Bamlanivimab/etesevimab for COVID-19: real-time meta analysis of 19 studies

@CovidAnalysis, March 2024, Version 36
https://c19early.org/lmeta.html

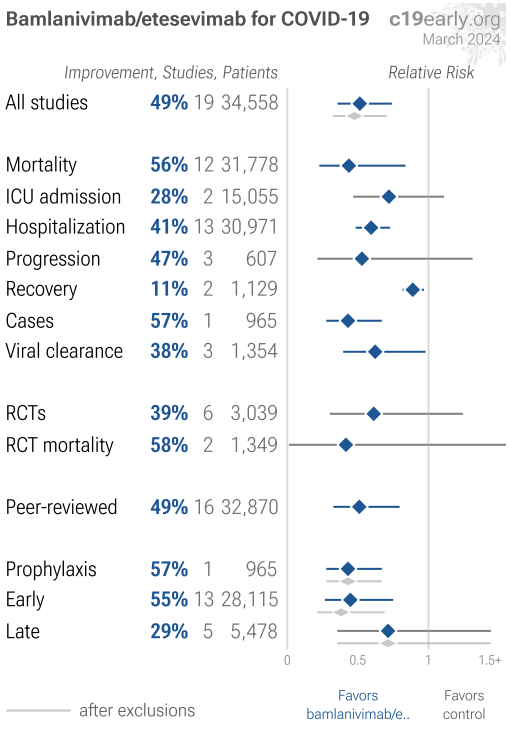
Abstract

Statistically significant lower risk is seen for mortality, hospitalization, recovery, cases, and viral clearance. 14 studies from 12 independent teams (all from the same country) show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 49% [26-64%] lower risk. Results are similar for higher quality and peer-reviewed studies and slightly worse for Randomized Controlled Trials. Results are consistent with early treatment being more effective than late treatment.

Results are robust — in exclusion sensitivity analysis 8 of 19 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

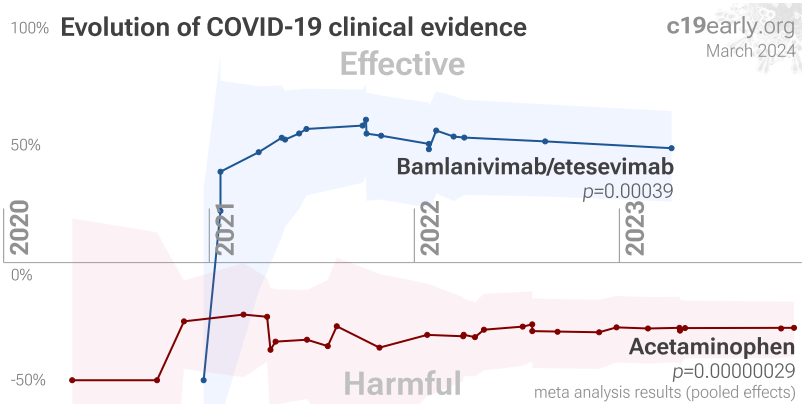
Efficacy is highly variant dependent. *In Vitro* studies suggest a lack of efficacy for omicron *Haars, Liu, Pochtovyi, Sheward, VanBlargan*. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.



Prescription treatments have been preferentially used by patients at lower risk *Wilcock*. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments may be more effective.

All data to reproduce this paper and sources are in the appendix.



HIGHLIGHTS

Bamlanivimab/etesevimab reduces risk for COVID-19 with very high confidence for hospitalization and in pooled analysis, high confidence for mortality and viral clearance, low confidence for recovery and cases, and very low confidence for ICU admission and progression. Efficacy is variant dependent.

Bamlanivimab/etesevimab was the 23rd treatment shown effective with ≥3 clinical studies in June 2021, now with p = 0.00039 from 19 studies, and recognized in 4 countries.

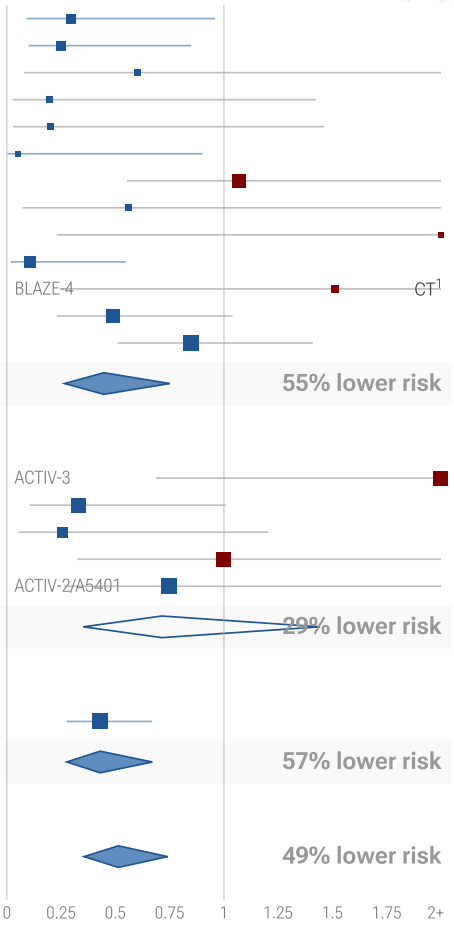
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.

19 bamlanivimab/etesevimab COVID-19 studies

c19early.org
March 2024

	Improvement	RR [CI]		Treatment	Control
Gottlieb (RCT)	71%	0.29 [0.09-0.96]	hosp./ER	4/101	7/52
Alam	75%	0.25 [0.10-0.85]	death	160 (n)	86 (n)
Karr	40%	0.60 [0.08-4.51]	hosp.	4/40	1/6
Corwin	80%	0.20 [0.03-1.42]	death	1/780	35/5,337
Webb	80%	0.20 [0.03-1.46]	death	1/479	57/5,536
Dougan (DB RCT)	95%	0.05 [0.00-0.90]	death	0/518	9/517
Cooper	-7%	1.07 [0.55-2.07]	death	12/2,900	33/8,534
Rubin	44%	0.56 [0.07-4.33]	death	1/191	10/1,066
Delasobera	-119%	2.19 [0.23-20.9]	death	3/253	1/185
Dale	89%	0.11 [0.02-0.55]	death	5/56	9/19
Dougan (RCT)	-51%	1.51 [0.26-8.90]	hosp.	3/127	2/128
Wilden	51%	0.49 [0.23-1.04]	hosp.	n/a	n/a
Kip	15%	0.85 [0.51-1.41]	death/hosp.	20/349	47/695
Early treatment	55%	0.45 [0.27-0.75]		54/5,954	211/22,161
Tau² = 0.42, I² = 56.9%, p = 0.0024					
	Improvement	RR [CI]		Treatment	Control
ACTIV-3/TIC.. (RCT)	-100%	2.00 [0.69-5.83]	death	9/163	5/151
Bariola	67%	0.33 [0.10-1.01]	death	4/234	12/234
Ganesh	74%	0.26 [0.05-1.20]	death	2/1,789	8/1,832
Priest (PSM)	0%	1.00 [0.33-3.07]	death	6/379	6/379
Chew (RCT)	25%	0.75 [0.26-2.10]	hosp.	6/159	8/158
Late treatment	29%	0.71 [0.35-1.44]		27/2,724	39/2,754
Tau² = 0.29, I² = 45.8%, p = 0.35					
	Improvement	RR [CI]		Treatment	Control
Lilly (RCT)	57%	0.43 [0.28-0.67]	symp. case	483 (n)	482 (n)
Prophylaxis	57%	0.43 [0.28-0.67]		483 (n)	482 (n)
Tau² = 0.00, I² = 0.0%, p = 0.00021					
All studies	49%	0.51 [0.36-0.74]		81/9,161	250/25,397



[1] CT: study uses combined treatment

Tau² = 0.28, I² = 52.3%, p = 0.00039

Effect extraction pre-specified
(most serious outcome, see appendix)

A

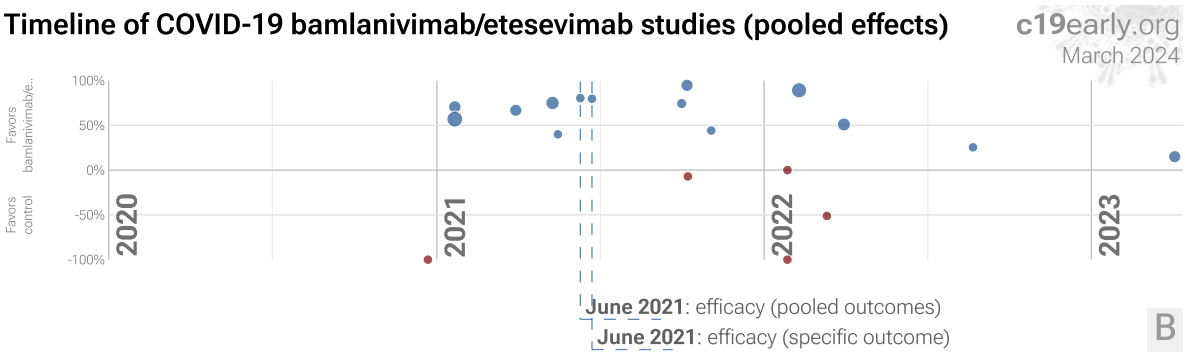


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in bamlanivimab/etesevimab studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and one or more specific outcome.

Introduction

Immediate treatment recommended. SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological issues *Hampshire, Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui, Niarakis*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk *c19early.org*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis. We analyze all significant controlled studies of bamlanivimab/etesevimab for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing. Figure 2 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

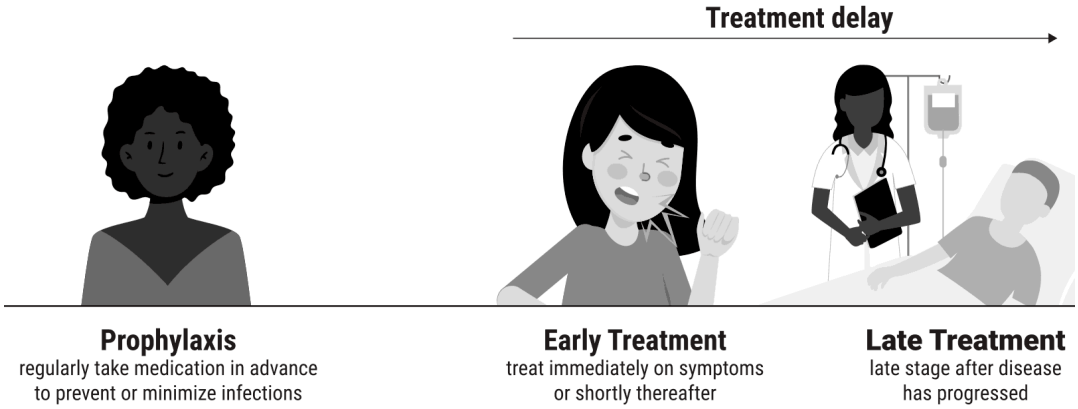


Figure 2. Treatment stages.

Variant Dependence

Efficacy for monoclonal antibodies is typically variant dependent. Table 1 shows efficacy by variant for several monoclonal antibodies.

	Bamlanivimab/ etesevimab	*Casirivimab/ imdevimab*	*Sotrovimab*	*Bebtelovimab*	*Tixagevimab/ cilgavimab*
Alpha B.1.1.7					
Beta/Gamma BA1.351/P.1					
Delta B.1.617.2					
Omicron BA.1/BA.1.1					
Omicron BA.2					
Omicron BA.5					
Omicron BA.4.6					
Omicron BQ.1.1					

Table 1. Predicted efficacy by variant from *Davis* (not updated for more recent variants). : likely effective : likely ineffective : unknown. Submit updates.

Results

Table 2 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 3 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, 11, and 12 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	49% [26-64%] ***	19	34,558	260
After exclusions	52% [30-68%] ***	17	21,867	244
Peer-reviewed studies	49% [20-67%] **	16	32,870	215
Randomized Controlled Trials	39% [-24-70%]	6	3,039	110
Mortality	56% [16-77%] *	12	31,778	154
ICU admission	28% [-11-53%]	2	15,055	29
Hospitalization	41% [27-52%] ****	13	30,971	168
Recovery	11% [3-18%] **	2	1,129	59
Viral	38% [2-60%] *	3	1,354	81
RCT mortality	58% [-1321-99%]	2	1,349	34

Table 2. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	55% [25-73%] **	29% [-44-65%]	57% [33-72%] ***
After exclusions	62% [31-79%] **	29% [-44-65%]	57% [33-72%] ***
Peer-reviewed studies	59% [29-76%] **	12% [-85-58%]	
Randomized Controlled Trials	64% [-72-92%]	-21% [-218-54%]	57% [33-72%] ***
Mortality	67% [19-87%] *	31% [-76-73%]	
ICU admission	17% [-30-47%]	49% [-9-76%]	
Hospitalization	45% [30-56%] ****	32% [-7-57%]	
Recovery	11% [3-18%] **	-14% [-45397-100%]	
Viral	44% [-48-79%]	26% [10-38%] **	
RCT mortality	95% [10-100%] *	-100% [-483-31%]	

Table 3. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

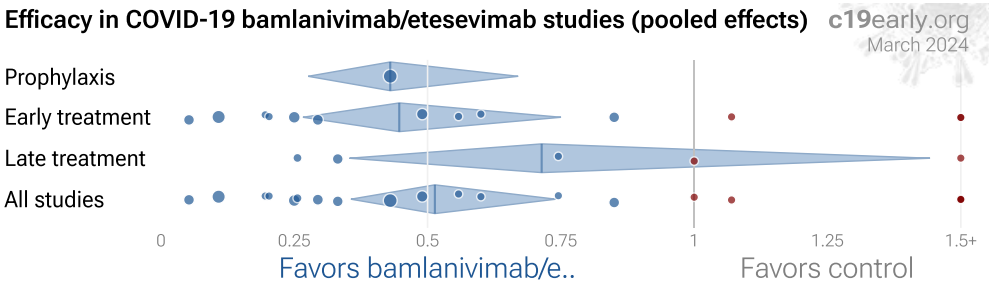


Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

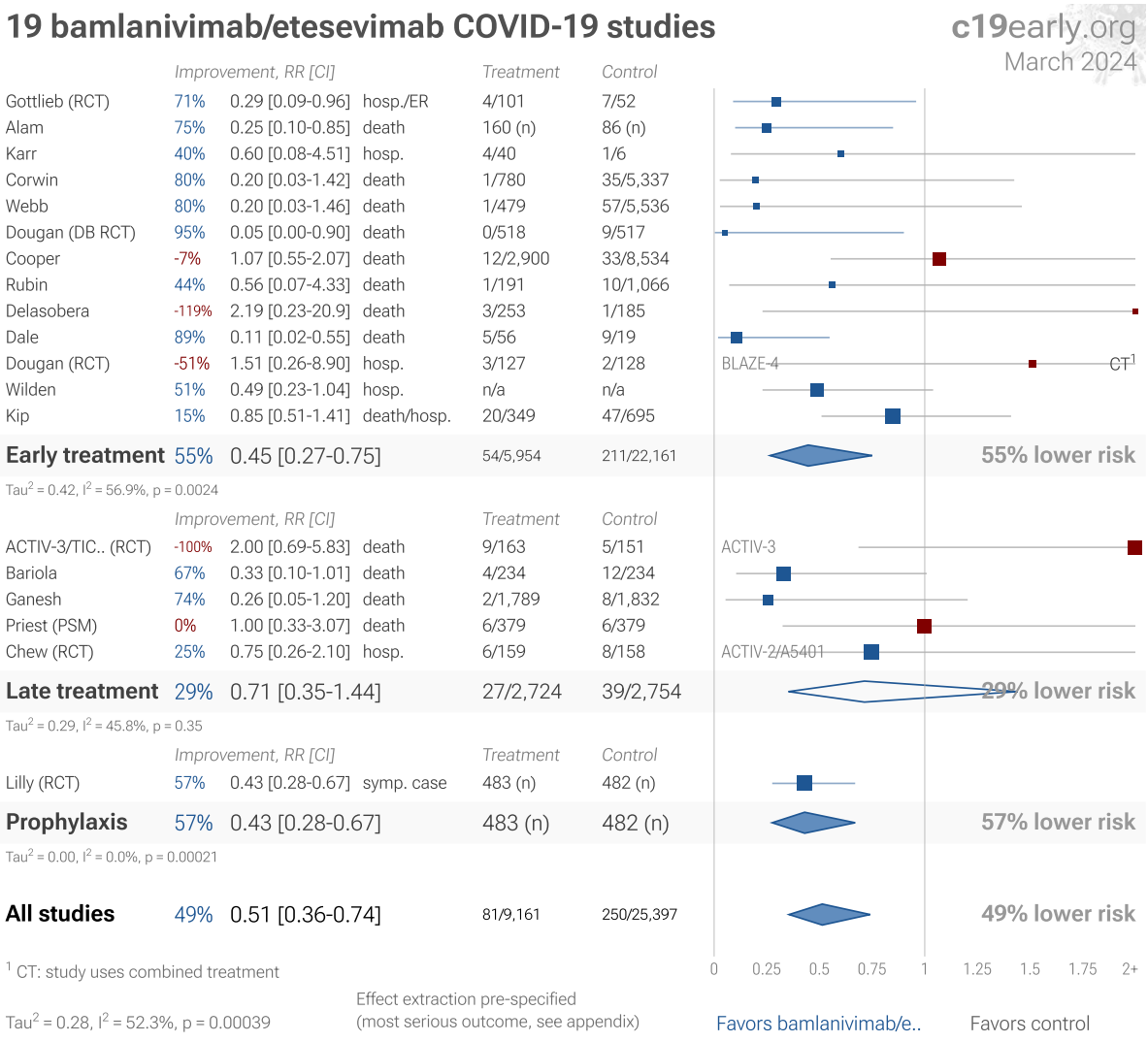


Figure 4. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

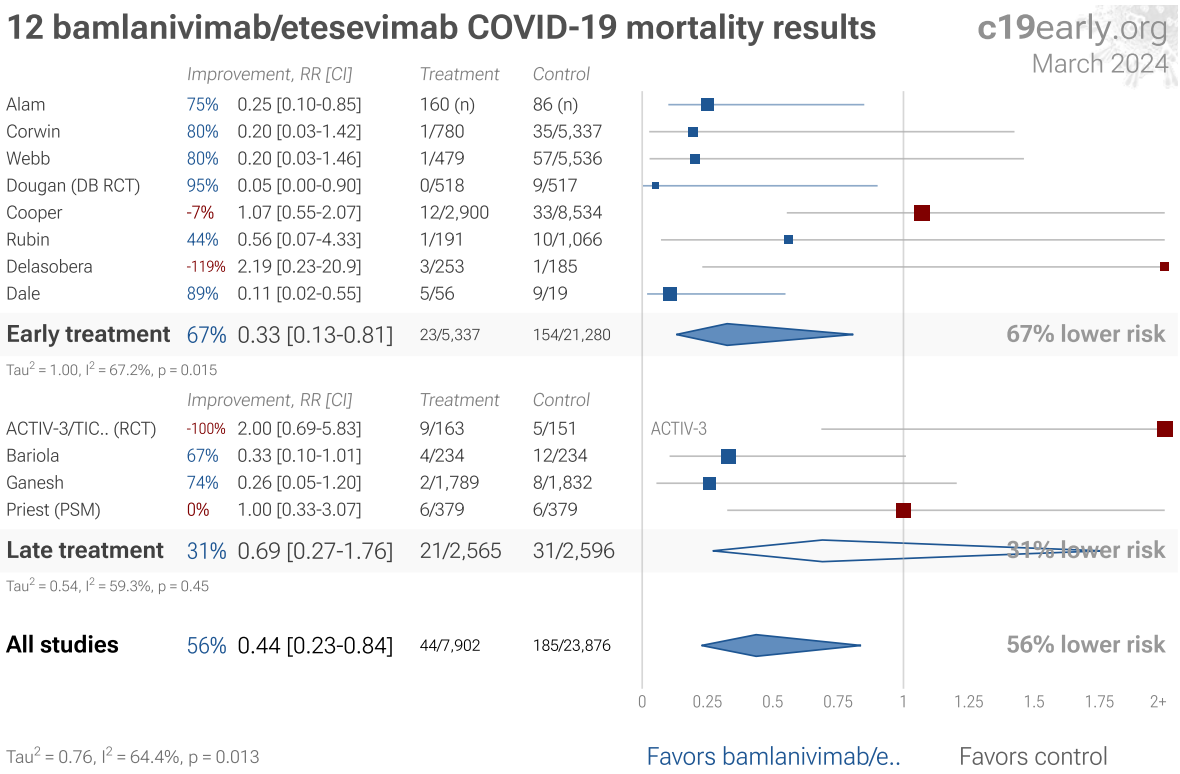


Figure 5. Random effects meta-analysis for mortality results.

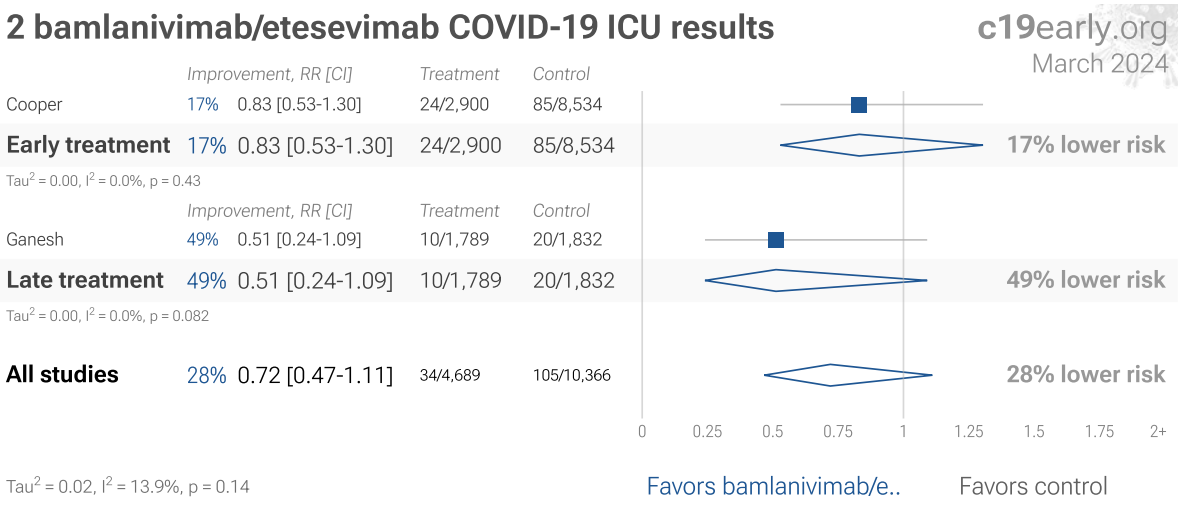


Figure 6. Random effects meta-analysis for ICU admission.

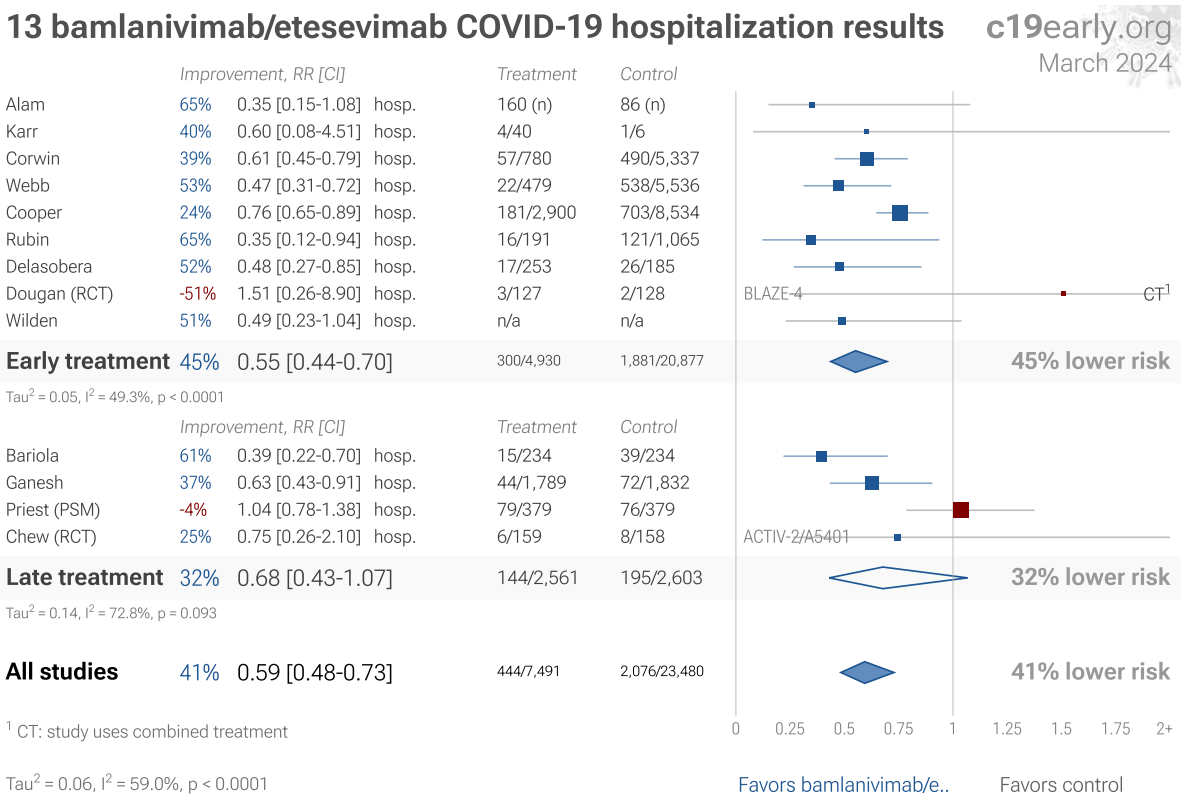


Figure 7. Random effects meta-analysis for hospitalization.

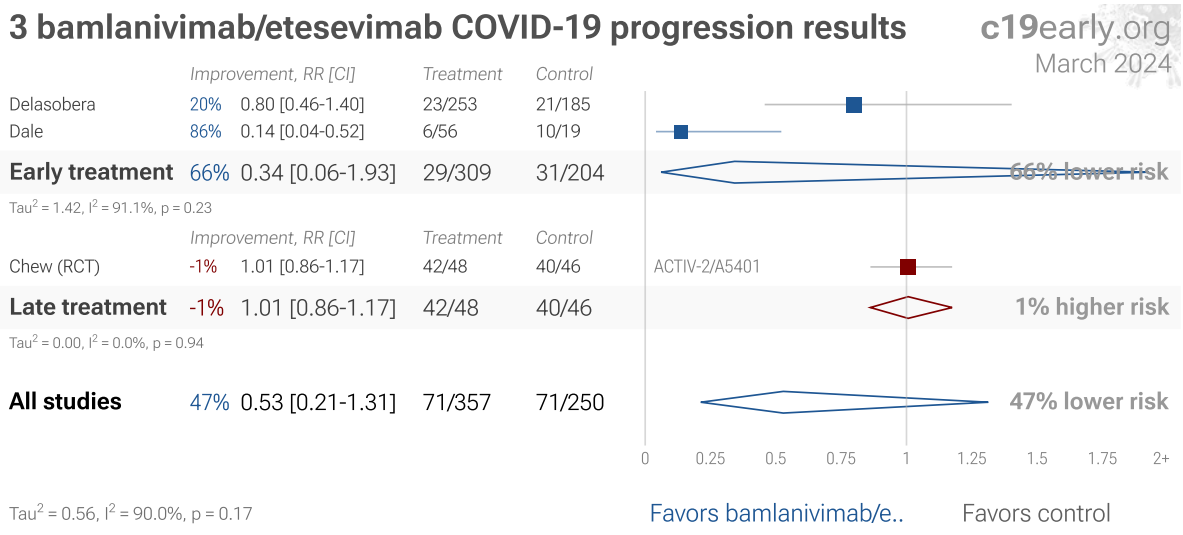


Figure 8. Random effects meta-analysis for progression.

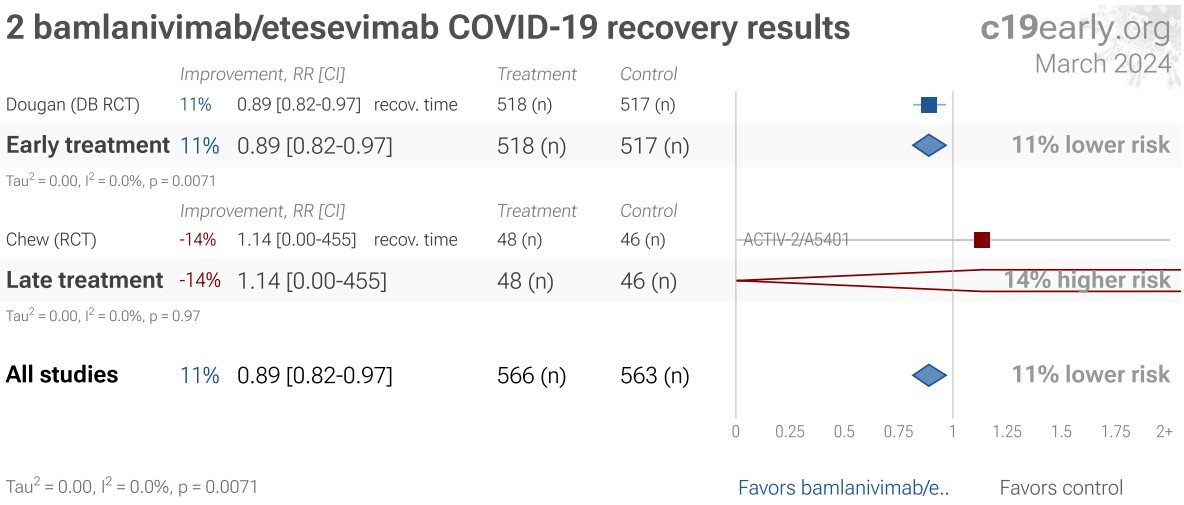


Figure 9. Random effects meta-analysis for recovery.

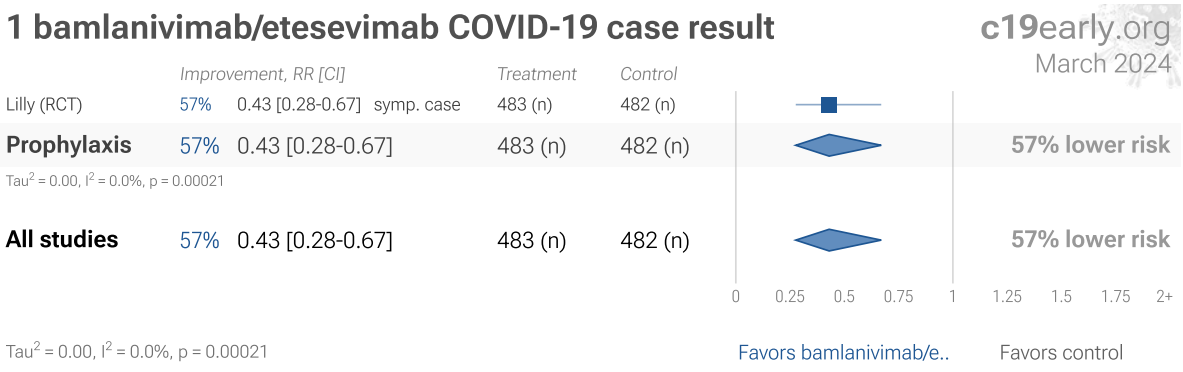


Figure 10. Random effects meta-analysis for cases.

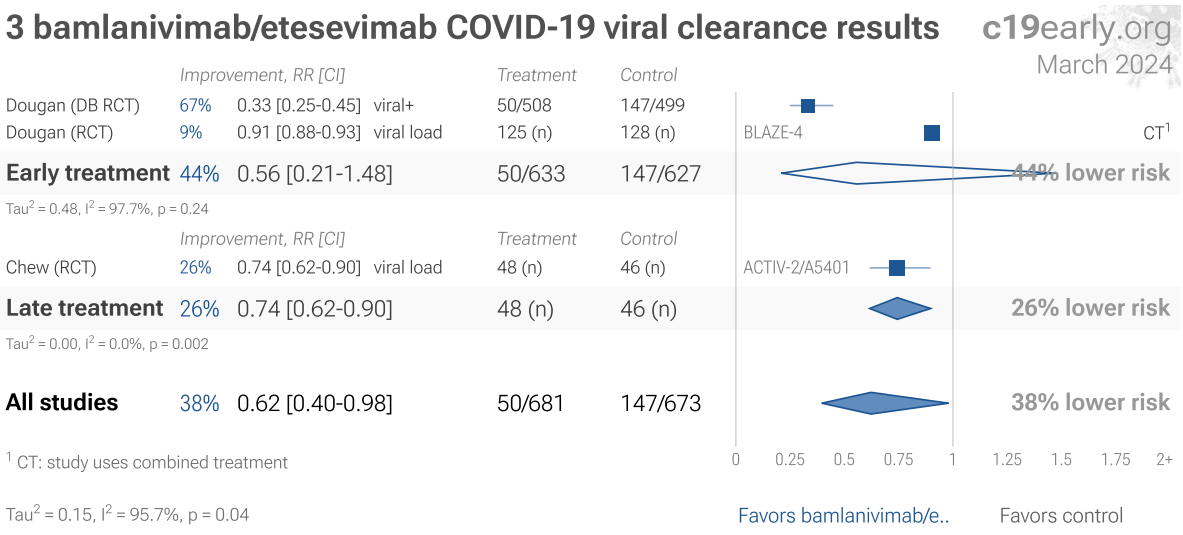


Figure 11. Random effects meta-analysis for viral clearance.

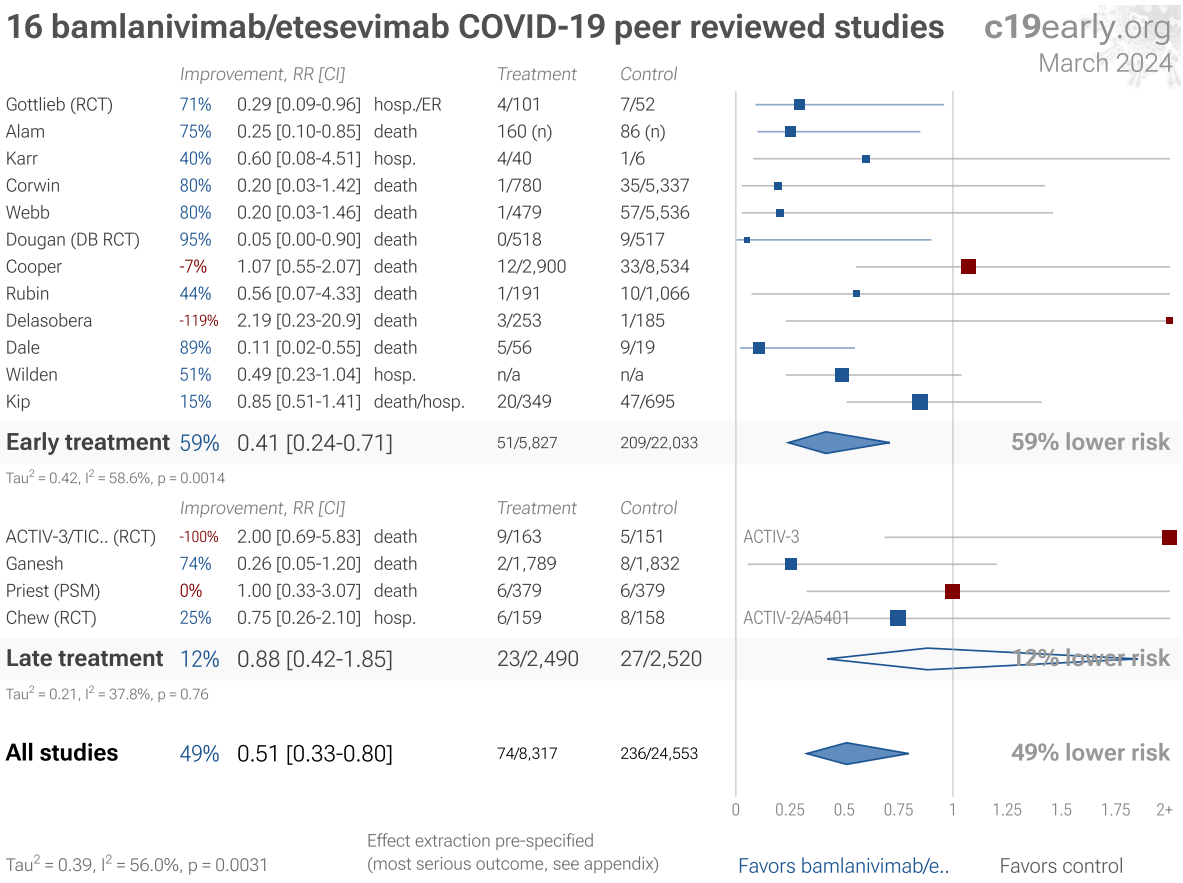


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. Figure 14 and 15 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 2 and Table 3.

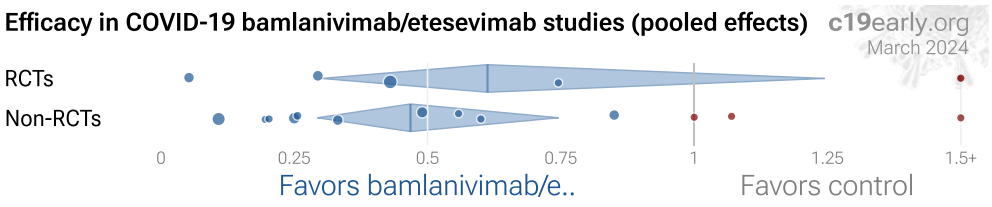


Figure 13. **Results for RCTs and non-RCT studies.**

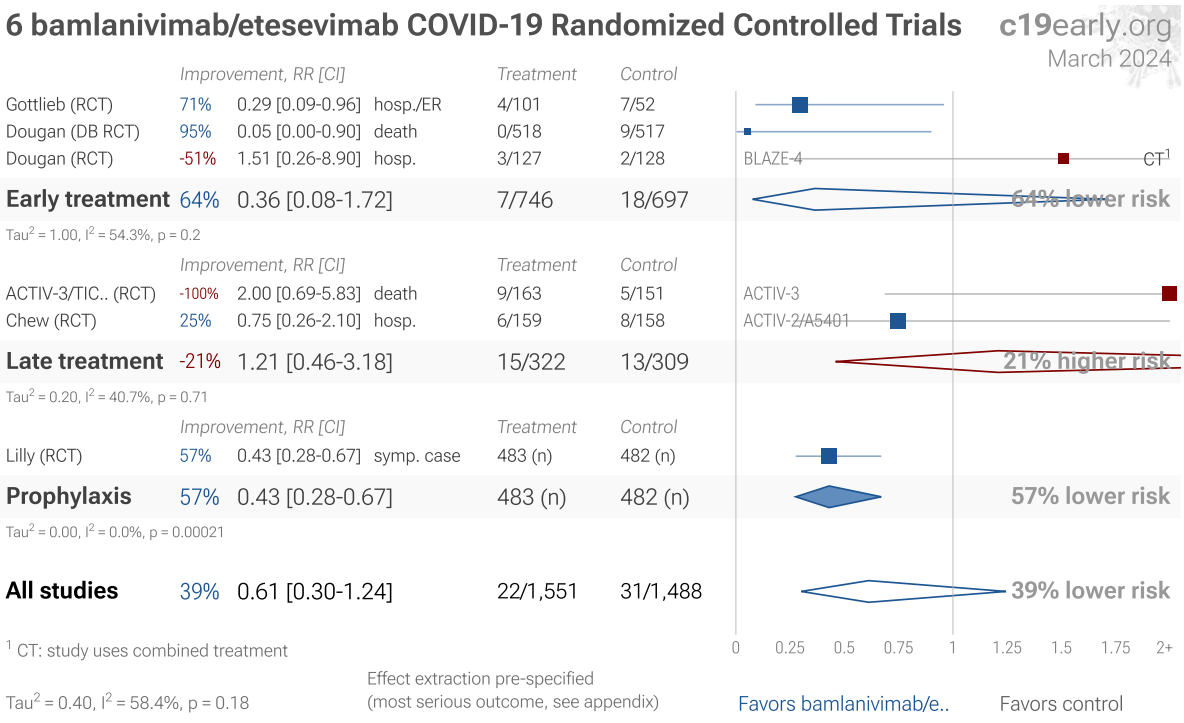


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

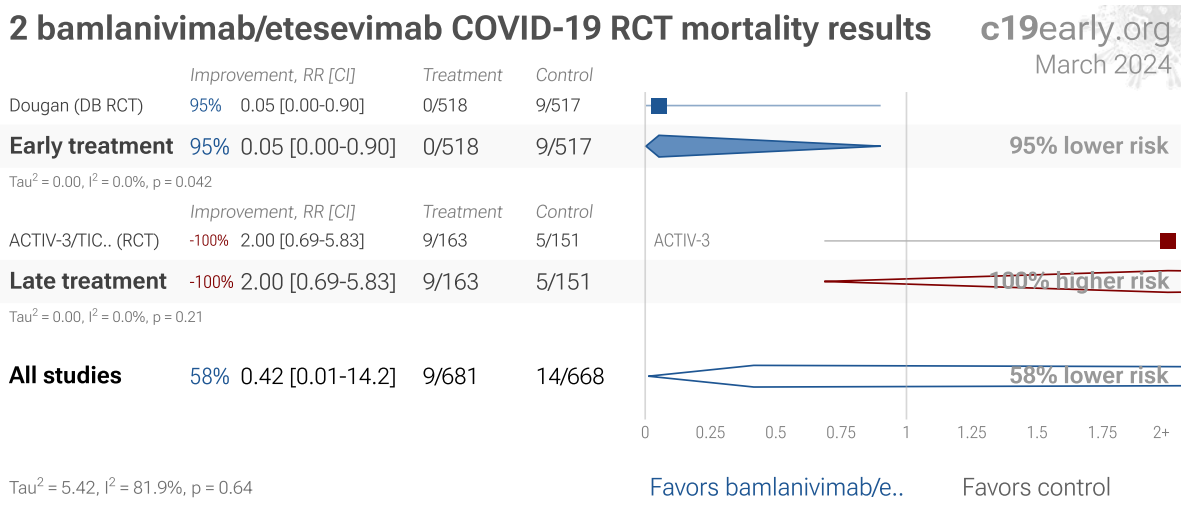


Figure 15. **Random effects meta-analysis for RCT mortality results.**

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *Jadad*, and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs. RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

Using all studies identifies efficacy 6+ months faster (7+ months for low-cost treatments). Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

Summary. We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which can be easily influenced by potential bias, may ignore or underemphasize serious issues not captured in the checklists, and may overemphasize issues unlikely to alter outcomes in specific cases (for example certain specifics of randomization with a very large effect size and well-matched baseline characteristics).

The studies excluded are as below. Figure 16 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Cooper, unadjusted results with no group details.

Rubin, significant unadjusted confounding possible.

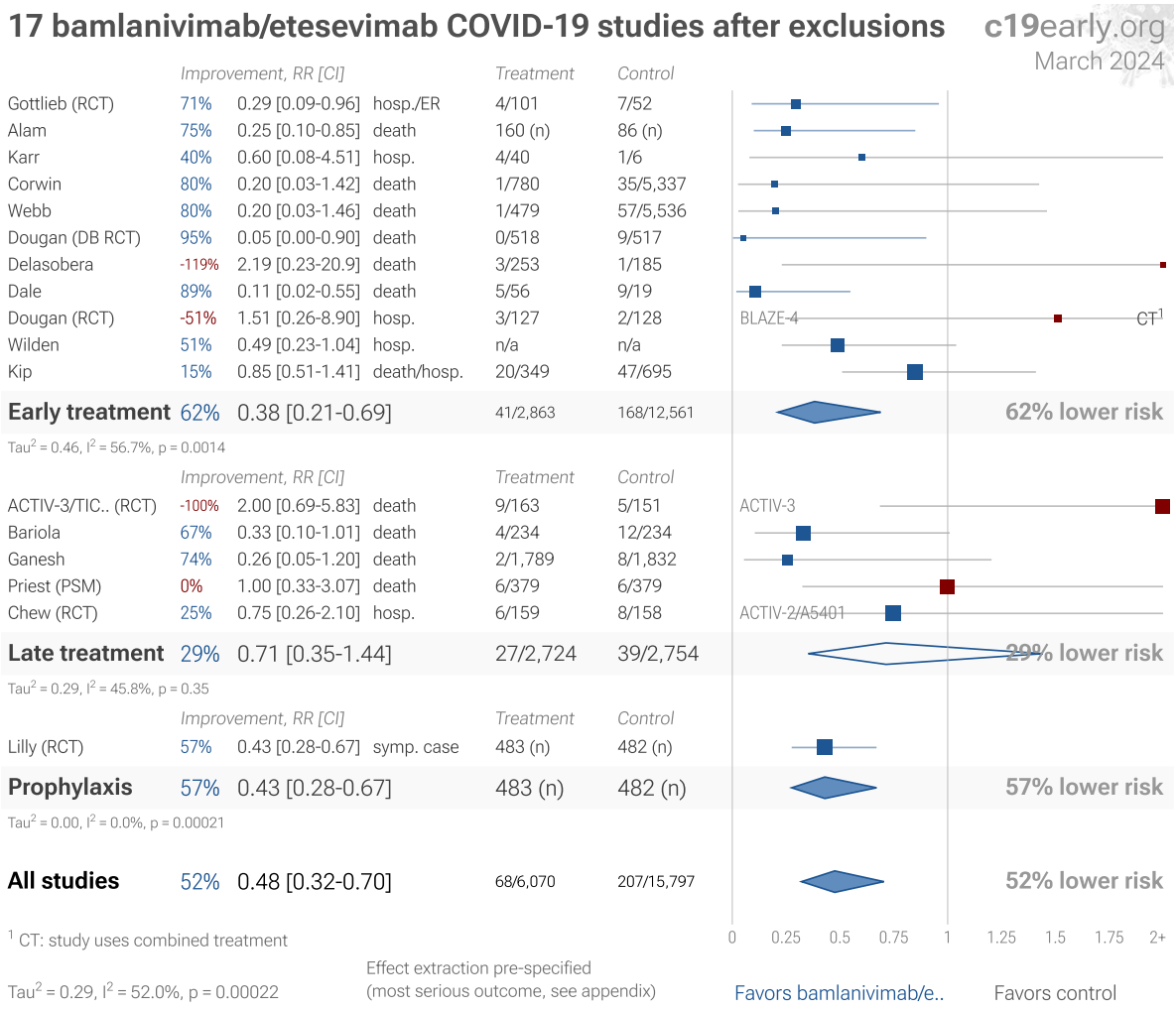


Figure 16. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post exposure prophylaxis	86% fewer cases *Ikematsu*
<24 hours	-33 hours symptoms *Hayden*
24-48 hours	-13 hours symptoms *Hayden*
Inpatients	-2.5 hours to improvement *Kumar*

Table 4. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 17 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

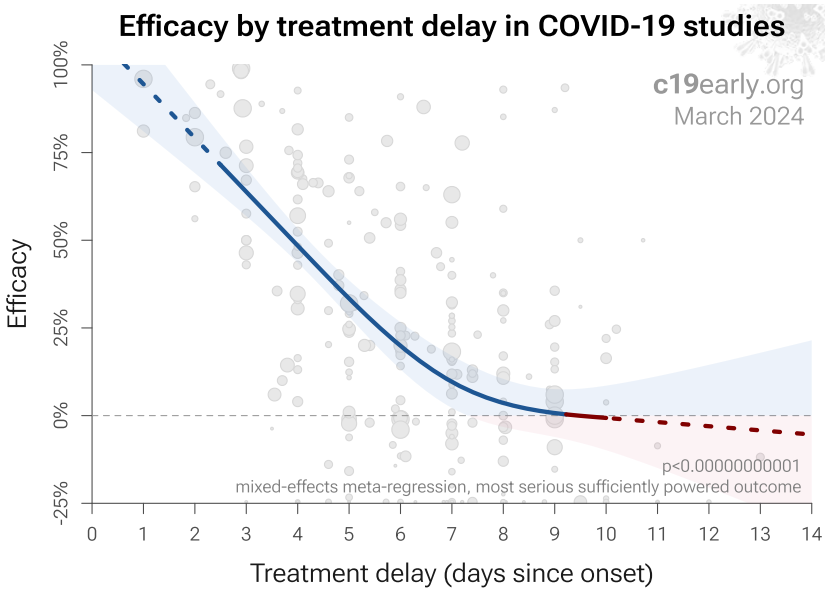


Figure 17. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

Patient demographics. Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results (as in *López-Medina et al.*).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *Peacock, Willett*.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

Other treatments. The use of other treatments may significantly affect outcomes, including supplements, other medications, or other kinds of treatment such as prone positioning. Treatments may be synergistic *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*, therefore efficacy may depend strongly on combined treatments.

Medication quality. The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 18. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy 4 months faster (6 months for RCTs). Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

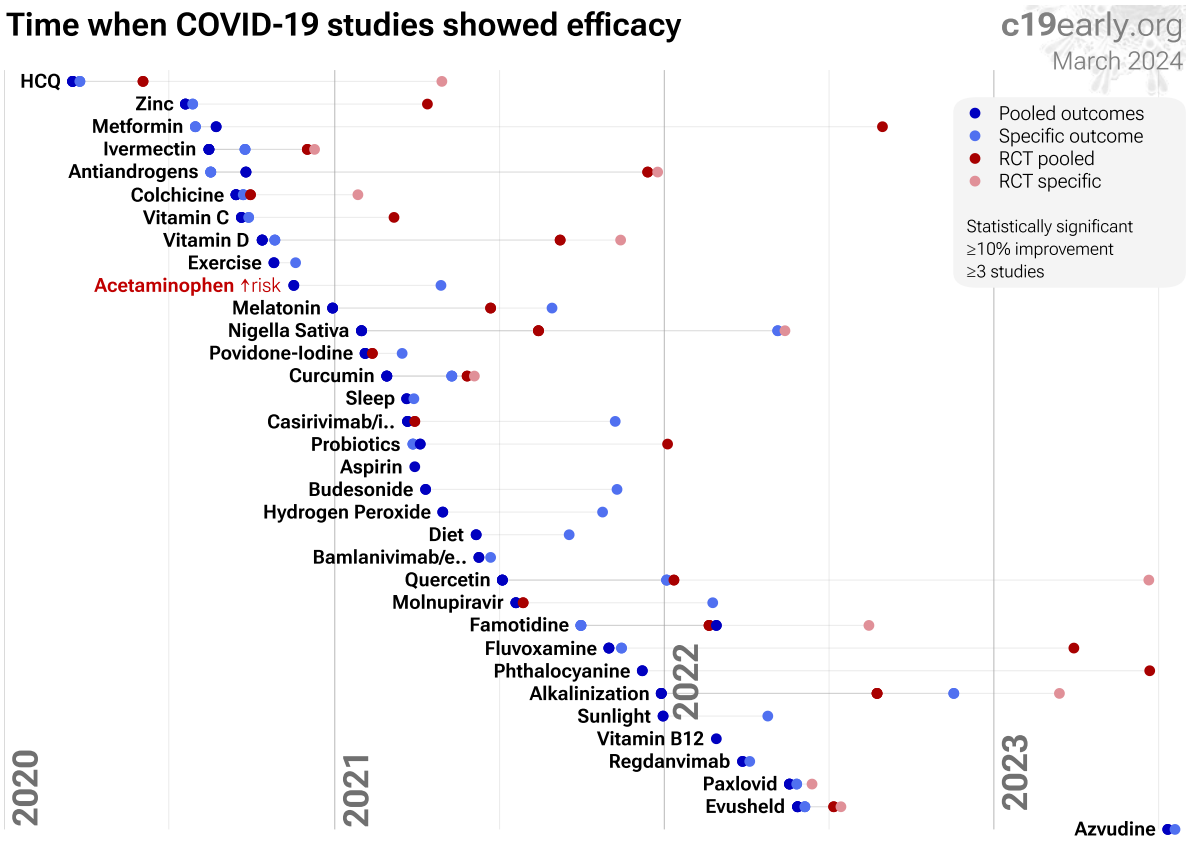


Figure 18. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Meta analysis. The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Discussion

Retrospective studies may overestimate efficacy. *Wilcock et al.* show that COVID-19 prescription treatments have been preferentially used by patients at lower risk. Retrospective studies may overestimate efficacy, and data for accurate adjustment may not be available. For example, patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

Publication bias. Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For bamlanivimab/etesevimab, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 19 shows a scatter plot of results for prospective and retrospective studies. Prospective studies show 39% [-24-70%] improvement in meta analysis, compared to 53% [25-71%] for retrospective studies, suggesting possible positive publication bias, with a non-significant trend towards retrospective studies reporting higher efficacy.

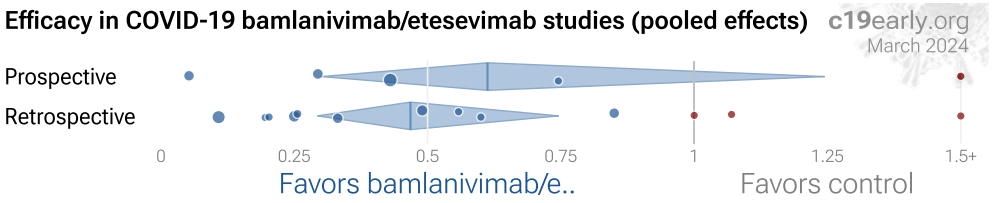


Figure 19. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 20 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

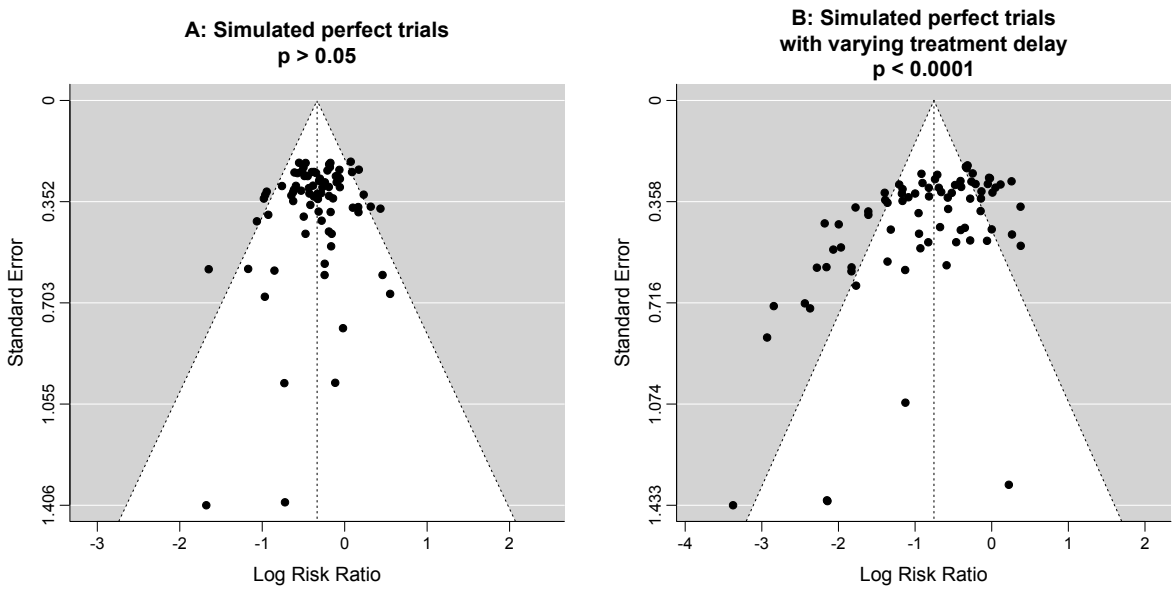


Figure 20. Example funnel plot analysis for simulated perfect trials.

Limitations. Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses by specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials affiliated with special interests may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical

advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes. 1 of 19 studies combine treatments. The results of bamlanivimab/etesevimab alone may differ. 1 of 6 RCTs use combined treatment.

Reviews. *Focosi et al.* present a review covering bamlanivimab/etesevimab for COVID-19.

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors *Lui, Lv, Malone, Murigneux, Niarakis*, providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 21 shows an overview of the results for bamlanivimab/etesevimab in the context of multiple COVID-19 treatments, and Figure 22 shows a plot of efficacy vs. cost for COVID-19 treatments.

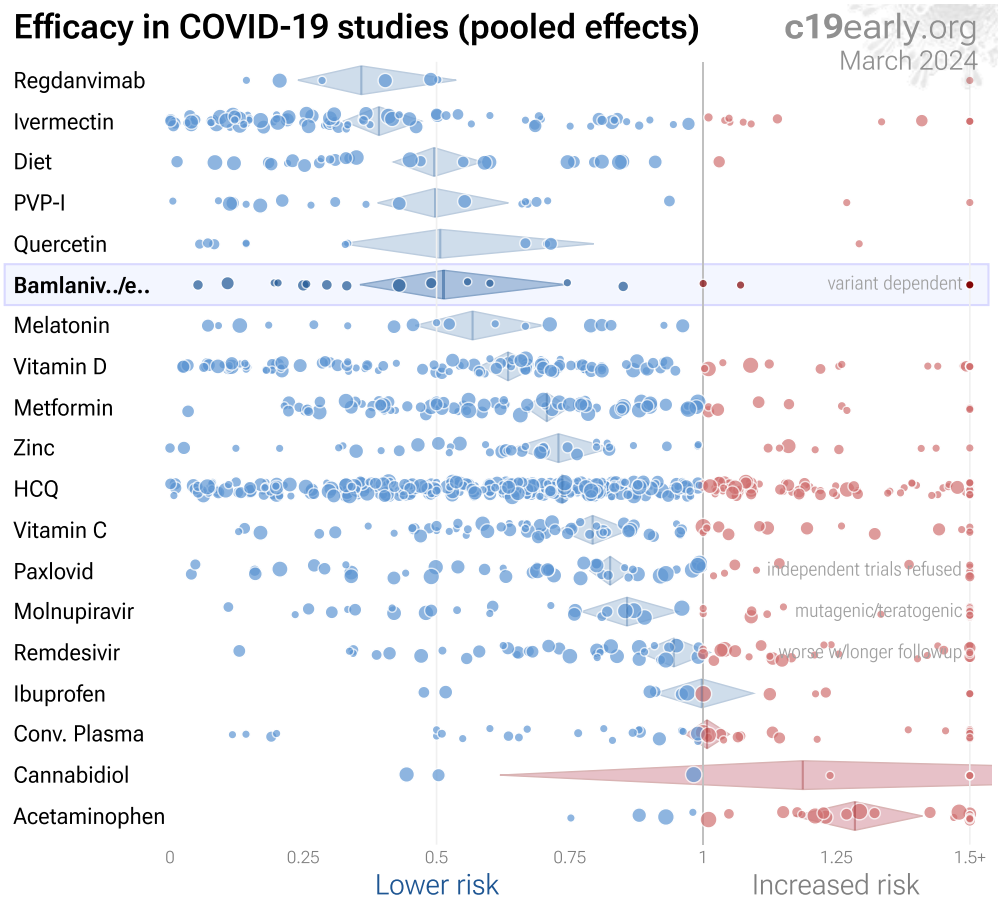


Figure 21. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,066 proposed treatments show efficacy *c19early.org (B)*.

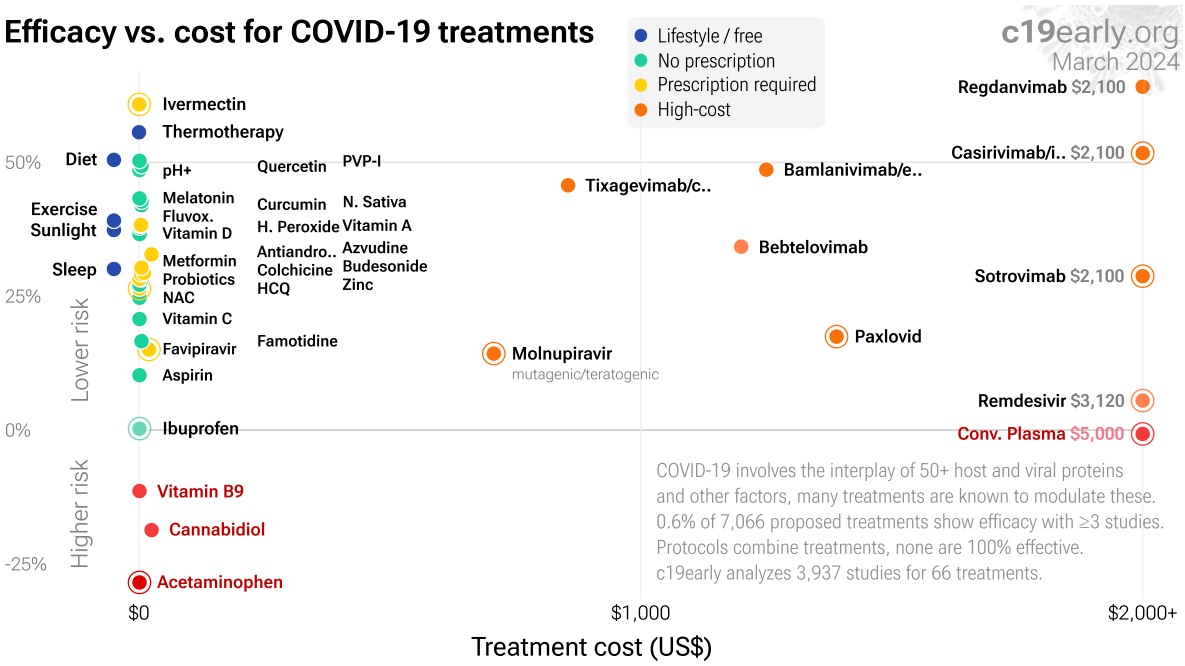


Figure 22. Efficacy vs. cost for COVID-19 treatments.

Conclusion

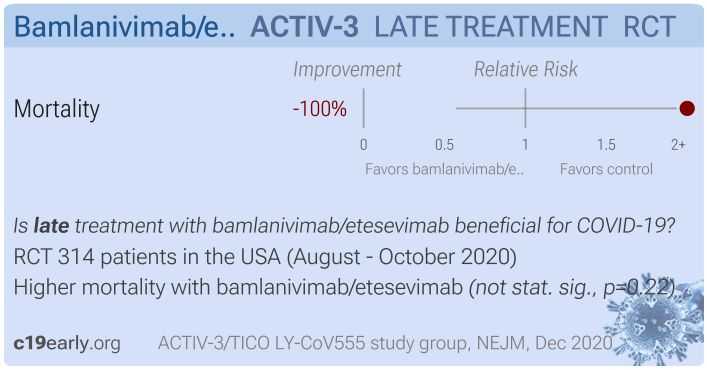
Bamlanivimab/etesevimab is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, recovery, cases, and viral clearance. 14 studies from 12 independent teams (all from the same country) show statistically significant improvements. Meta analysis using the most serious outcome reported shows 49% [26-64%] lower risk. Results are similar for higher quality and peer-reviewed studies and slightly worse for Randomized Controlled Trials. Results are consistent with early treatment being more effective than late treatment. Results are robust — in exclusion sensitivity analysis 8 of 19 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Efficacy is highly variant dependent. *In Vitro* studies suggest a lack of efficacy for omicron *Haars, Liu, Pochtovyi, Sheward, VanBlargan*. mAb use may create new variants that spread globally *Focosi, Leducq*, and may be associated with prolonged viral loads, clinical deterioration, and immune escape *Choudhary, Günther, Leducq*.

Prescription treatments have been preferentially used by patients at lower risk *Wilcock*. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

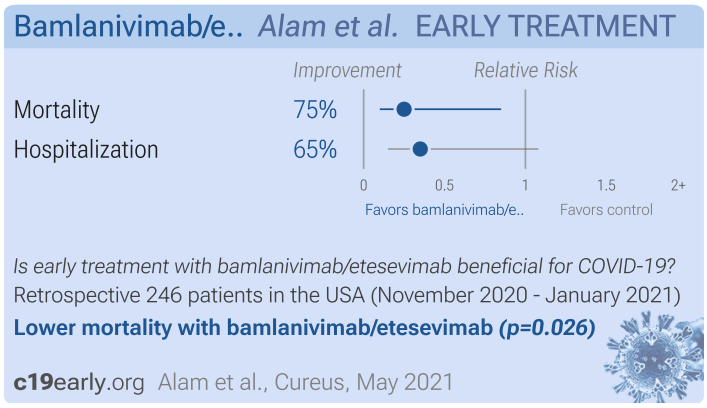
Study Notes

ACTIV-3/TICO LY-CoV555 study group



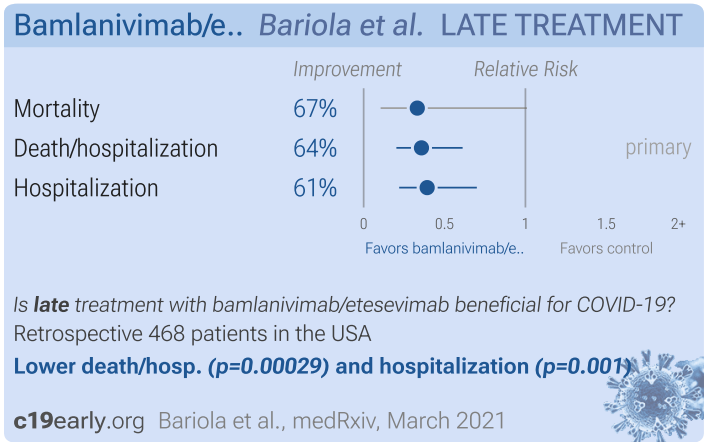
ACTIV-3/TICO LY-CoV555 study group: Late stage RCT of LY-CoV555 added to remdesivir, showing non-statistically significant higher mortality with the addition of LY-CoV555.

Alam



Alam: Retrospective 246 nursing home patients showing lower mortality with early bamlanivimab treatment.

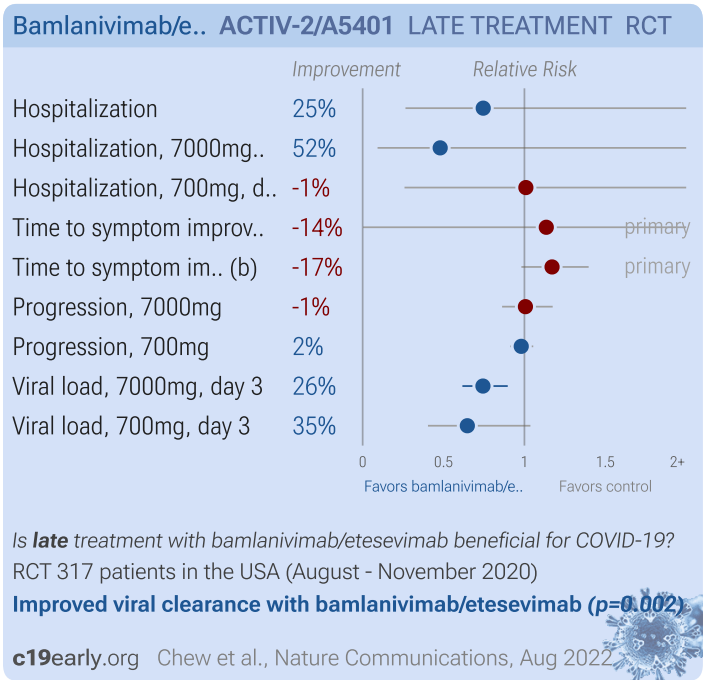
Bariola



Bariola: Retrospective 234 patients receiving bamlanivimab and 234 matched controls, showing lower hospitalization and mortality with treatment. Greater benefit was seen with administration within 4 days of their positive COVID-19 test.

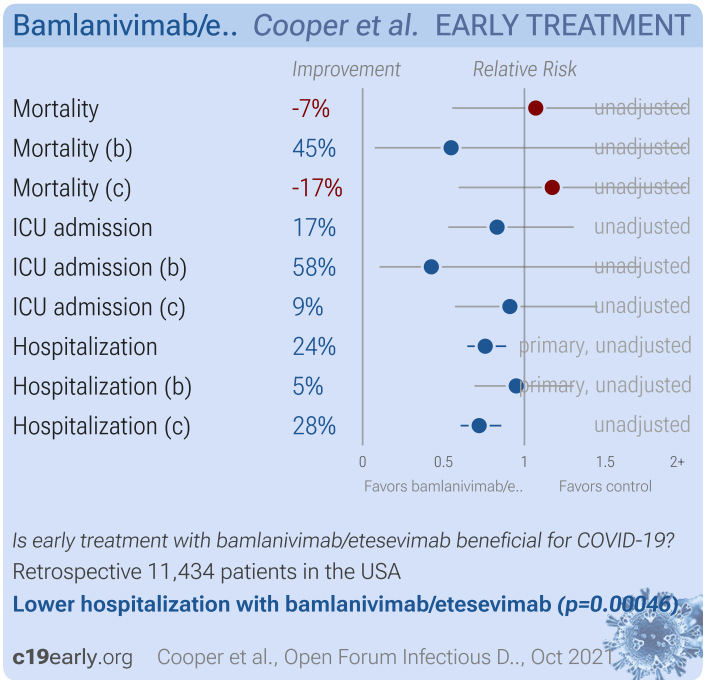
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending bamlanivimab/etesevimab also recommended them, or because the patient seeking out bamlanivimab/etesevimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Chew



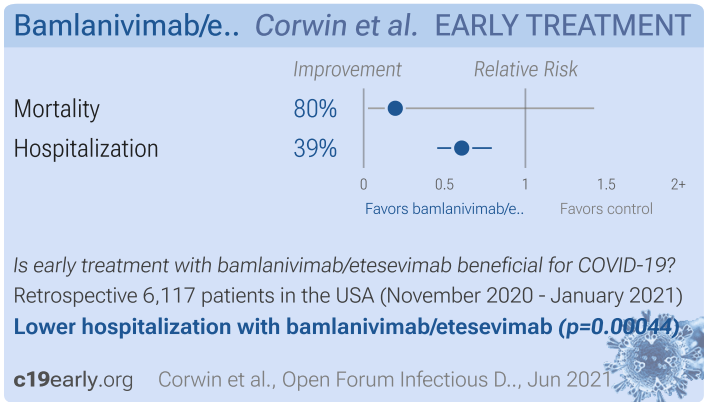
Chew: RCT 317 outpatients in the USA showing faster viral load and inflammatory biomarker decline, but no significant differences in clinical outcomes.

Cooper



Cooper: Retrospective 2,879 patients and matched controls in the USA, showing significantly lower mortality and hospitalization with monoclonal antibody treatment (bamlanivimab, bamlanivimab/etesevimab, or casirivimab/imdevimab). There was significantly lower hospitalization with casirivimab/imdevimab compared to bamlanivimab or bamlanivimab/etesevimab. PSM and multivariate analysis is only provided for all treatments combined.

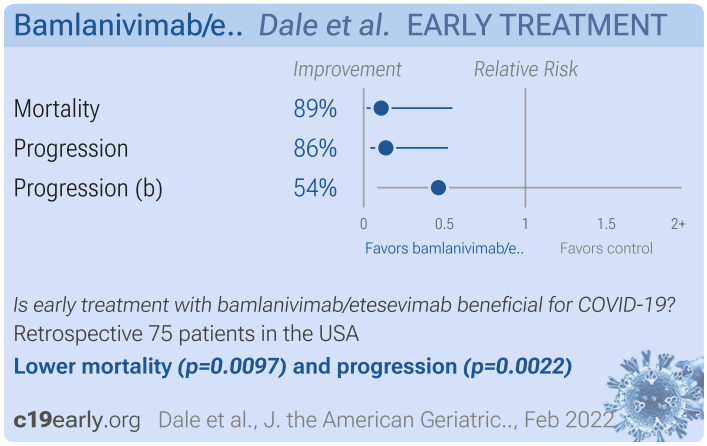
Corwin



Corwin: Retrospective 780 bamlanivimab patients and 5,337 patients not receiving treatment, showing lower hospitalization and ER visits with treatment.

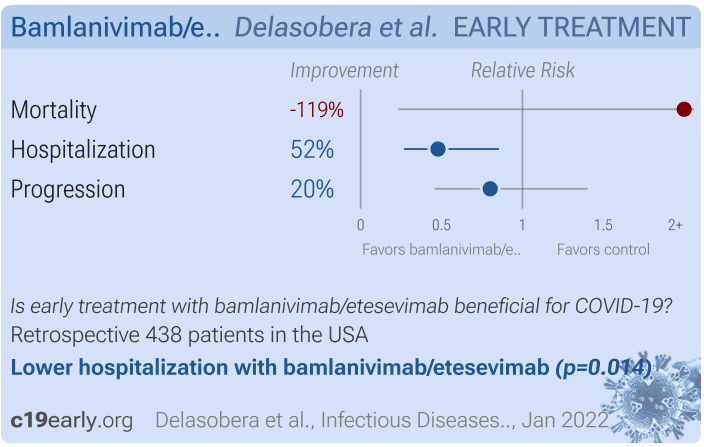
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending bamlanivimab/etesevimab also recommended them, or because the patient seeking out bamlanivimab/etesevimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Dale



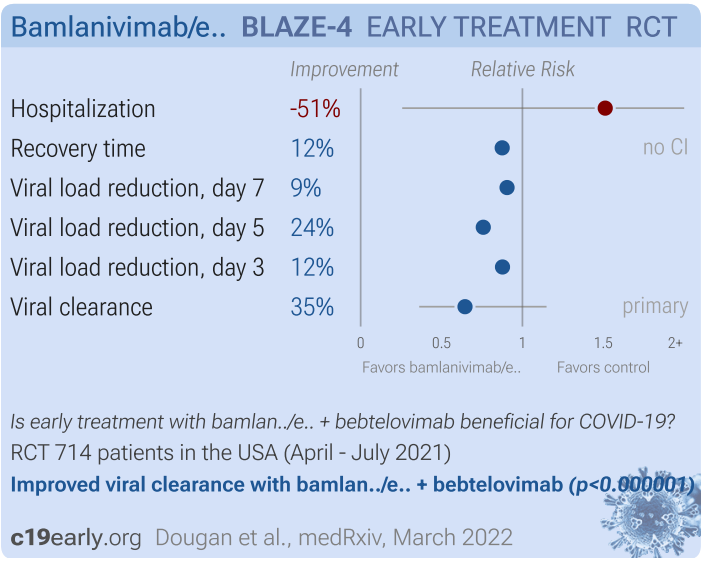
Dale: Retrospective 75 COVID+ patients in a skilled nursing facility in the USA, 56 treated within a median of 2 days from symptom onset with bamlanivimab, showing significantly lower mortality with treatment.

Delasobera



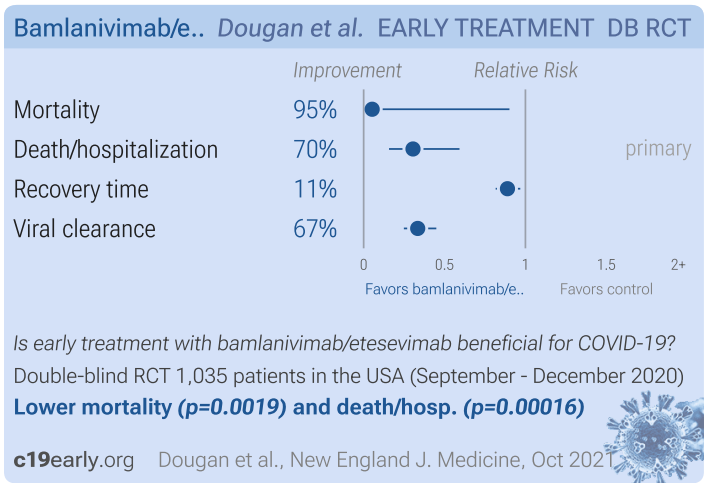
Delasobera: Retrospective 438 patients in the USA, 253 treated with bamlanivimab, showing significantly lower hospitalization with treatment.

Dougan



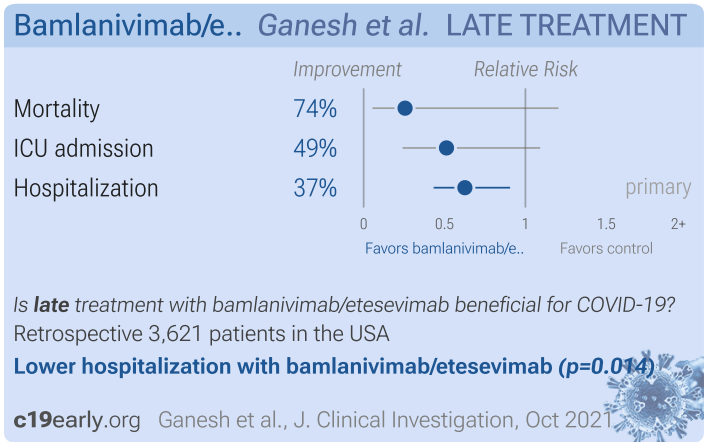
Dougan: RCT showing improved viral clearance with bamlanivimab/etesevimab combined with bebtelovimab. Results refer to the placebo controlled portion of the trial.

Dougan



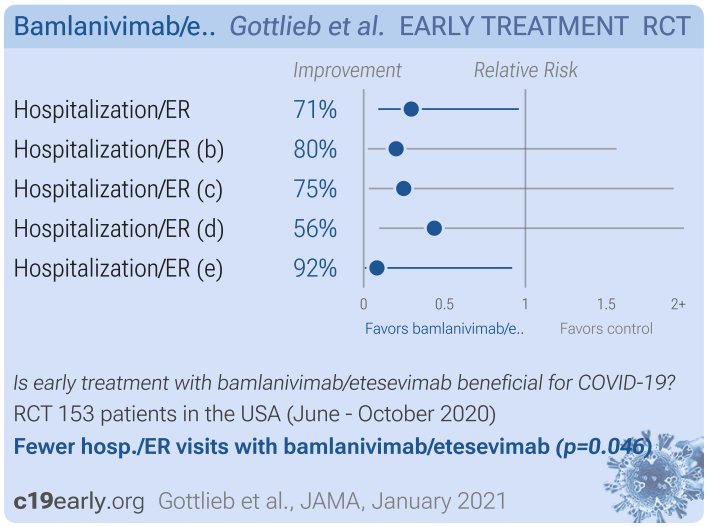
Dougan (B): Results from the BLAZE-1 RCT of combined bamlanivimab/etesevimab, showing significantly lower mortality and combined mortality/hospitalization with treatment. NCT04427501.

Ganesh



Ganesh: Retrospective 2,335 bamlanivimab patients and 2,335 PSM controls in the USA, showing significantly lower hospitalization with treatment.

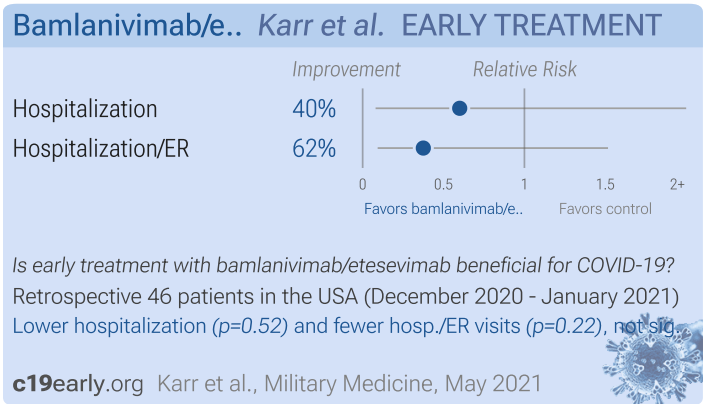
Gottlieb



Gottlieb: RCT for LY-CoV555 monotherapy and LY-CoV555/LY-CoV016 combination therapy with 592 patients showing lower hospitalization/ER visits with treatment.

For viral load at day 11, a statistically significant reduction was found with combination therapy but not monotherapy.

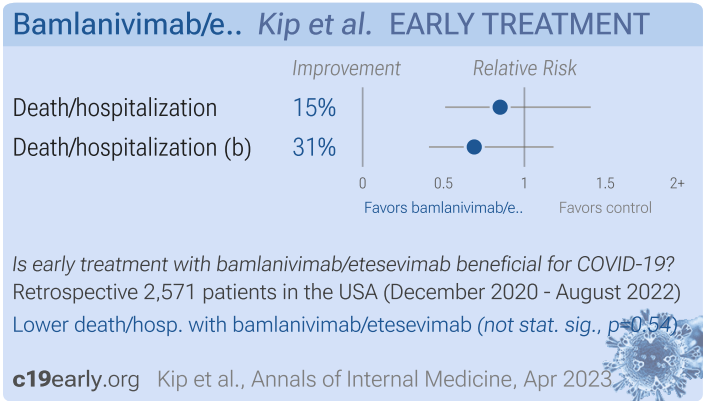
Karr



Karr: Retrospective 40 outpatients showing improvement in symptoms and lower risk of hospitalization/ER visits with bamlanivimab, without statistical significance.

Different counts for hospitalization are provided in the abstract and text: "Three of 40 (7.5%) patients in the treatment group required inpatient admission" and "In the treatment group, 4 of 40 (10%) patients were hospitalized after infusion."

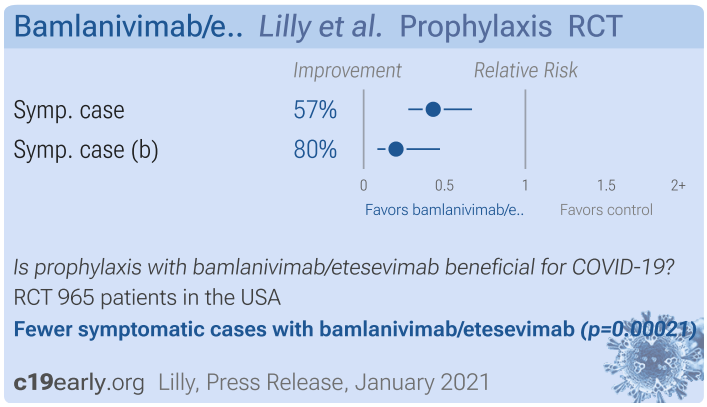
Kip



Kip: Retrospective 2,571 patients treated with mAbs in the USA, and 5,135 control patients, showing lower combined mortality/hospitalization for bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab, with statistical significance only for casirivimab/imdevimab.

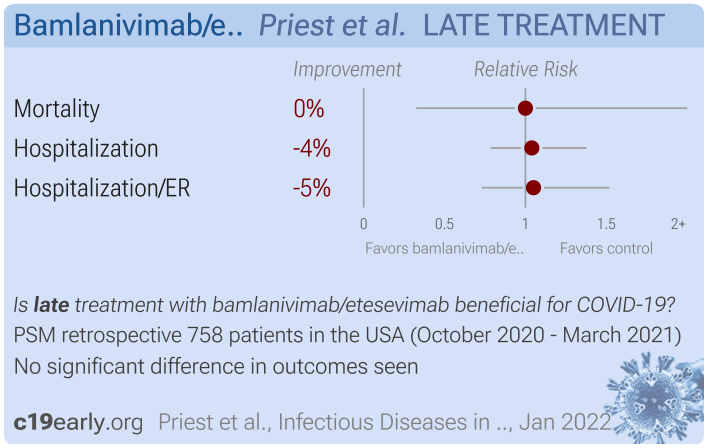
Confounding by treatment propensity. This study analyzes a population where only a fraction of eligible patients received the treatment. Patients receiving treatment may be more likely to follow other recommendations, more likely to receive additional care, and more likely to use additional treatments that are not tracked in the data (e.g., nasal/oral hygiene *c19early.org (C), c19early.org (D)*, vitamin D *c19early.org (E)*, etc.) — either because the physician recommending bamlanivimab/etesevimab also recommended them, or because the patient seeking out bamlanivimab/etesevimab is more likely to be familiar with the efficacy of additional treatments and more likely to take the time to use them. Therefore, these kind of studies may overestimate the efficacy of treatments.

Lilly



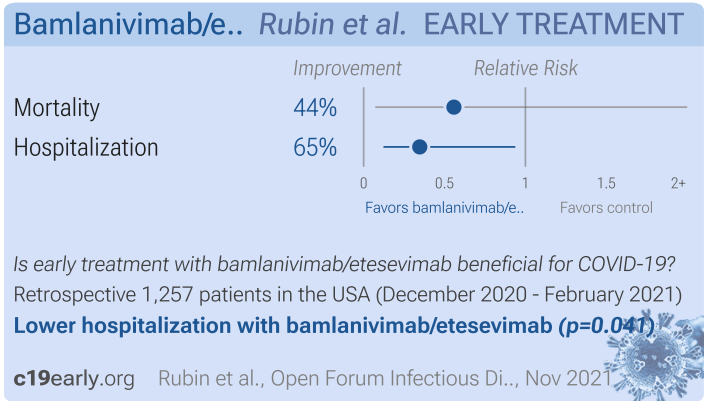
Lilly: Press release on the BLAZE-2 trial at nursing homes showing significantly lower symptomatic COVID-19 with treatment.

Priest



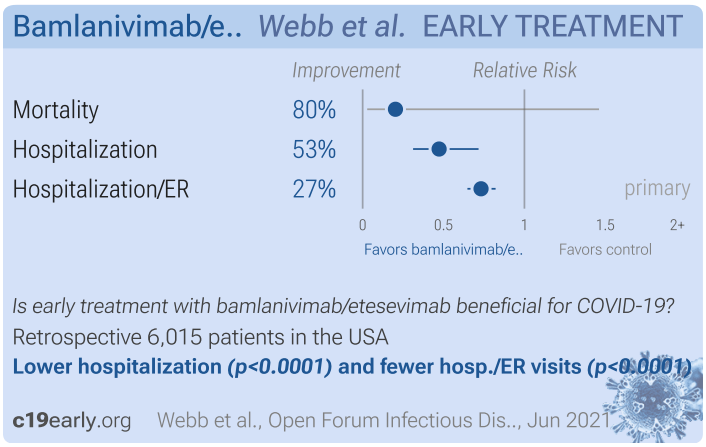
Priest: Retrospective 379 bamlanivimab patients and 379 matched controls in the USA, showing no significant differences with treatment.

Rubin



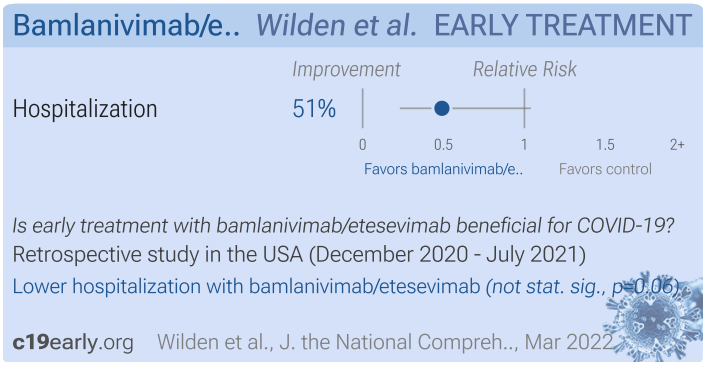
Rubin: Retrospective database analysis of 1257 PCR+ outpatients with age ≥65, BMI≥35, 191 receiving bamlanivimab via lottery. Authors note that the alpha variant was most common during the study period, and that efficacy against other variants can be much lower. Authors note confounding due to prioritization in the lottery and differential reporting in the database.

Webb



Webb: Retrospective 479 patients treated with bamlanivimab showing lower mortality, hospital admission, and emergency department visits with treatment. Authors incorrectly state that "no other COVID-19 therapies for ambulatory patients have proven effective".

Wilden



Wilden: Retrospective 395 patients in the USA receiving casirivimab/imdevimab or bamlanivimab, showing lower risk of hospitalization with treatment, statistically significant for casirivimab/imdevimab.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are bamlanivimab, etesevimab and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of bamlanivimab/etesevimab for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical

outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta *Deng* with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a p-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective *McLean, Treanor*.

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A summary of study results is below. Please submit updates and corrections at https://c19early.org/lmeta.html.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Alam, 5/10/2021, retrospective, USA, peer-reviewed, mean age 82.4, 9 authors, study period 15 November, 2020 - 31 January, 2021.	risk of death, 75.0% lower, OR 0.25, $p = 0.03$, treatment 160, control 86, RR approximated with OR.
	risk of hospitalization, 65.0% lower, OR 0.35, $p = 0.08$, treatment 160, control 86, RR approximated with OR.
Cooper, 10/8/2021, retrospective, USA, peer-reviewed, 9 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 7.0% higher, RR 1.07, $p = 0.86$, treatment 12 of 2,900 (0.4%), control 33 of 8,534 (0.4%), unadjusted, all bamlanivimab.

	risk of death, 45.3% lower, RR 0.55, *p* = 1.00, treatment 1 of 473 (0.2%), control 33 of 8,534 (0.4%), NNT 571, unadjusted, bamlanivimab/etesevimab.
	risk of death, 17.2% higher, RR 1.17, *p* = 0.59, treatment 11 of 2,427 (0.5%), control 33 of 8,534 (0.4%), unadjusted, bamlanivimab.
	risk of ICU admission, 16.9% lower, RR 0.83, *p* = 0.51, treatment 24 of 2,900 (0.8%), control 85 of 8,534 (1.0%), NNT 594, unadjusted, all bamlanivimab.
	risk of ICU admission, 57.5% lower, RR 0.42, *p* = 0.33, treatment 2 of 473 (0.4%), control 85 of 8,534 (1.0%), NNT 174, unadjusted, bamlanivimab/etesevimab.
	risk of ICU admission, 9.0% lower, RR 0.91, *p* = 0.81, treatment 22 of 2,427 (0.9%), control 85 of 8,534 (1.0%), NNT 1117, unadjusted, bamlanivimab.
	risk of hospitalization, 24.2% lower, RR 0.76, *p* < 0.001, treatment 181 of 2,900 (6.2%), control 703 of 8,534 (8.2%), NNT 50, unadjusted, all bamlanivimab, primary outcome.
	risk of hospitalization, 5.0% lower, RR 0.95, *p* = 0.86, treatment 37 of 473 (7.8%), control 703 of 8,534 (8.2%), NNT 241, unadjusted, bamlanivimab/etesevimab, primary outcome.
	risk of hospitalization, 28.0% lower, RR 0.72, *p* < 0.001, treatment 144 of 2,427 (5.9%), control 703 of 8,534 (8.2%), NNT 43, unadjusted, bamlanivimab.
Corwin, 6/10/2021, retrospective, USA, peer-reviewed, 8 authors, study period 23 November, 2020 - 17 January, 2021.	risk of death, 80.5% lower, RR 0.20, *p* = 0.08, treatment 1 of 780 (0.1%), control 35 of 5,337 (0.7%), NNT 190.
	risk of hospitalization, 39.4% lower, RR 0.61, *p* < 0.001, treatment 57 of 780 (7.3%), control 490 of 5,337 (9.2%), odds ratio converted to relative risk.
Dale, 2/9/2022, retrospective, USA, peer-reviewed, 14 authors, average treatment delay 2.0 days.	risk of death, 89.2% lower, RR 0.11, *p* = 0.010, treatment 5 of 56 (8.9%), control 9 of 19 (47.4%), NNT 2.6, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of progression, 86.3% lower, RR 0.14, *p* = 0.002, treatment 6 of 56 (10.7%), control 10 of 19 (52.6%), NNT 2.4, adjusted per study, odds ratio converted to relative risk, oxygen therapy, multivariable.
	risk of progression, 53.8% lower, RR 0.46, *p* = 0.35, treatment 6 of 56 (10.7%), control 3 of 19 (15.8%), adjusted per study, odds ratio converted to relative risk, ER visit or hospitalization, multivariable.
Delasobera, 1/27/2022, retrospective, USA, peer-reviewed, 12 authors.	risk of death, 119.4% higher, RR 2.19, *p* = 0.64, treatment 3 of 253 (1.2%), control 1 of 185 (0.5%).

	risk of hospitalization, 52.2% lower, RR 0.48, p = 0.01, treatment 17 of 253 (6.7%), control 26 of 185 (14.1%), NNT 14.
	risk of progression, 19.9% lower, RR 0.80, p = 0.52, treatment 23 of 253 (9.1%), control 21 of 185 (11.4%), NNT 44, ER followup visit.
Dougan, 3/12/2022, Randomized Controlled Trial, USA, preprint, 22 authors, study period 19 April, 2021 - 19 July, 2021, this trial uses multiple treatments in the treatment arm (combined with bebtelovimab) - results of individual treatments may vary, trial NCT04634409 (history) (BLAZE-4).	**risk of hospitalization, 51.2% higher, RR 1.51, p = 0.68**, treatment 3 of 127 (2.4%), control 2 of 128 (1.6%).
	relative viral load reduction, 9.5% better, RR 0.91, p < 0.001, treatment mean 4.0 (±0.2) n=125, control mean 3.62 (±0.2) n=128, day 7.
	relative viral load reduction, 24.2% better, RR 0.76, p < 0.001, treatment mean 2.81 (±0.19) n=125, control mean 2.13 (±0.19) n=128, day 5.
	relative viral load reduction, 12.3% better, RR 0.88, p < 0.001, treatment mean 1.38 (±0.2) n=125, control mean 1.21 (±0.2) n=128, day 3.
	risk of no viral clearance, 35.5% lower, RR 0.65, p = 0.17, treatment 16 of 127 (12.6%), control 25 of 128 (19.5%), NNT 14, persistently high viral load, day 7, primary outcome.
Dougan (B), 10/7/2021, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 33 authors, study period 4 September, 2020 - 8 December, 2020, average treatment delay 4.0 days, trial NCT04427501 (history).	**risk of death, 94.7% lower, RR 0.05, p = 0.002**, treatment 0 of 518 (0.0%), control 9 of 517 (1.7%), NNT 57, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), COVID-19 deaths.
	risk of death/hospitalization, 69.5% lower, RR 0.30, p < 0.001, treatment 11 of 518 (2.1%), control 36 of 517 (7.0%), NNT 21, primary outcome.
	recovery time, 11.1% lower, relative time 0.89, p = 0.007, treatment 518, control 517, sustained resolution of symptoms.
	risk of no viral clearance, 66.6% lower, RR 0.33, p < 0.001, treatment 50 of 508 (9.8%), control 147 of 499 (29.5%), NNT 5.1, day 7, persistently high viral load.
Gottlieb, 1/21/2021, Randomized Controlled Trial, USA, peer-reviewed, 27 authors, study period 17 June, 2020 - 6 October, 2020, average treatment delay 4.0 days.	**risk of hospitalization/ER, 70.6% lower, RR 0.29, p = 0.046**, treatment 4 of 101 (4.0%), control 7 of 52 (13.5%), NNT 11, LY-CoV555 all dosages.
	risk of hospitalization/ER, 79.9% lower, RR 0.20, p = 0.13, treatment 1 of 37 (2.7%), control 7 of 52 (13.5%), NNT 9.3, LY-CoV555 700mg.
	risk of hospitalization/ER, 75.2% lower, RR 0.25, p = 0.25, treatment 1 of 30 (3.3%), control 7 of 52 (13.5%), NNT 9.9, LY-CoV555 2800mg.
	risk of hospitalization/ER, 56.3% lower, RR 0.44, p = 0.31, treatment 2 of 34 (5.9%), control 7 of 52 (13.5%), NNT 13, LY-

	CoV555 7000mg.
	risk of hospitalization/ER, 91.8% lower, RR 0.08, p = 0.04, treatment 0 of 31 (0.0%), control 7 of 52 (13.5%), NNT 7.4, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), LY-CoV555/LY-CoV016.
Karr, 5/16/2021, retrospective, USA, peer-reviewed, 5 authors, study period 3 December, 2020 - 12 January, 2021.	risk of hospitalization, 40.0% lower, RR 0.60, p = 0.52, treatment 4 of 40 (10.0%), control 1 of 6 (16.7%), NNT 15, day 30.
	risk of hospitalization/ER, 62.5% lower, RR 0.38, p = 0.22, treatment 5 of 40 (12.5%), control 2 of 6 (33.3%), NNT 4.8, day 30.
Kip, 4/4/2023, retrospective, USA, peer-reviewed, 16 authors, study period 8 December, 2020 - 31 August, 2022.	risk of death/hospitalization, 15.0% lower, RR 0.85, p = 0.54, treatment 20 of 349 (5.7%), control 47 of 695 (6.8%), NNT 97, bamlanivimab/etesevimab, alpha and delta variants, day 28.
	risk of death/hospitalization, 31.0% lower, RR 0.69, p = 0.17, treatment 17 of 221 (7.7%), control 49 of 442 (11.1%), NNT 29, bamlanivimab, pre-alpha and alpha variants, day 28.
Rubin, 11/3/2021, retrospective, USA, peer-reviewed, 7 authors, study period 9 December, 2020 - 25 February, 2021, average treatment delay 6.0 days, excluded in exclusion analyses: significant unadjusted confounding possible, conflicts of interest: research funding from the drug patent holder, consulting for the pharmaceutical industry.	risk of death, 44.2% lower, RR 0.56, p = 1.00, treatment 1 of 191 (0.5%), control 10 of 1,066 (0.9%), NNT 241.
	risk of hospitalization, 65.3% lower, RR 0.35, p = 0.04, treatment 16 of 191 (8.4%), control 121 of 1,065 (11.4%), odds ratio converted to relative risk, IPTW weighted logistic regression.
Webb, 6/23/2021, retrospective, USA, peer-reviewed, 14 authors.	risk of death, 79.7% lower, RR 0.20, p = 0.09, treatment 1 of 479 (0.2%), control 57 of 5,536 (1.0%), NNT 122.
	risk of hospitalization, 52.7% lower, RR 0.47, p < 0.001, treatment 22 of 479 (4.6%), control 538 of 5,536 (9.7%), NNT 20.
	risk of hospitalization/ER, 26.8% lower, RR 0.73, p < 0.001, treatment 65 of 479 (13.6%), control 1,018 of 5,536 (18.4%), NNT 21, odds ratio converted to relative risk, primary outcome.
Wilden, 3/31/2022, retrospective, USA, peer-reviewed, 9 authors, study period December 2020 - July 2021.	risk of hospitalization, 51.0% lower, OR 0.49, p = 0.06, adjusted per study, multivariable, RR approximated with OR.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

ACTIV-3/TICO LY-CoV555 study group, 12/22/2020, Randomized Controlled Trial, USA, peer-reviewed, 1 author, study period 5 August, 2020 - 13 October, 2020, average treatment delay 7.0 days, trial NCT04501978 (history) (ACTIV-3).	risk of death, 100% higher, HR 2.00, $p = 0.22$, treatment 9 of 163 (5.5%), control 5 of 151 (3.3%), adjusted per study, proportional hazards regression.
Bariola, 3/30/2021, retrospective, USA, preprint, 22 authors.	risk of death, 66.8% lower, RR 0.33, $p = 0.05$, treatment 4 of 234 (1.7%), control 12 of 234 (5.1%), NNT 29, odds ratio converted to relative risk.
	risk of death/hospitalization, 64.3% lower, RR 0.36, $p < 0.001$, treatment 16 of 234 (6.8%), control 45 of 234 (19.2%), NNT 8.1, odds ratio converted to relative risk, primary outcome.
	risk of hospitalization, 60.7% lower, RR 0.39, $p = 0.001$, treatment 15 of 234 (6.4%), control 39 of 234 (16.7%), NNT 9.8, odds ratio converted to relative risk.
Chew, 8/22/2022, Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 26 authors, study period 19 August, 2020 - 15 November, 2020, average treatment delay 6.0 days, trial NCT04427501 (history) (ACTIV-2/A5401).	risk of hospitalization, 25.5% lower, RR 0.75, $p = 0.60$, treatment 6 of 159 (3.8%), control 8 of 158 (5.1%), NNT 78, combined.
	risk of hospitalization, 52.1% lower, RR 0.48, $p = 0.43$, treatment 2 of 48 (4.2%), control 4 of 46 (8.7%), NNT 22, 7000mg, day 28.
	risk of hospitalization, 0.9% higher, RR 1.01, $p = 1.00$, treatment 4 of 111 (3.6%), control 4 of 112 (3.6%), 700mg, day 28.
	relative time to symptom improvement, 13.5% higher, relative time 1.14, $p = 0.97$, treatment 48, control 46, 7000mg, primary outcome.
	relative time to symptom improvement, 17.1% higher, relative time 1.17, $p = 0.08$, treatment 111, control 112, 700mg, primary outcome.
	risk of progression, 0.6% higher, RR 1.01, $p = 1.00$, treatment 42 of 48 (87.5%), control 40 of 46 (87.0%), at least one symptom more severe than baseline, 7000mg.
	risk of progression, 2.0% lower, RR 0.98, $p = 0.62$, treatment 102 of 111 (91.9%), control 105 of 112 (93.8%), NNT 54, at least one symptom more severe than baseline, 700mg.
	viral load, 25.6% lower, relative load 0.74, $p = 0.002$, treatment 48, control 46, 7000mg, day 3.
	viral load, 35.3% lower, relative load 0.65, $p = 0.07$, treatment 111, control 112, 700mg, day 3.
Ganesh, 10/1/2021, retrospective, USA, peer-reviewed, median age 63.0, 20 authors.	risk of death, 74.4% lower, RR 0.26, $p = 0.11$, treatment 2 of 1,789 (0.1%), control 8 of 1,832 (0.4%), NNT 308, day 28.
	risk of ICU admission, 48.8% lower, RR 0.51, $p = 0.10$, treatment 10 of 1,789 (0.6%), control 20 of 1,832 (1.1%), NNT 188, day 28.

	risk of hospitalization, 37.4% lower, RR 0.63, p = 0.01, treatment 44 of 1,789 (2.5%), control 72 of 1,832 (3.9%), NNT 68, day 28, primary outcome.
Priest, 1/27/2022, retrospective, propensity score matching, USA, peer-reviewed, 5 authors, study period October 2020 - March 2021, average treatment delay 6.0 days.	risk of death, no change, RR 1.00, p = 1.00, treatment 6 of 379 (1.6%), control 6 of 379 (1.6%).
	risk of hospitalization, 3.9% higher, RR 1.04, p = 0.86, treatment 79 of 379 (20.8%), control 76 of 379 (20.1%), all-cause hospital revisit.
	risk of hospitalization/ER, 5.0% higher, OR 1.05, p = 0.86, treatment 379, control 379, RR approximated with OR.

Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Lilly, 1/21/2021, Randomized Controlled Trial, USA, preprint, 1 author.	risk of symptomatic case, 57.0% lower, RR 0.43, p < 0.001, treatment 483, control 482, group sizes estimated because they were not supplied.
	risk of symptomatic case, 80.0% lower, RR 0.20, p < 0.001, treatment 150, control 149, nursing home residents, group sizes estimated because they were not supplied.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

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