visual inspection of the forest plot and measures to quantify heterogeneity (τ^2=0.11, I^2=28.2%) indicated little heterogeneity that may not be important. TSA showed that we did not have enough information to confirm or reject that ritonavir-boosted nirmatrelvir versus placebo reduced the risk of hospitalisations with a relative risk reduction of 20% (online supplemental figure S10). The time points of assessment were unclear[42] or 34 days after randomisation.[20] This outcome result was assessed at high risk of bias (online supplemental table S3).

Bamlanivimab/etesevimab versus placebo

We identified 1 trial randomising 1035 participants to bamlanivimab/etesevimab versus placebo.[14] This trial randomised participants with at least one risk factor of COVID-19 progression to 2800 mg bamlanivimab/2800 mg etesevimab versus placebo. This trial was assessed at overall low risk of bias (online supplemental table S3). It was not possible to perform any meta-analyses or subgroup analyses due to lack of relevant data.

All-cause mortality

In total, 0 out of 518 participants (0.0%) died in the bamlanivimab/etesevimab group versus 10 out of 517 participants (1.9%) in the placebo group (Fisher's exact test: p=0.0076).[14] The time point of assessment was 29 days after randomisation.[14] This outcome result was assessed as low risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S6).

Hospitalisations

This trial only reported COVID-19-related hospitalisations. A total of 11 out of 518 participants (2.1%) were hospitalised related to COVID-19 in the bamlanivimab/etesevimab group versus 33 out of 517 participants (6.4%) in the placebo group (Fisher's exact test: p=0.0006).[14] The time point of assessment was 29 days after randomisation.[14] This outcome result was assessed as low risk of bias (online supplemental table S3).

Sotrovimab versus placebo

We identified 1 trial randomising 1057 participants to sotrovimab versus placebo.[13] This trial randomised participants with at least one risk factor of COVID-19 progression to 500 mg of sotrovimab versus placebo. This trial was assessed at overall low risk of bias (online supplemental table S3). It was not possible to perform any meta-analyses or subgroup analyses due to lack of relevant data.

Serious adverse events

In total, 11 out of 523 participants (2.1%) had a serious adverse event in the sotrovimab group versus 32 out of 526 participants (6.1%) in the placebo group (Fisher's exact test: p=0.0015).[13] The time point of assessment was 29 days after randomisation.[13] This outcome result was assessed as low risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S7).

Hospitalisations

In total, 6 out of 528 participants (1.1%) were hospitalised in the sotrovimab group versus 29 out of 529 participants (5.5%) in the placebo group (Fisher's exact test: p=0.0001).[13] The time point of assessment was 29 days after randomisation.[13] This outcome result was assessed as low risk of bias (online supplemental table S3).

Mechanical ventilation

In total, 0 out of 528 participants (0.0%) received mechanical ventilation in the sotrovimab group versus 6 out of 529 participants (1.1%) in the placebo group (Fisher's exact test: p=0.0308).[13] The time point of assessment was 29 days after randomisation.[13] This outcome result was assessed as low risk of bias (online supplemental table S3).

Intensive care

In total, 0 out of 528 participants (0.0%) were admitted to intensive care in the sotrovimab group versus 10 out of 529 participants (1.9%) in the placebo group (Fisher's exact test: p=0.0019).[13] The time point of assessment was 29 days after randomisation.[13] This outcome result was assessed as low risk of bias (online supplemental table S3).

Casirivimab/imdevimab versus placebo

We identified 3 trials randomising 5170 participants to casirivimab/imdevimab versus placebo.[15 46 47]

Serious adverse events

Meta-analysis showed evidence of a beneficial effect of casirivimab/imdevimab versus placebo on serious adverse events (RR 0.34, 95% CI 0.24 to 0.48; τ^2=0.0, I^2=0.0%; p<0.0001) (online supplemental figure S11). Visual inspection of the forest plot and measures to quantify heterogeneity (τ^2=0.0, I^2=0.0%) indicated no heterogeneity. TSA showed that we had enough information to confirm that casirivimab/imdevimab versus placebo reduced the risk of serious adverse events (online supplemental figure S12). The time points of assessment were unclear[15] or 29 days after randomisation.[46 47] This outcome result was assessed at high risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S8).

None of the subgroup analyses comparing the effects in different trial populations (p=0.892) or drug dose (p=0.621) showed evidence of a difference (online supplemental figures 13 and 14). It was not possible to perform the remaining predefined subgroup analyses due to lack of relevant data.

Hospitalisations

Meta-analysis showed evidence of a beneficial effect of casirivimab/imdevimab versus placebo on hospitalisations (RR 0.31, 95% CI 0.21 to 0.47; τ^2=0.0, I^2=0.0%; p<0.0001) (online supplemental figure S15). Visual inspection of the forest plot and measures to quantify heterogeneity (τ^2=0.0, I^2=0.0%) indicated no heterogeneity. TSA showed that we did not have enough information to confirm or reject that casirivimab/imdevimab versus placebo reduced the risk of hospitalisations with a relative risk reduction of 20% (online supplemental figure S16). The time point of assessment was 29 days after randomisation.[46 47] This outcome result was assessed at high risk of bias (online supplemental table S3).

Intensive care

In total, 9 out of 2091 participants (0.4%) were admitted to intensive care in the casirivimab/imdevimab group versus 18 out of 1341 participants (1.3%) in the placebo group (Fisher's exact test: p=0.0047).[46] The time point

of assessment was 29 days after randomisation.[46] This outcome result was assessed at high risk of bias (online supplemental table S3).

Non-serious adverse events

In total, 52 out of 155 participants (33.5%) had a treatment-emergent non-serious adverse event in the casirivimab/imdevimab group versus 75 out of 156 participants (48.1%) in the placebo group (Fisher's exact test: p=0.0111).[15] The time point of assessment was unclear.[15] This outcome result was assessed at high risk of bias (online supplemental table S3).

Remdesivir versus placebo

We identified 1 trial randomising 584 participants to remdesivir versus placebo.[19] This trial randomised participants with at least one risk factor of COVID-19 progression to 200 mg of remdesivir on day 1 and 100 mg on days 2 and 3 versus placebo. This trial was assessed at overall high risk of bias (online supplemental table S3). It was not possible to perform any meta-analyses or subgroup analyses due to lack of relevant data.

Serious adverse events

In total, 5 out of 279 participants (1.8%) had a serious adverse event in the remdesivir group versus 19 out of 283 participants (6.7%) in the placebo group (Fisher's exact test: p=0.0056).[19] The time point of assessment was 28 days after randomisation.[19] This outcome result was assessed at high risk of bias, and the certainty of the evidence was very low (online supplemental tables S3 and S9).

Hospitalisations

In total, 5 out of 279 participants (1.8%) were hospitalised in the remdesivir group versus 18 out of 283 participants (6.4%) in the placebo group (Fisher's exact test: p=0.0092).[19] The time point of assessment was 28 days after randomisation.[19] This outcome result was assessed at high risk of bias (online supplemental table S3).

Remaining results

Due to the number of comparisons, we have reported non-significant results in online supplemental file 3 including online supplemental figures S17–S19 and tables S10–S11.

DISCUSSION

We conducted a systematic review assessing the effects of interventions authorised by EMA or FDA for outpatient treatment of COVID-19. Only molnupiravir and ritonavir-boosted nirmatrelvir improved both our primary outcomes, but molnupiravir showed the most consistent benefit and ranked highest among the approved interventions for prevention of COVID-19 progression to severe disease. Several others of the approved interventions showed indications of beneficial effects on different outcomes, but with less consistent results.

Our systematic review has several strengths. We used modern, up-to-date methods for assessing the methodological quality of the included trials.[25 29 40] The methodology was based on the Cochrane Handbook for Systematic Reviews of Interventions,[25] the eight-step assessment suggested by Jakobsen et al[29] and TSA.[31] Our methodology was predefined and described in detail before the literature searches were initiated.[21] We assessed the risks of bias using the RoB 2,[25] and the overall certainty of the evidence was assessed using GRADE (bias risk of the trials, consistency of effect, imprecision, indirectness and publication bias).[40] Therefore, the present review takes into account both risks of random errors ('play of chance') and systematic errors (bias).

Our systematic review also has limitations. First, it must be considered that different variants of COVID-19 have emerged—different variants of COVID-19 may respond differently to a given intervention leading to different effects in different time periods. Many of the included trials were conducted between autumn 2020 and the spring 2021, and the current variant of concern, omicron, was not documented until November 2021.[51] Second, the included trials randomised patients with different risk profiles, the definition of outcomes varied between trials, outcomes were assessed at different time points, and some trials were single centre trials[14 17 43 49 50] while others were multinational,[15 16 19 20 42 44–48 52] We accounted for these issues by performing subgroup analyses and sensitivity analyses, when possible, but lack of relevant data limited the validity of these analyses. Third, trial sequential analyses showed that almost all of the present meta-analyses were underpowered, which increase the risks of type II errors—more data are needed to confirm or reject clinically important intervention effects. Forth, most included trials were at risk of systematic errors. Thus, our results presumably overestimate the beneficial effects and underestimate the harmful effects of the interventions.[53–60] Fifth, this review only included interventions already authorised by EMA or FDA, although other interventions with potential benefit have been suggested.[61] Sixth, some trial data were extracted based only on preprints. Therefore, these trial results might change following peer-review, which could impact the meta-analyses, risk-of-bias assessments, and GRADE assessments. The above-mentioned limitations, and especially the continuous emergence of new COVID-19 variants and the clinical heterogeneity between trials, need to be considered when interpreting our results.

We conclude that the data on these preventive interventions are limited, and the evidence is of very low certainty. Concerns regarding the true effect sizes and possible long-term safety profile of the interventions have been raised.[62 63] It is worth considering how these interventions have been granted emergency authorisation by EMA or FDA,[64–66] and why the guidelines in, for example, the UK recommend molnupiravir, ritonavir-boosted nirmatrelvir, sotrovimab or remdesivir depending on patient characteristics in treatment of outpatients in high risk of disease progression.[67] Even though COVID-19 continues to present a major health issue globally, it must

be emphasised how limited and uncertain the available evidence is. Promising interventions and newly proposed interventions should undergo continued evaluation through clinical trials, until the level of evidence is more certain.

Conclusions

The certainty of the evidence was very low, but, from the results of this study, molnupiravir showed the most consistent benefit and ranked highest among the approved interventions for prevention of COVID-19 progression to severe disease in outpatients. The lack of certain evidence should be considered when treating patients with COVID-19 for prevention of disease progression.

Differences between the protocol and the review

We erroneously reported the adjusted TSA alpha as 2% in our published protocol.[21] This has been corrected to 3.3% according to two primary outcomes.[29] Furthermore, we chose to add 'hospitalisations' as outcome post hoc, but before data analyses as this is a very patient-important outcome when focusing on prevention of disease progression in outpatients as well as the burden of the disease to society. We chose to add 'drug dose' and 'trials population' as subgroup analyses post hoc, but before data analyses to explore possible heterogeneity as many new drug doses are explored in possibly very different populations.

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