Antiandrogens for COVID-19: real-time meta analysis of 50 studies

@CovidAnalysis, March 2024, Version 47
https://c19early.org/aameta.html

Abstract

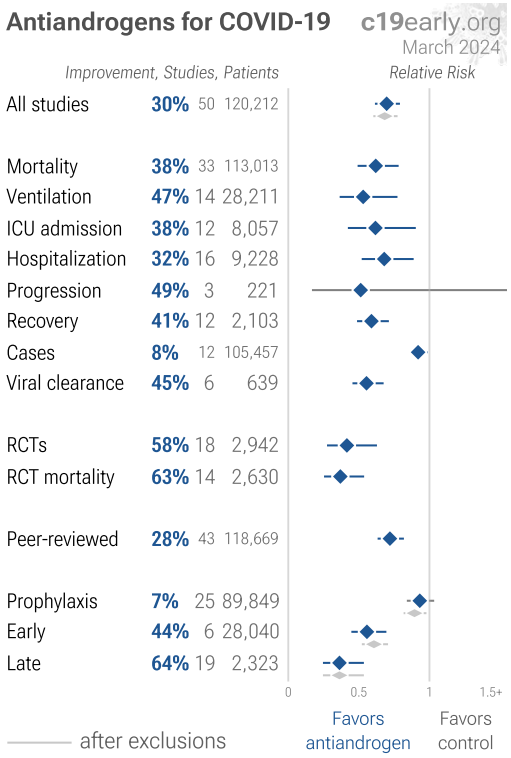
Statistically significant lower risk is seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. 30 studies from 24 independent teams in 12 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 30% [21-39%] lower risk. Results are similar for higher quality and peer-reviewed studies and better for Randomized Controlled Trials.

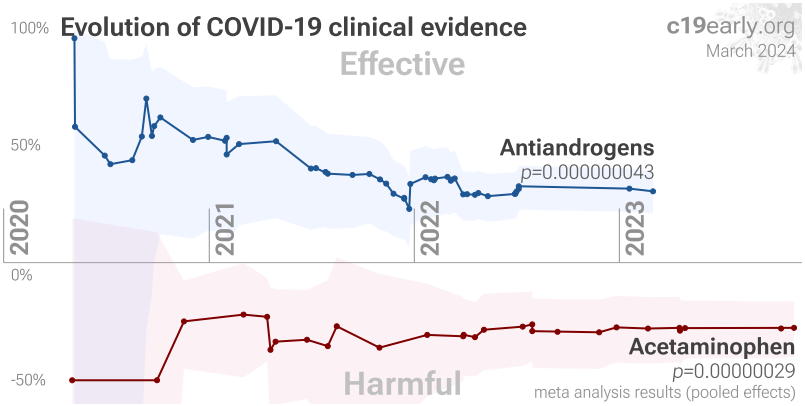
Results are robust — in exclusion sensitivity analysis 24 of 50 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

This analysis combines the results of several different antiandrogens. Results for individual treatments may vary.

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. Other meta analyses show significant improvements with antiandrogens for mortality *Cheema, Kotani*, hospitalization *Cheema*, recovery *Cheema*, and progression *Kotani*.



HIGHLIGHTS

Antiandrogens reduce risk for COVID-19 with very high confidence for mortality, ventilation, hospitalization, recovery, viral clearance, and in pooled analysis, high confidence for ICU admission and cases, and very low confidence for progression. Combined results of several different antiandrogens.

Antiandrogens were the 5th treatment shown effective with ≥3 clinical studies in August 2020, now known with p = 0.000000043 from 50 studies.

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.

50 antiandrogen COVID-19 studies

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March 2024

	Improvement, RR [CI]			Treatment	Control
Cadegiani	77%	0.23 [0.08-0.66]	recov. time	8 (n)	262 (n)
McCoy (DB RCT)	80%	0.20 [0.01-4.13]	death	0/134	2/134
Cadegiani (DB RCT)	62%	0.38 [0.18-0.82]	no recov.	7/44	18/43
Cadegiani (DB RCT)	63%	0.37 [0.02-8.85]	death	0/75	1/102
Kintor (DB RCT)	67%	0.33 [0.01-8.16]	death	0/365	1/365
Hunt	39%	0.61 [0.51-0.73]	death	167/1,788	1,445/24,720
Early treatment	44%	0.56 [0.45-0.69]		174/2,414	1,467/25,626

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Goren	81%	0.19 [0.03-1.28]	ICU	1/12	17/36
Mareev (RCT)	11%	0.89 [0.65-1.22]	no recov.	33 (n)	33 (n)
Zarehoseinz.. (RCT)	75%	0.25 [0.03-2.14]	death	1/40	4/40
Ghandehari (RCT)	-22%	1.22 [0.08-18.2]	death	1/18	1/22
Ersoy (ICU)	46%	0.54 [0.36-0.81]	death	14/30	26/30
Welén (RCT)	80%	0.20 [0.01-4.65]	death	0/29	1/10
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Davarpanah	78%	0.22 [0.08-0.55]	hosp.	6/103	23/103
Kotfis (RCT)	17%	0.83 [0.25-2.74]	death	4/24	5/25
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Prophylaxis	7%	0.93 [0.84-1.03]		693/22,309	1,777/67,540

$Tau^2 = 0.02$, $I^2 = 69.4\%$, $p = 0.18$

All studies	30%	0.70 [0.61-0.79]		978/25,928	3,562/94,284

censored, see notes

44% lower risk

OT[1]

CT[2]

ICU patients

CT[2]

CT[2]

CT[2]

HITCH

64% lower risk

7% lower risk

30% lower risk

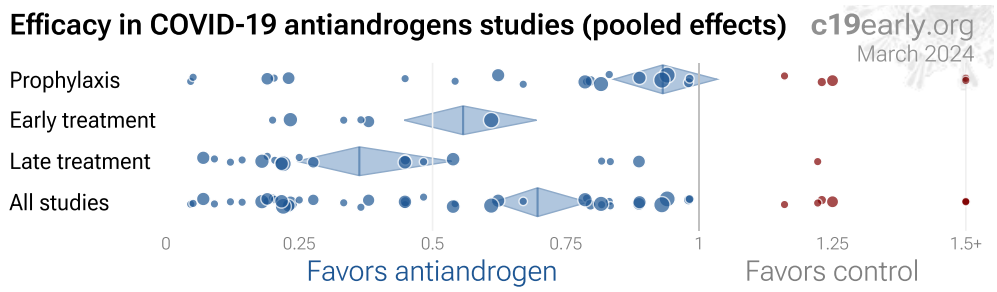
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+

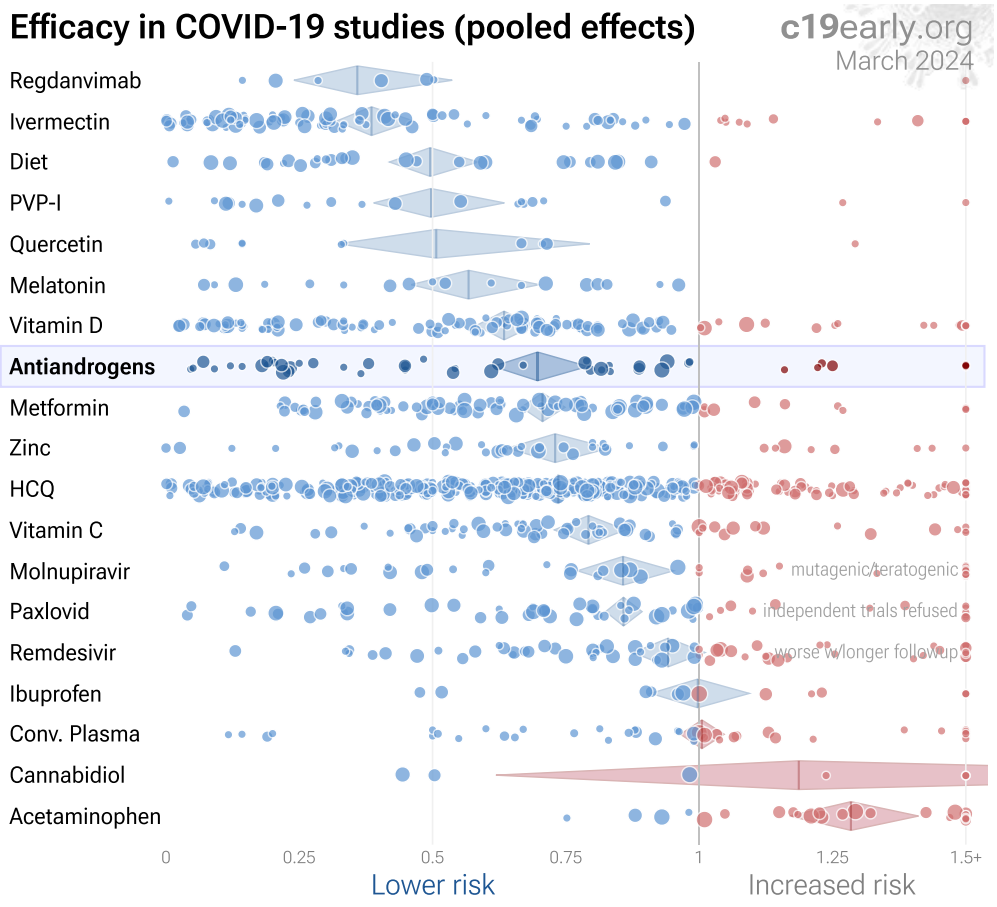
[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
$Tau^2 = 0.07$, $I^2 = 81.7\%$, $p < 0.0001$

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

Favors antiandrogen Favors control

A





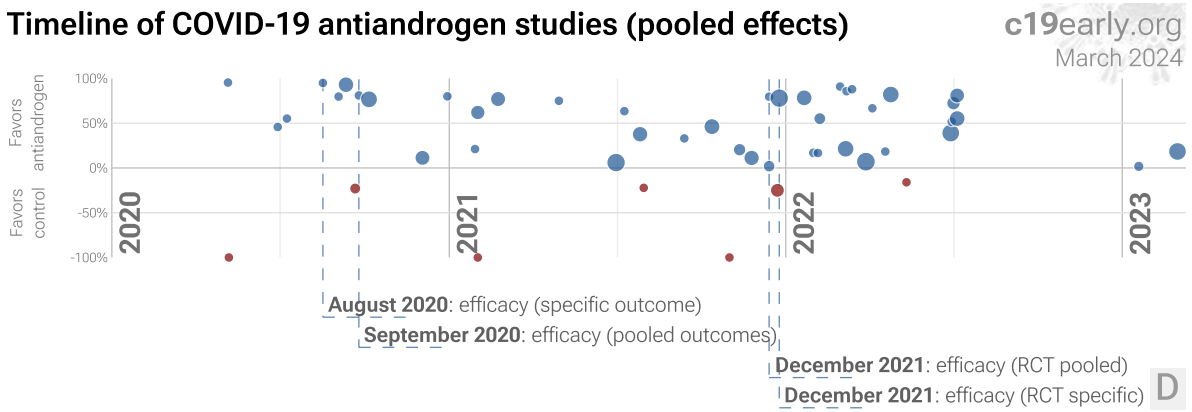


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. 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. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of**

results in antiandrogen studies. The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, pooled outcomes in RCTs, and one or more specific outcome in RCTs. Efficacy based on RCTs only was delayed by 15.9 months, compared to using all studies.

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 *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*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, 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 Antiandrogens 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.

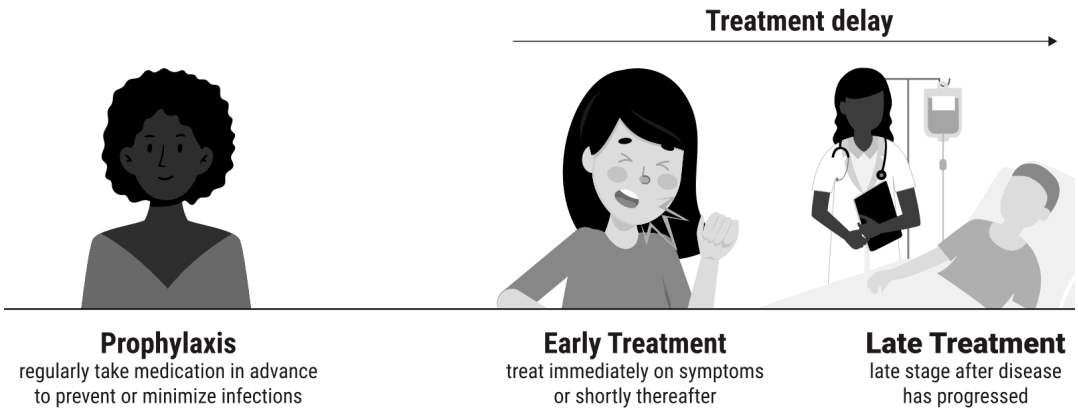


Figure 2. Treatment stages.

Preclinical Research

An *In Silico* study supports the efficacy of antiandrogens *Saih*.

An *In Vitro* study supports the efficacy of antiandrogens *Majidipur*.

An *In Vivo* animal study supports the efficacy of antiandrogens *Leach*.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 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, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	30% [21-39%] ****	50	120,212	537
After exclusions	32% [23-40%] ****	46	118,801	515
Peer-reviewed studies	28% [18-37%] ****	43	118,669	483
Randomized Controlled Trials	58% [37-73%] ****	18	2,942	220
Mortality	38% [22-51%] ****	33	113,013	370
Ventilation	47% [23-64%] **	14	28,211	174
ICU admission	38% [10-58%] *	12	8,057	108
Hospitalization	32% [11-48%] **	16	9,228	222
Recovery	41% [29-51%] ****	12	2,103	134
Cases	8% [1-14%] *	12	105,457	100
Viral	45% [32-55%] ****	6	639	53
RCT mortality	63% [46-75%] ****	14	2,630	161
RCT hospitalization	32% [3-53%] *	8	2,304	131

Table 1. **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	**44%** [31-55%] ****	**64%** [46-75%] ****	**7%** [-3-16%]
After exclusions	**39%** [29-48%] ****	**64%** [46-75%] ****	**11%** [2-18%] *
Peer-reviewed studies	**40%** [31-49%] ****	**61%** [40-75%] ****	**8%** [-2-17%]
Randomized Controlled Trials	**64%** [26-82%] **	**58%** [32-74%] ***	
Mortality	**39%** [29-48%] ****	**63%** [45-76%] ****	**7%** [-12-22%]
Ventilation	**95%** [60-99%] **	**44%** [23-59%] ***	**46%** [-12-74%]
ICU admission		**42%** [24-55%] ****	**31%** [-88-75%]
Hospitalization	**81%** [46-93%] **	**21%** [-10-43%]	**21%** [-23-50%]
Recovery	**68%** [41-83%] ***	**38%** [25-49%] ****	
Cases			**8%** [1-14%] *
Viral	**58%** [2-82%] *	**42%** [34-49%] ****	
RCT mortality	**71%** [-75-95%]	**62%** [41-75%] ****	
RCT hospitalization	**81%** [46-93%] **	**10%** [-20-33%]	

Table 2. **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. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

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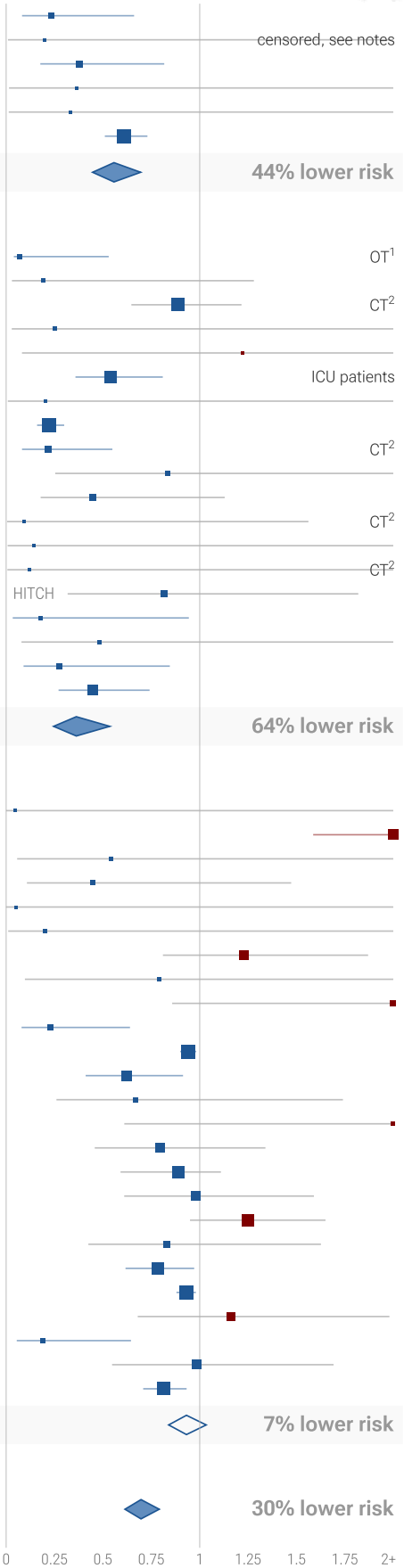

[1] OT: comparison with other treatment
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Effect extraction pre-specified
(most serious outcome, see appendix)

Figure 3. **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 of effect extraction see the appendix.

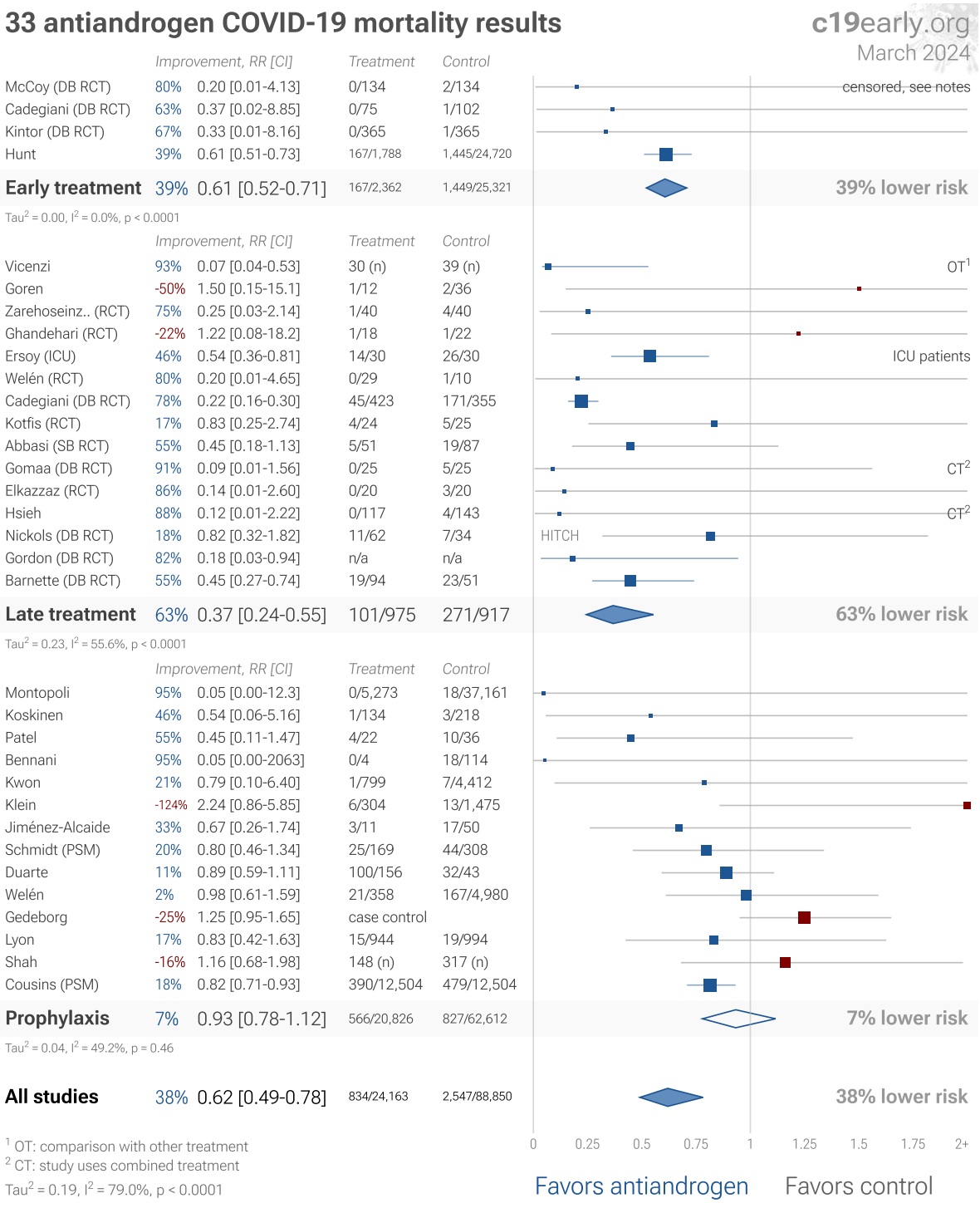


Figure 4. **Random effects meta-analysis for mortality results.**

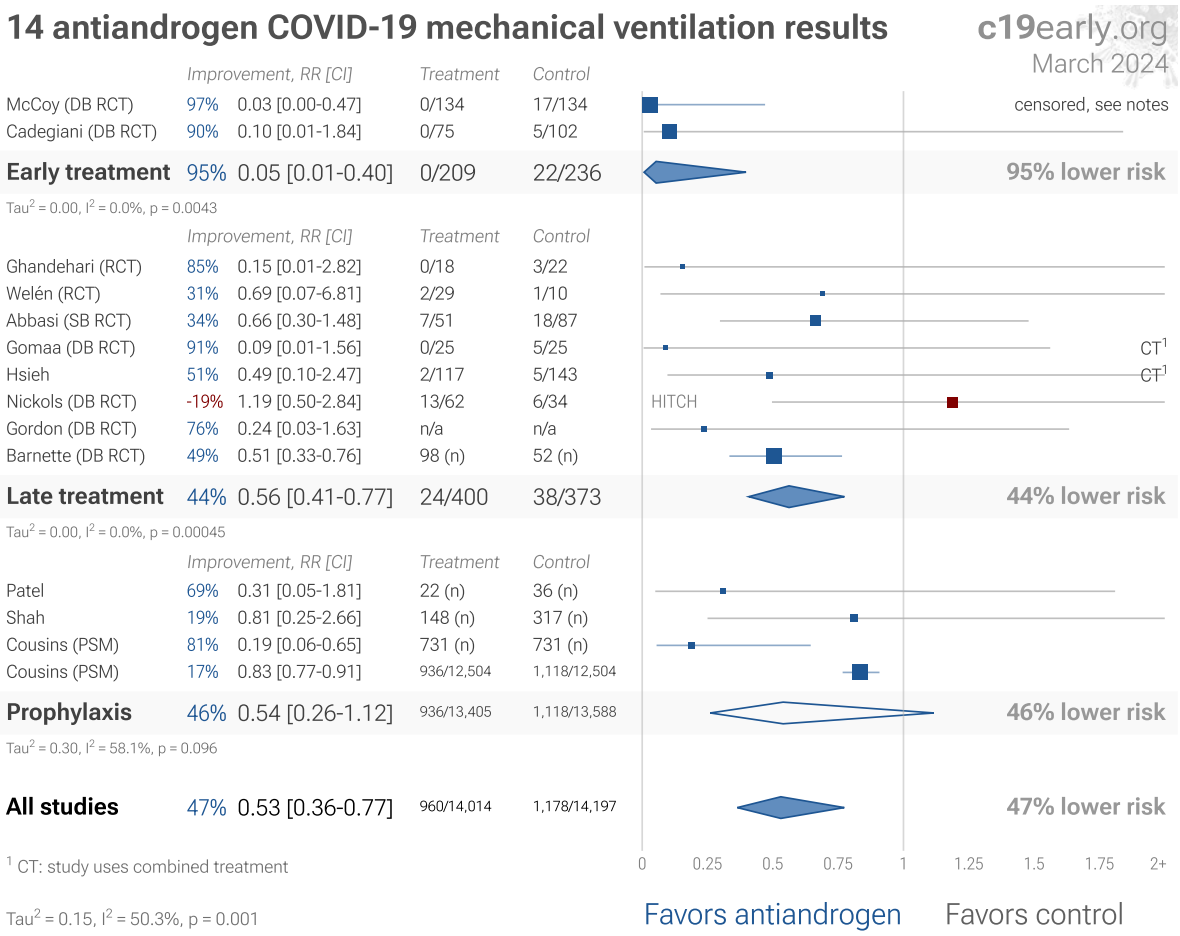


Figure 5. Random effects meta-analysis for ventilation.

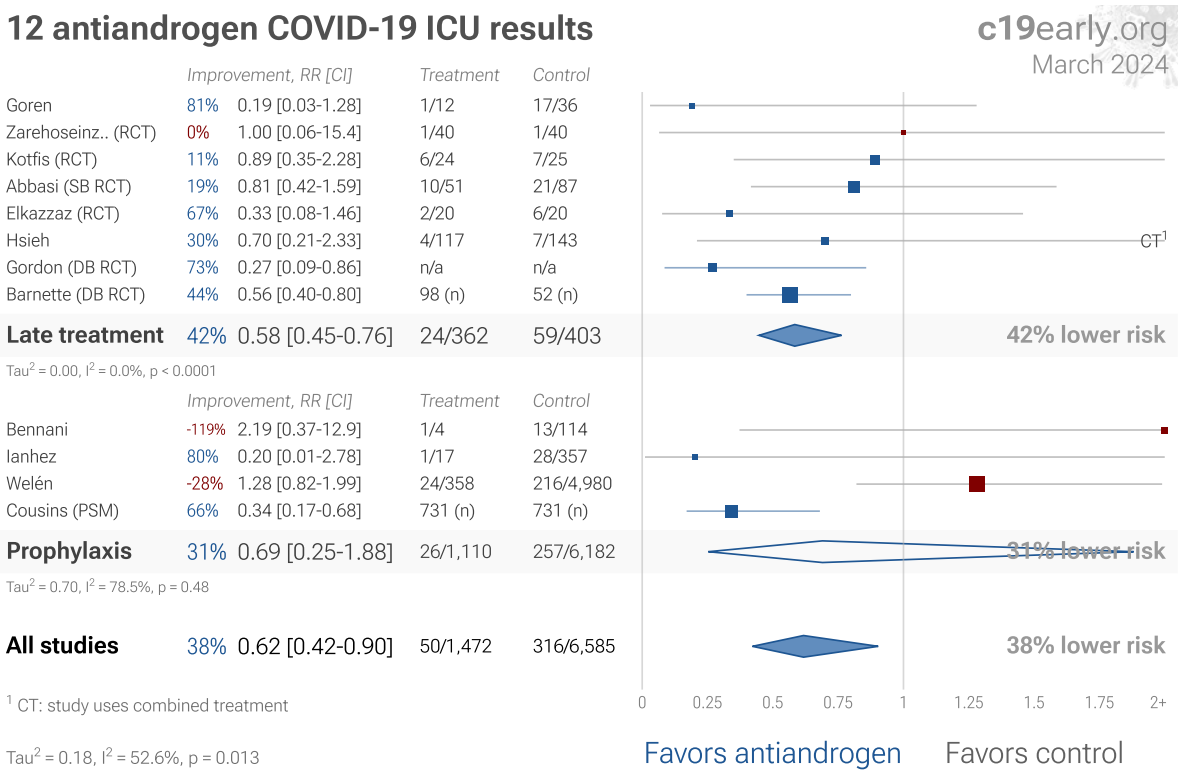


Figure 6. Random effects meta-analysis for ICU admission.

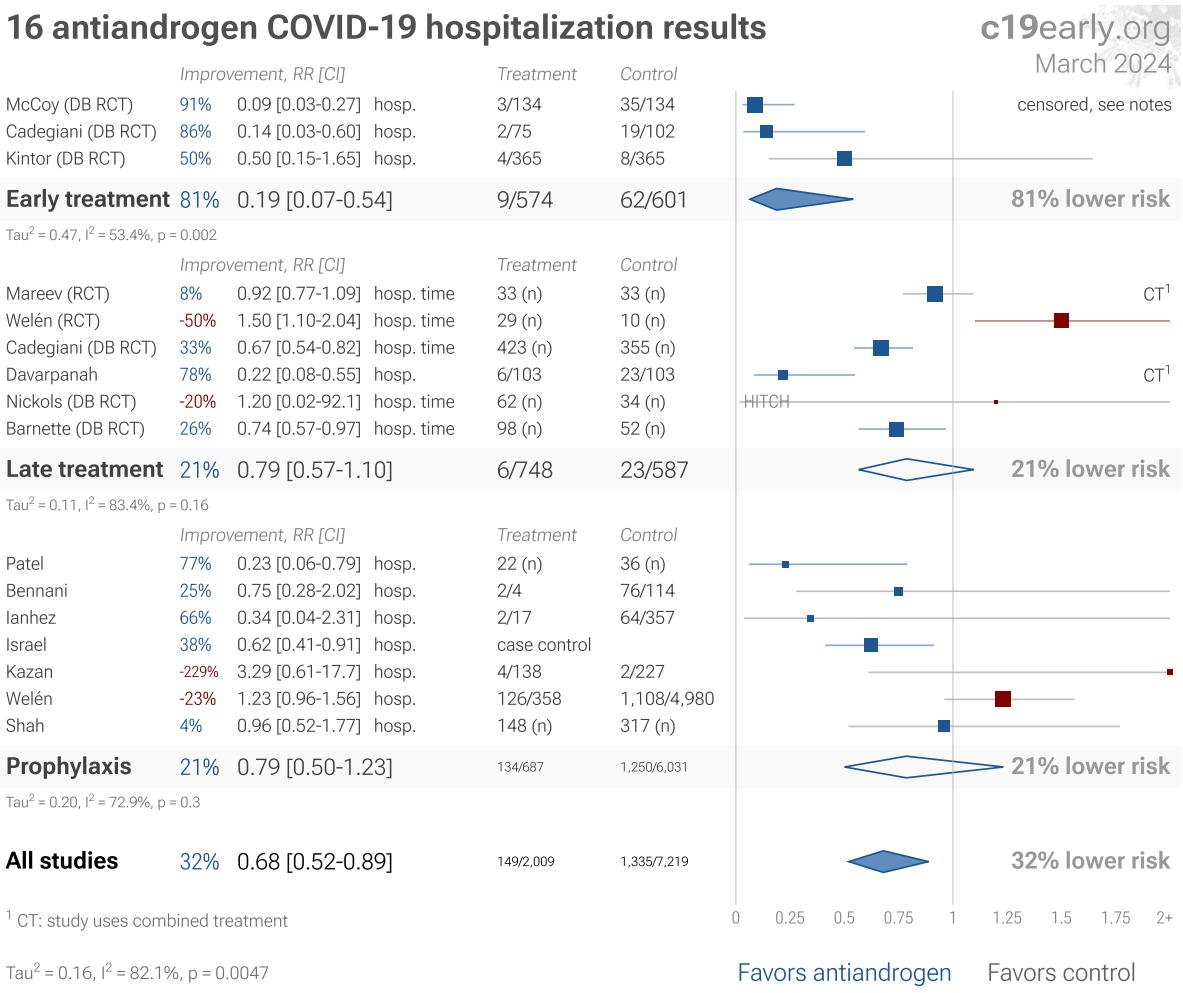


Figure 7. Random effects meta-analysis for hospitalization.

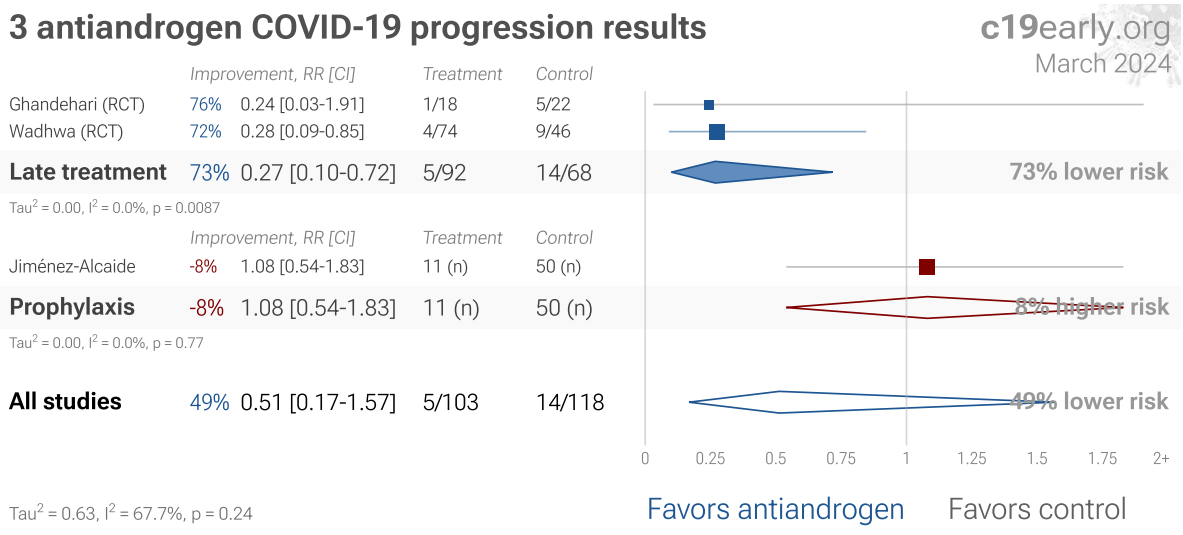


Figure 8. Random effects meta-analysis for progression.

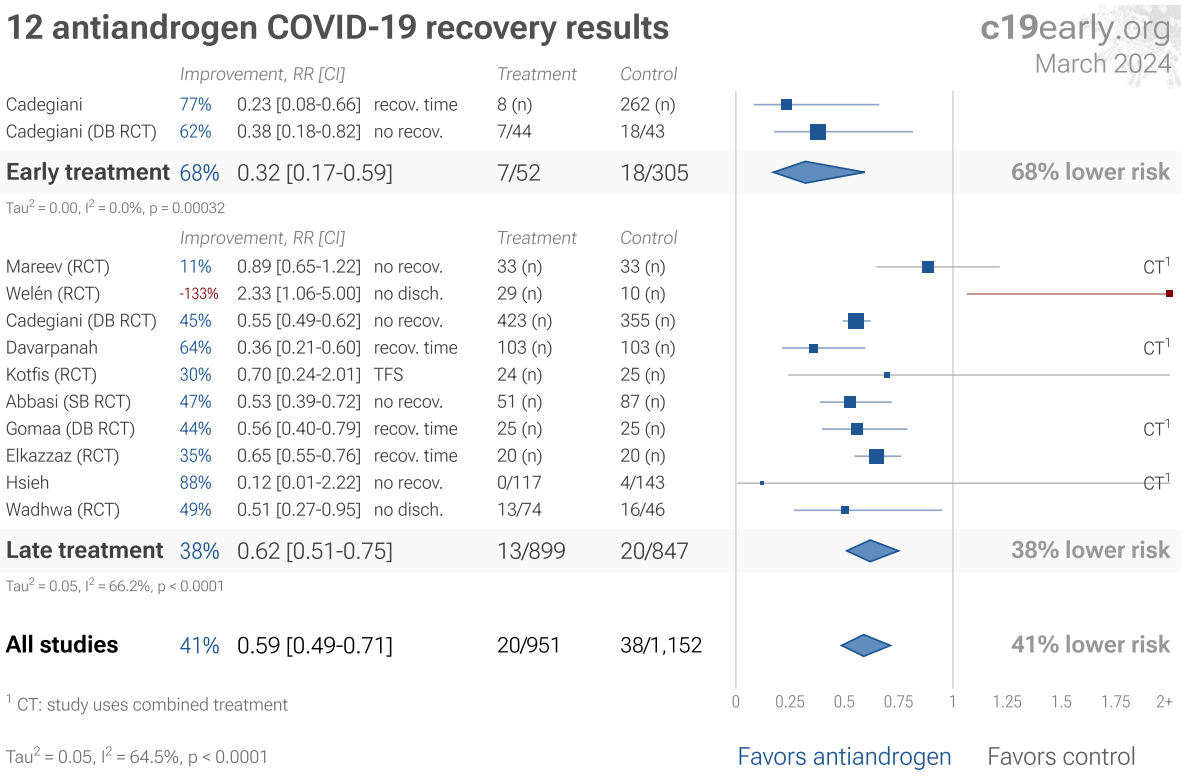


Figure 9. Random effects meta-analysis for recovery.

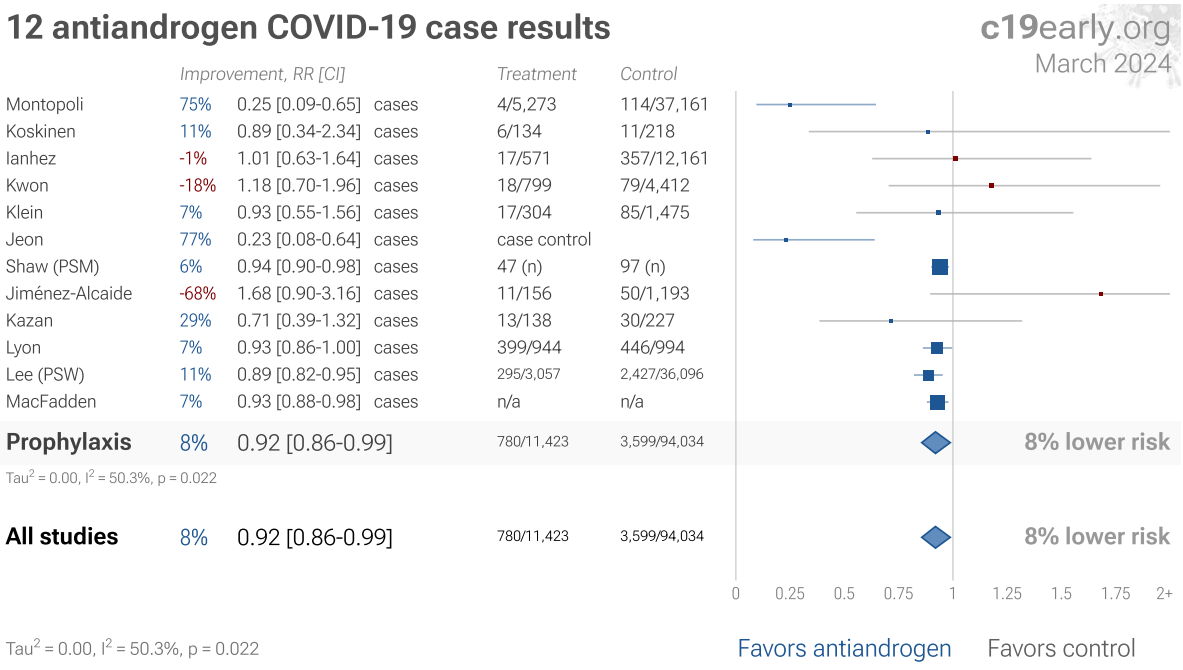


Figure 10. Random effects meta-analysis for cases.

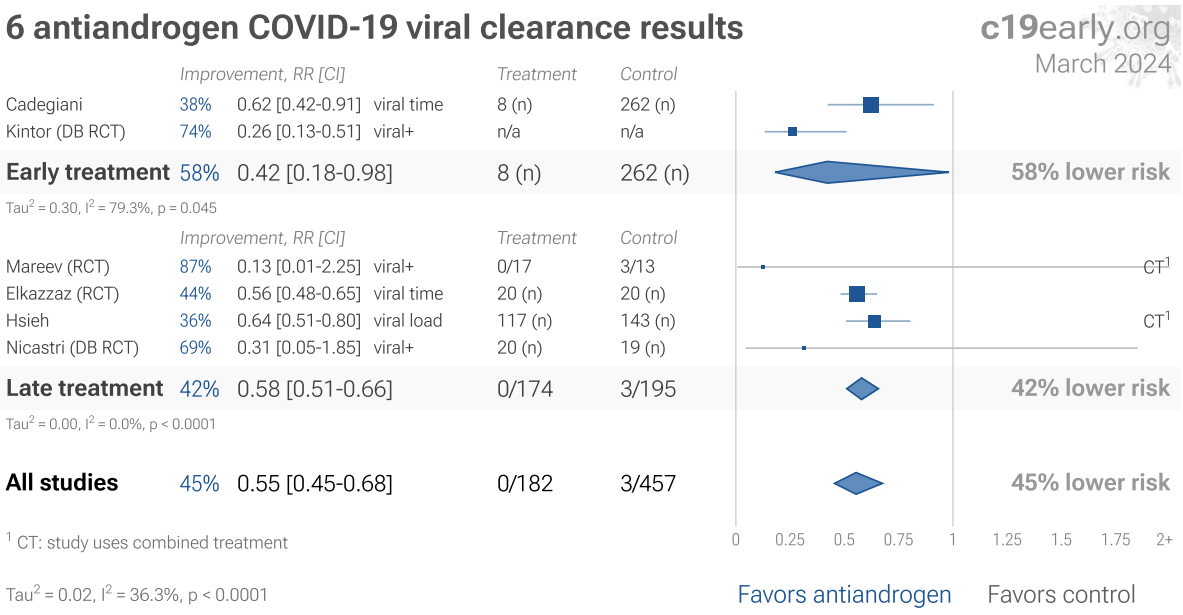


Figure 11. Random effects meta-analysis for viral clearance.

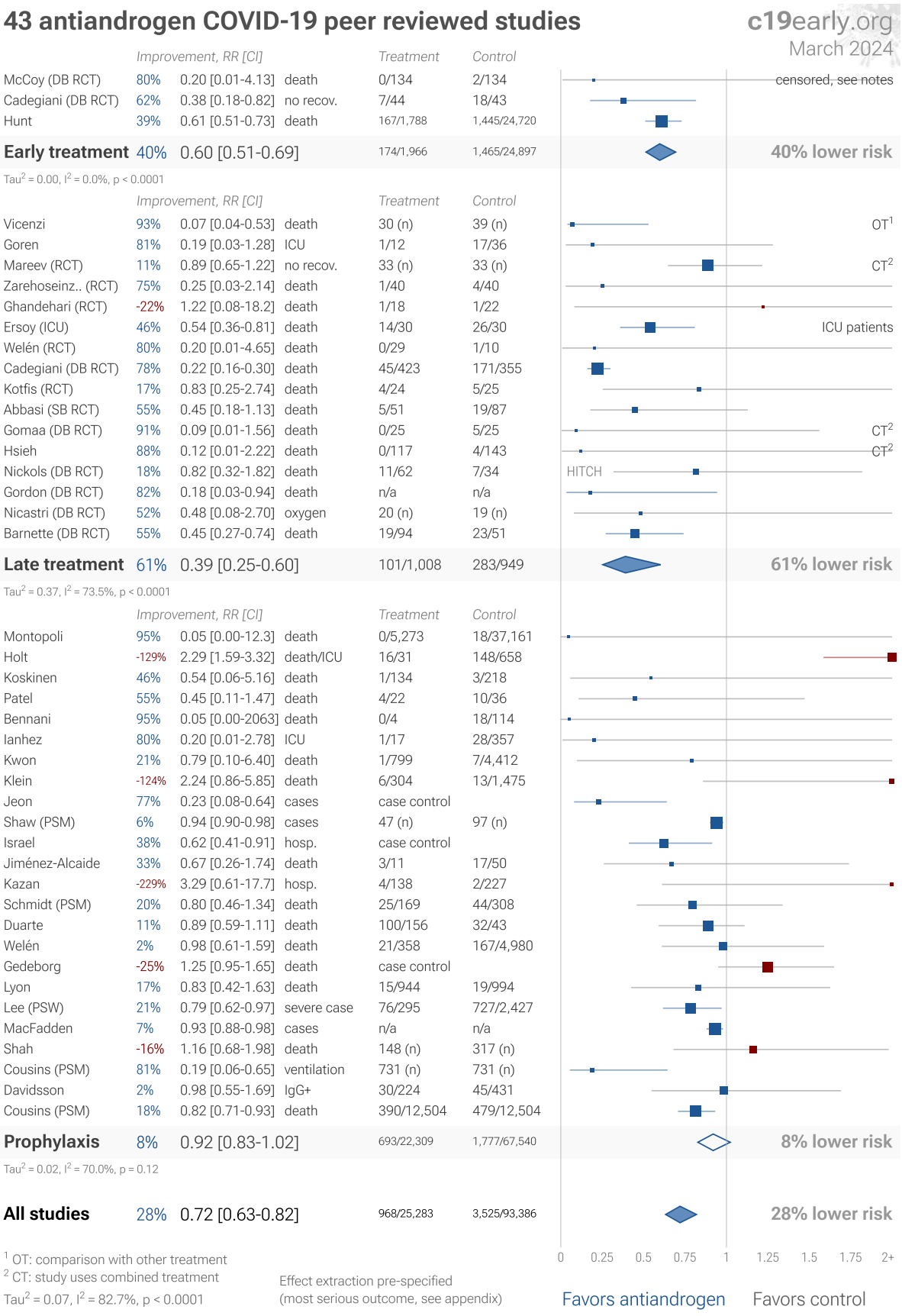


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with 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. The median effect size for RCTs is 65% improvement, compared to 27% for other studies. Figure 14, 15, and 16 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

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, 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 could 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 5.7+ months faster for COVID-19. 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.

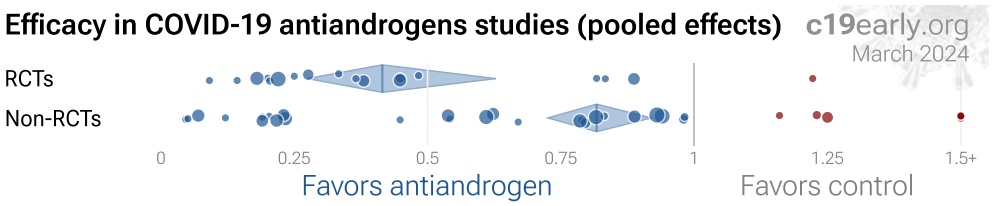


Figure 13. **Results for RCTs and non-RCT studies.**

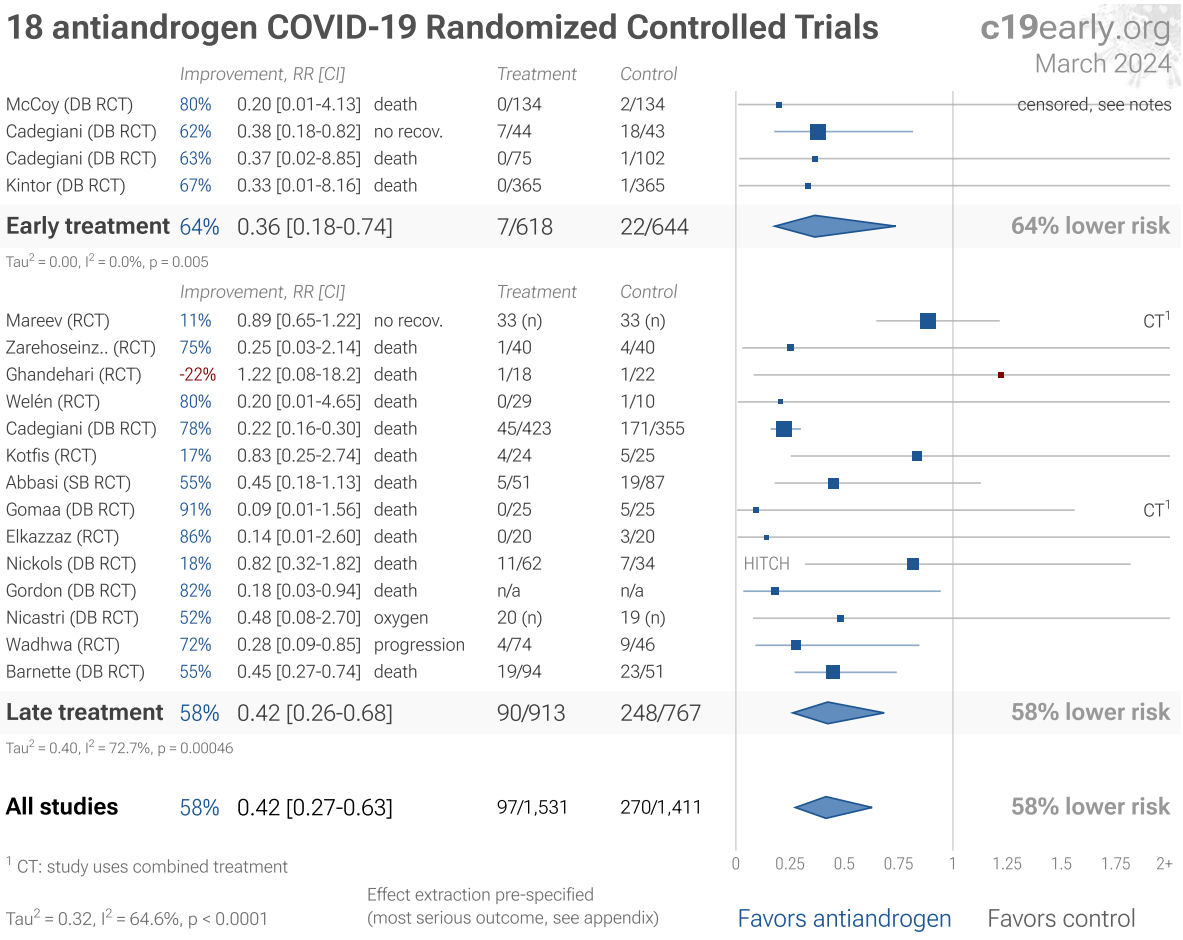


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

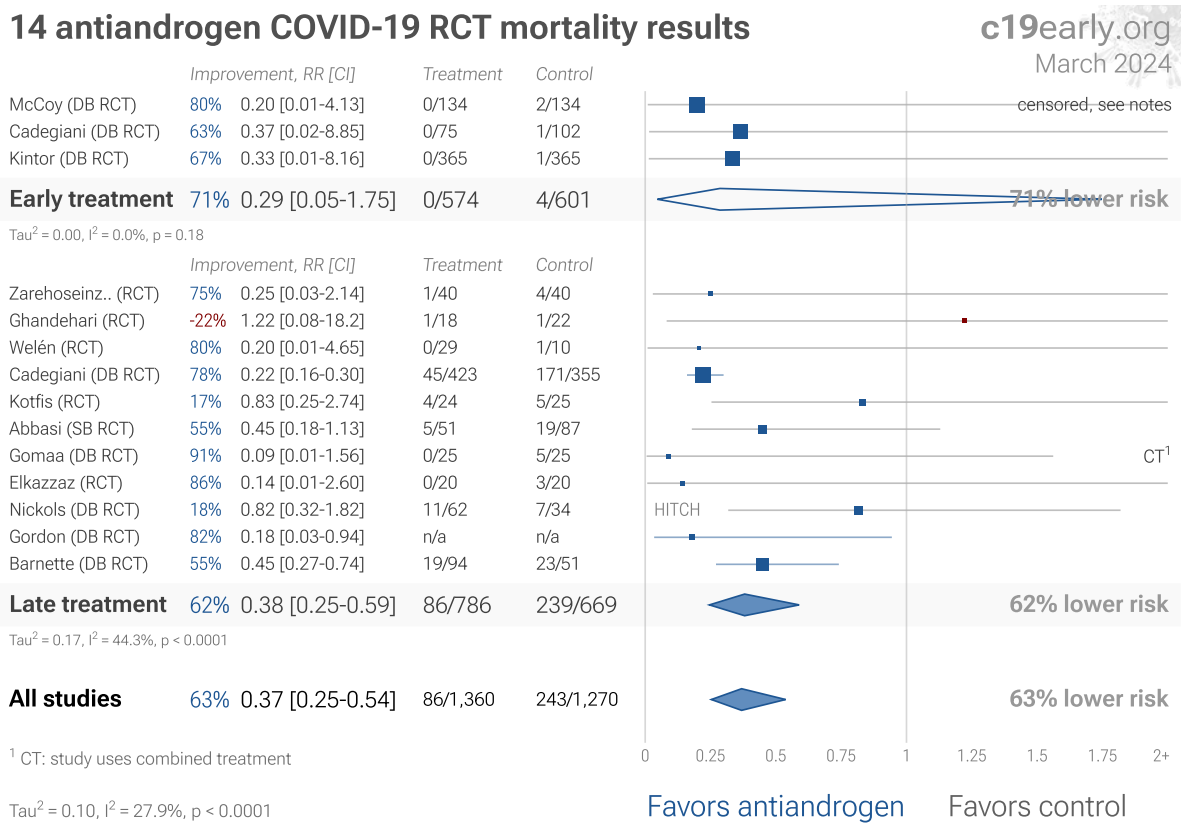


Figure 15. Random effects meta-analysis for RCT mortality results.

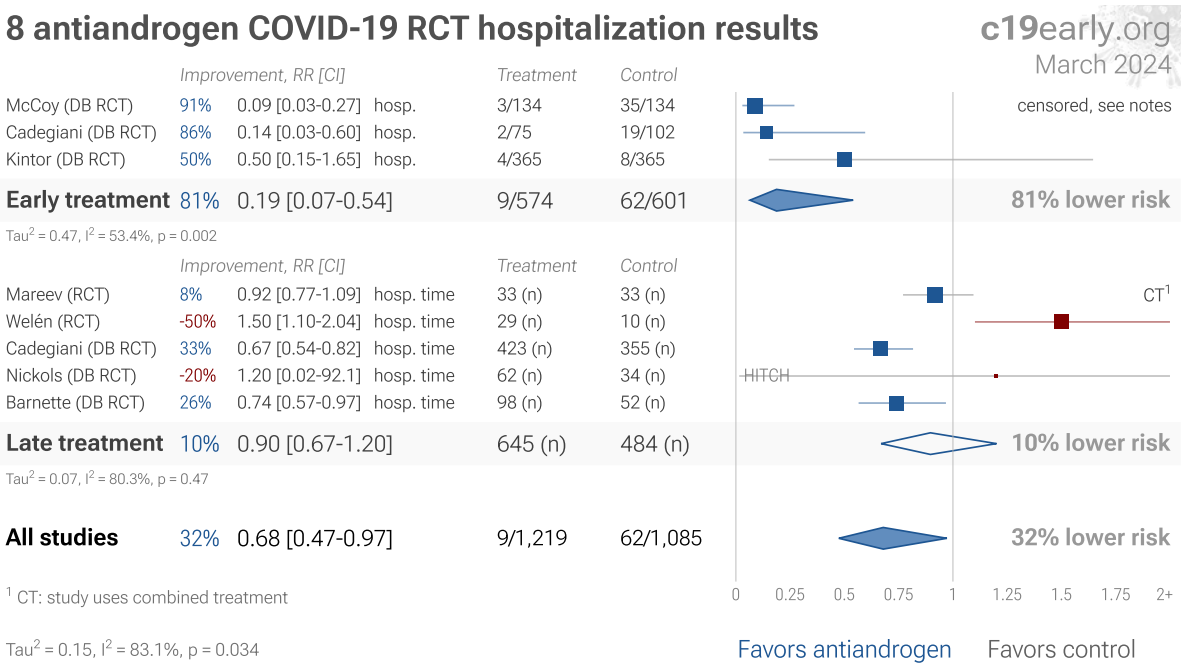


Figure 16. Random effects meta-analysis for RCT hospitalization results.

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 may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 17 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Cadegiani, potential randomization failure.

Cadegiani (B), significant unadjusted differences between groups.

Holt, unadjusted results with no group details.

Jiménez-Alcaide, excessive unadjusted differences between groups. Excluded results: case.

Kazan, excessive unadjusted differences between groups.

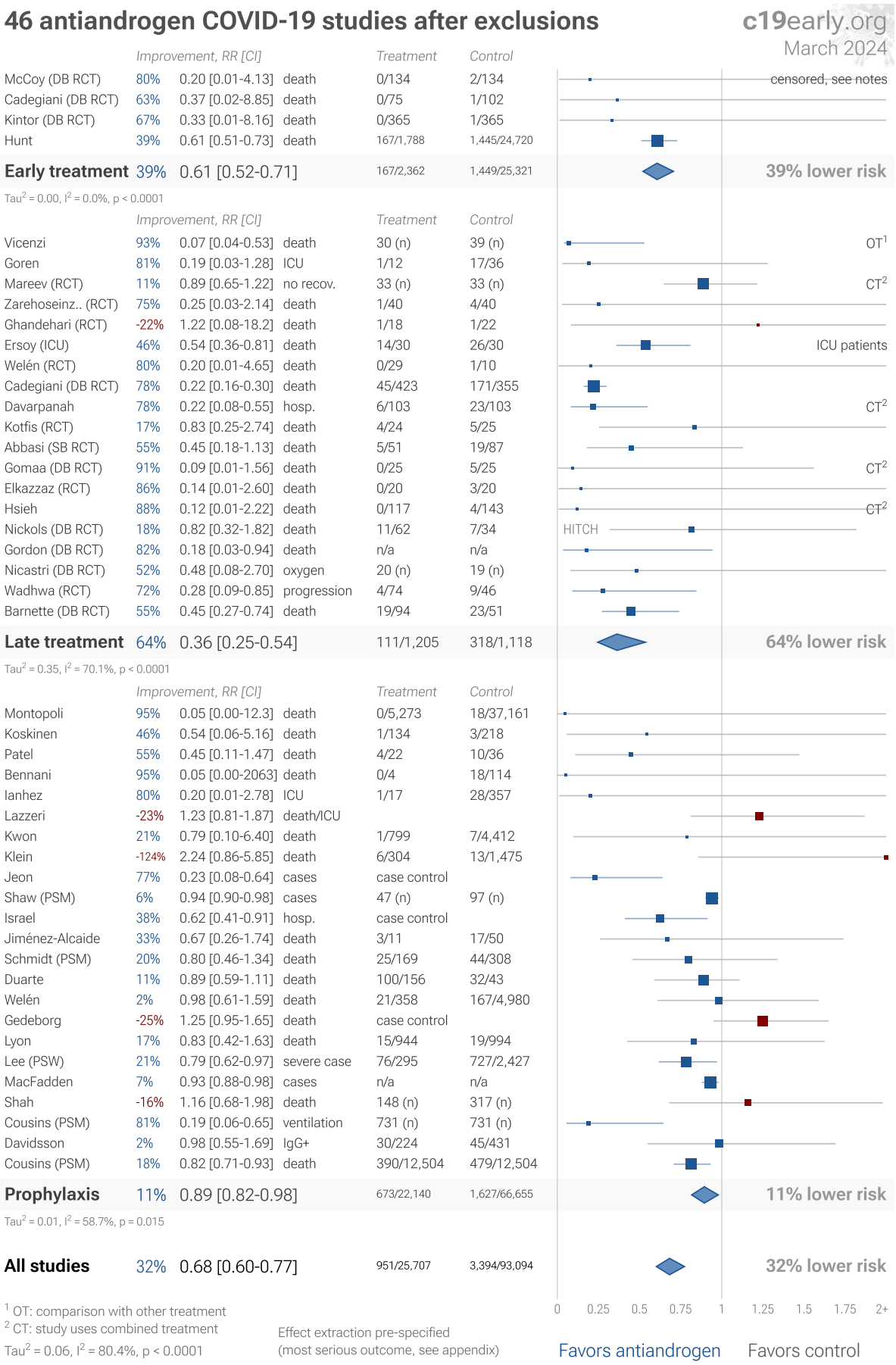


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction 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* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* 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* 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 3. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 18 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.

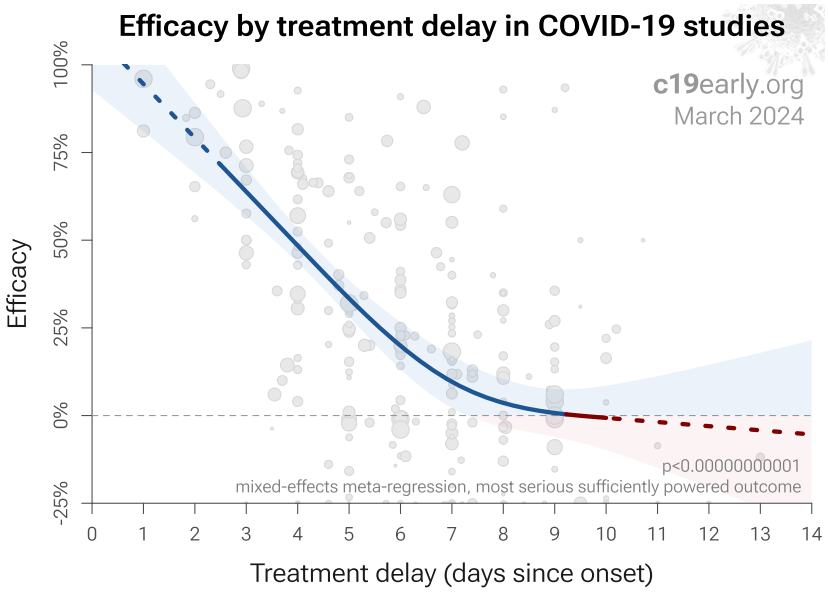


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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*).

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. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of 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 anything from supplements, other medications, or other kinds of treatment such as prone positioning.

Medication quality. The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu* 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 19. 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 faster. 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. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 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.

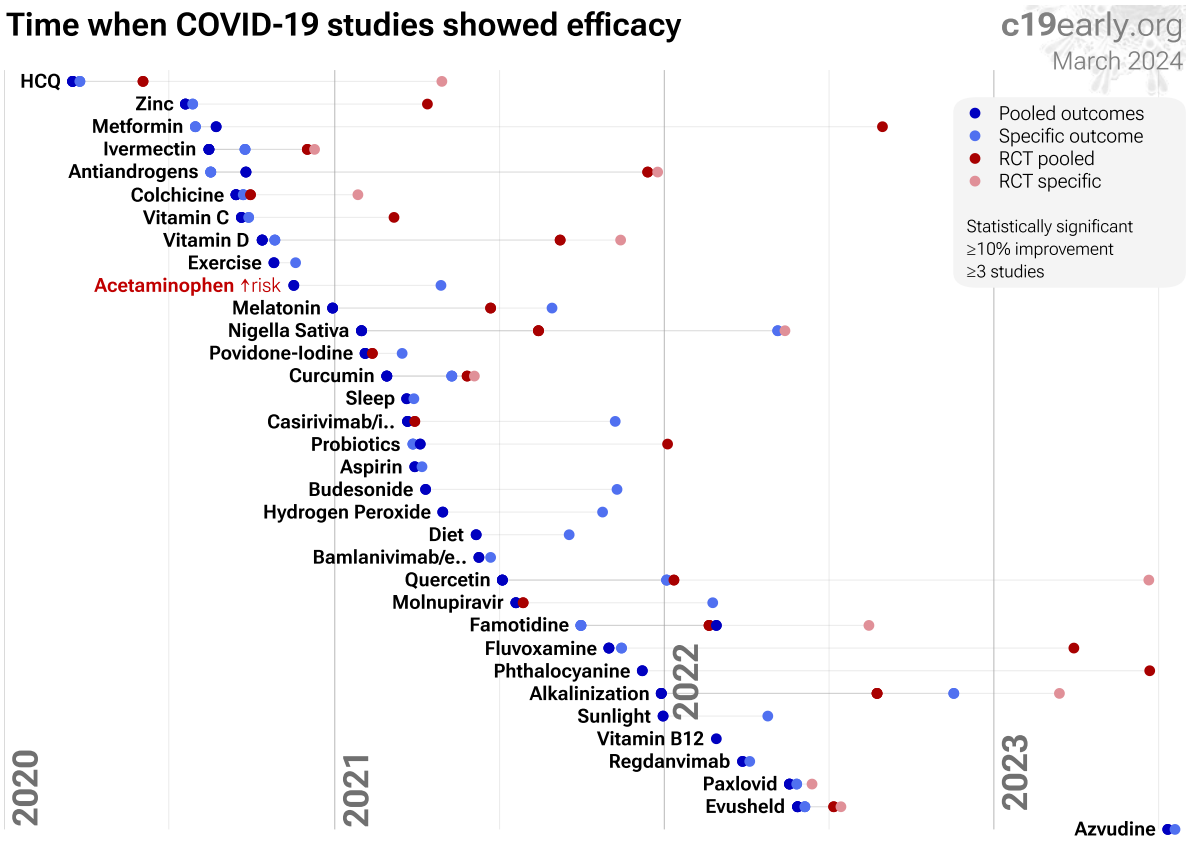


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso*.

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 20 shows a scatter plot of results for prospective and retrospective studies. 46% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 77% of prospective studies, consistent with a bias toward publishing negative results. The median effect size for retrospective studies is 21% improvement, compared to 74% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

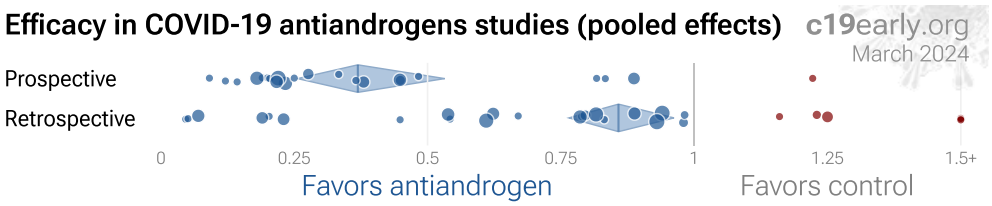


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 21 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.

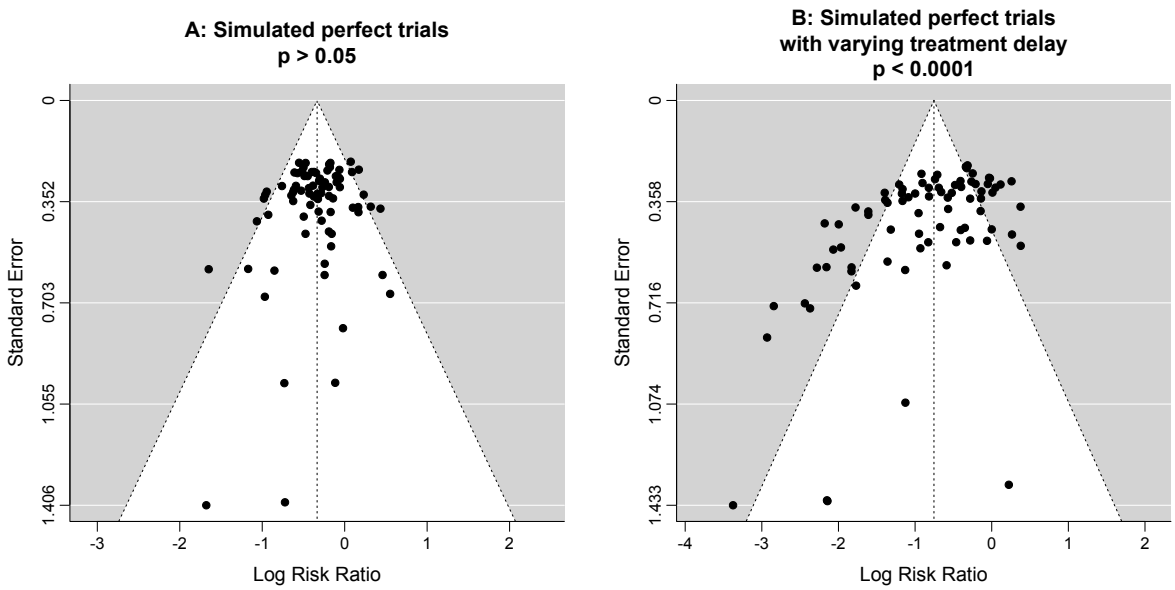


Figure 21. Example funnel plot analysis for simulated perfect trials.

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 the 50 studies compare against other treatments, which may reduce the effect seen. 4 of 50 studies combine treatments. The results of antiandrogens alone may differ. 2 of 18 RCTs use combined treatment. Other meta analyses show significant improvements with antiandrogens for mortality *Cheema, Kotani*, hospitalization *Cheema*, recovery *Cheema*, and progression *Kotani*.

Reviews. *Mauvais-Jarvis et al.* present a review covering antiandrogen for COVID-19.

Conclusion

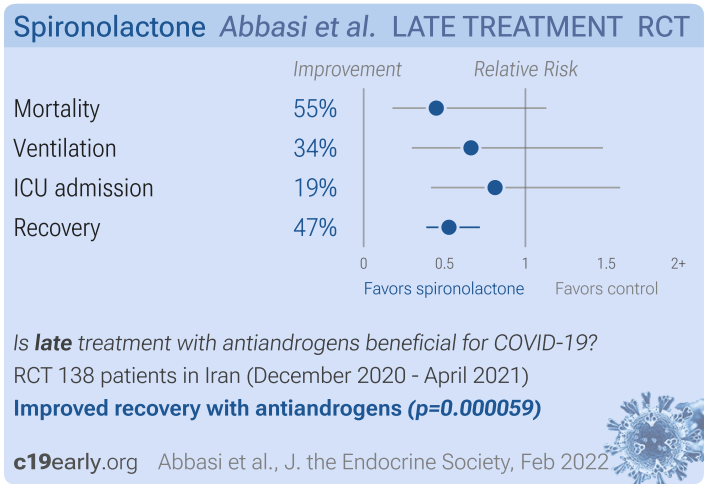
Antiandrogens are an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, ventilation, ICU admission, hospitalization, recovery, cases, and viral clearance. 30 studies from 24 independent teams in 12 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 30% [21-39%] lower risk. Results are similar for higher quality and peer-reviewed studies and better for Randomized Controlled Trials. Results are robust — in exclusion sensitivity analysis 24 of 50 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

This analysis combines the results of several different antiandrogens. Results for individual treatments may vary.

Other meta analyses show significant improvements with antiandrogens for mortality *Cheema, Kotani*, hospitalization *Cheema*, recovery *Cheema*, and progression *Kotani*.

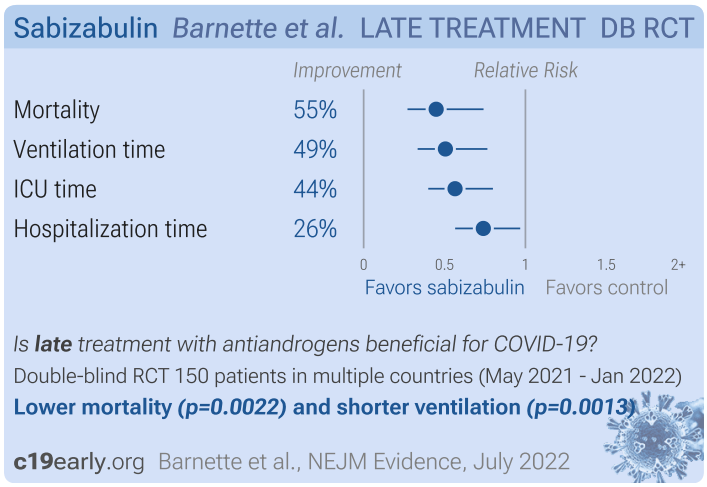
Study Notes

Abbasi



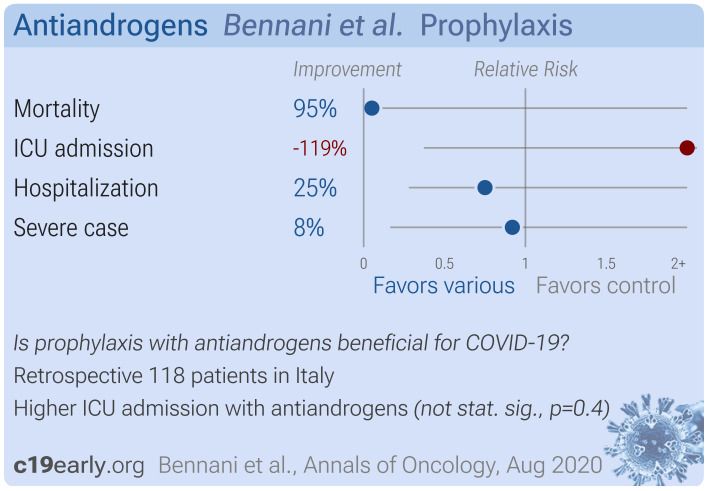
Abbasi: RCT including 51 spironolactone patients and 87 control patients in Iran, showing improved recovery with spironolactone, sitagliptin, and the combination of both.

Barnette



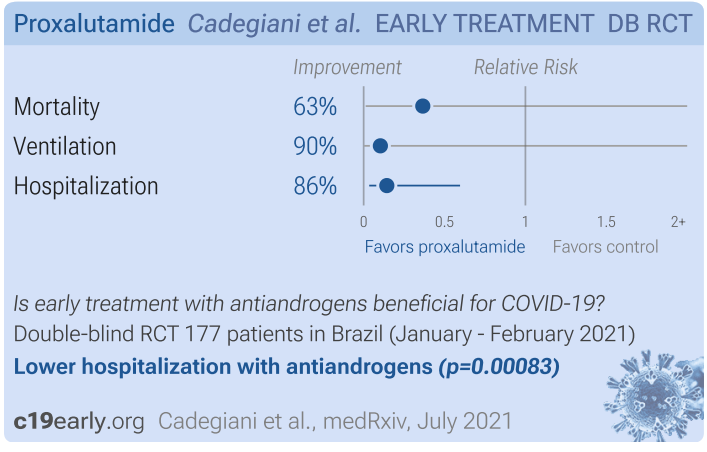
Barnette: RCT with 98 hospitalized moderate/severe patients treated with sabizabulin and 52 control patients, showing lower mortality with treatment. Sabizabulin 9mg for up to 21 days. For more discussion see *twitter.com, twitter.com (B), twitter.com (C)*.

Bennani



Bennani: Retrospective 118 prostate cancer patients, 4 on androgren deprivation therapy, not showing significant differences (as expected with only 4 patients in the treatment group).

Cadegiani



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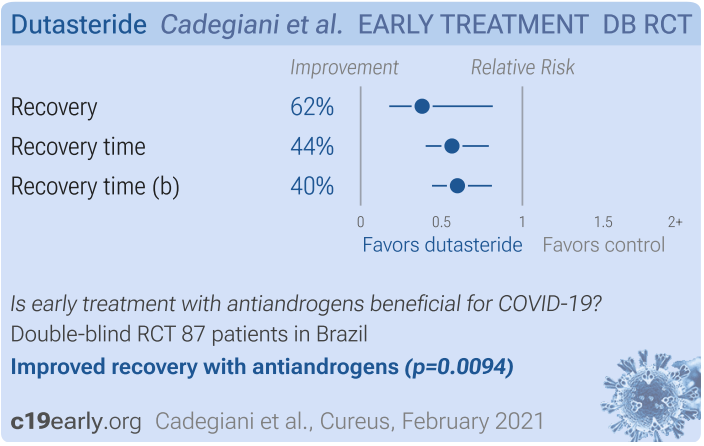
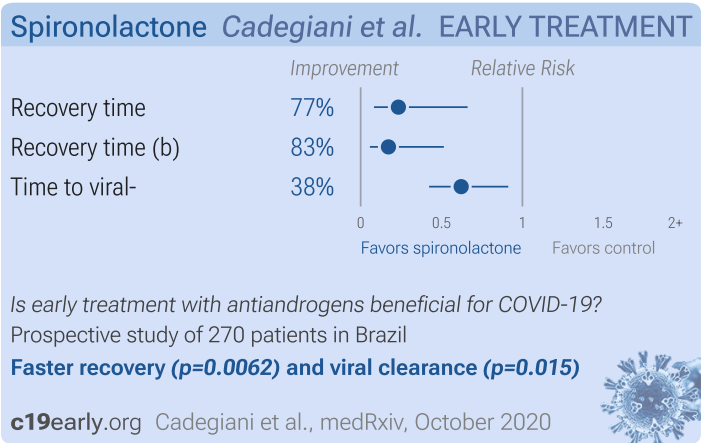
Cadegiani (C): RCT 177 women in Brazil, 75 treated with proxalutamide, showing significantly lower hospitalization with treatment.

Cadegiani



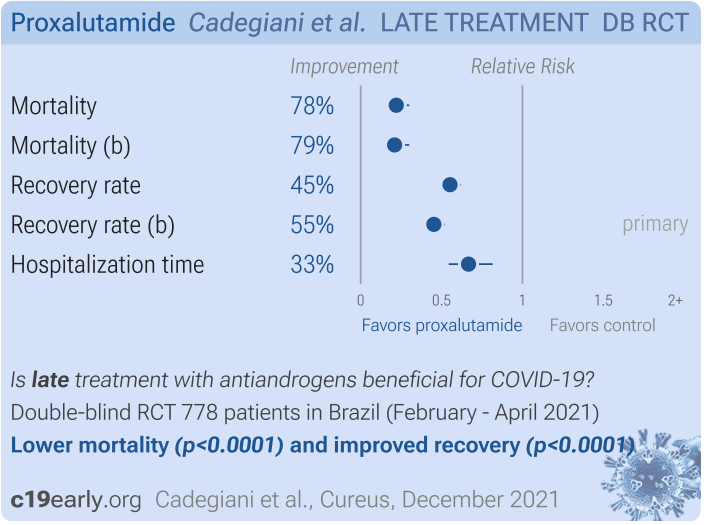
Cadegiani: RCT 130 outpatients in Brazil, 54 treated with dutasteride, showing faster recovery with treatment. All patients received nitazoxanide. There were no hospitalizations, mechanical ventilation, or deaths. Some percentages for viral clearance in Table 3 do not match the group sizes, and a third-party analysis suggests possible randomization failure. 34110420.2.0000.0008.

Cadegiani



Cadegiani (B): Prospective study of 270 female COVID-19 patients in Brazil, 75 with hyperandrogenism, of which 8 were on spironolactone. Results suggest that HA patients may be at increased risk, and that spironolactone use may reduce the risk compared to both other HA patients and non-HA patients. SOC included other treatments and there was no mortality or hospitalization.

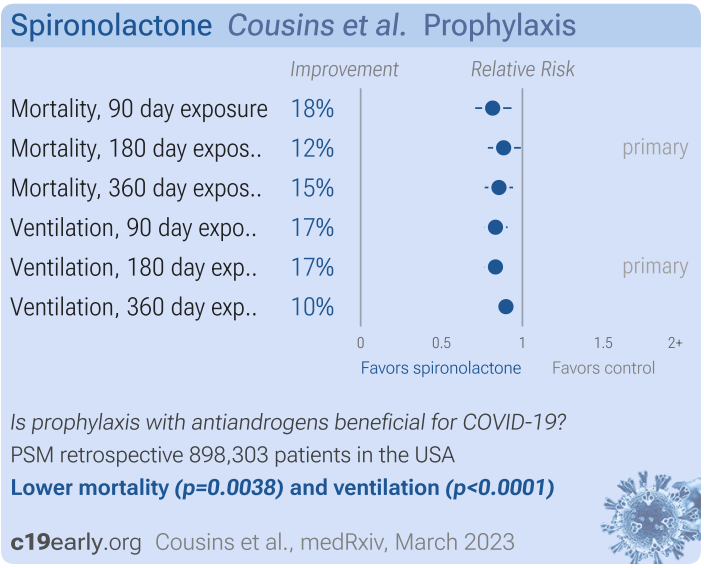
Cadegiani



SEE ALSO
The High-Impact Medical Journal Editors Harassment Of The World's Leading Clinical Researcher of Repurposed Dr...

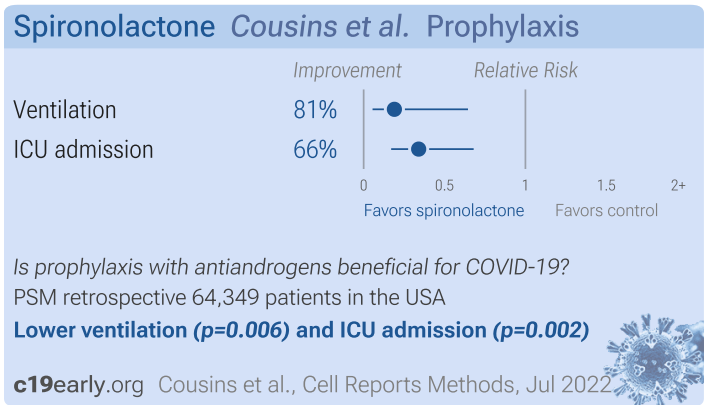
Cadegiani (D): RCT 778 hospitalized patients in Brazil, 423 treated with proxalutamide, showing significantly lower mortality and improved recovery with treatment. NCT04728802 and NCT05126628. Authors note that cases in this trial were predominantly the P.1 Gamma variant, for which proxalutamide may be more effective compared to other variants.

Cousins



Cousins: PSM retrospective 898,303 hospitalized COVID-19 patients in the USA, 16,324 on spironolactone, showing lower mortality and ventilation with spironolactone use.

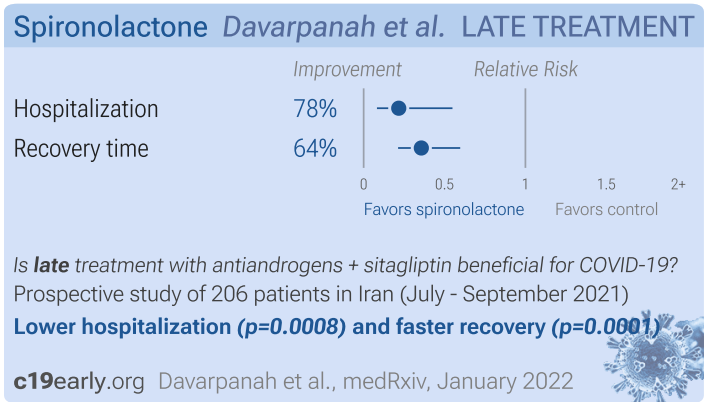
Cousins



Cousins (B): PSM retrospective 64,349 COVID-19 patients in the USA, showing spironolactone associated with lower ICU admission.

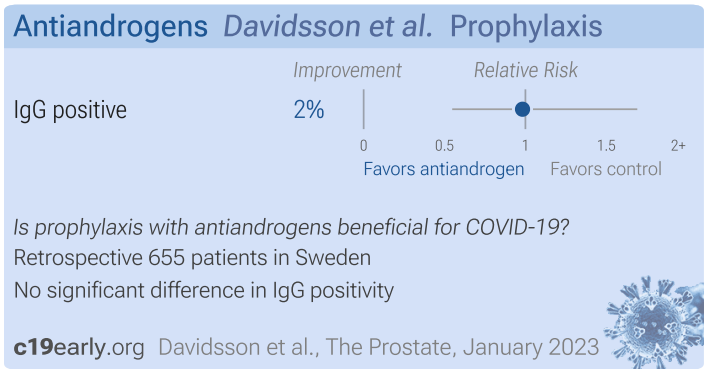
Authors also present In Vitro research showing dose-dependent inhibition in a human lung epithelial cell line.

Davarpanah



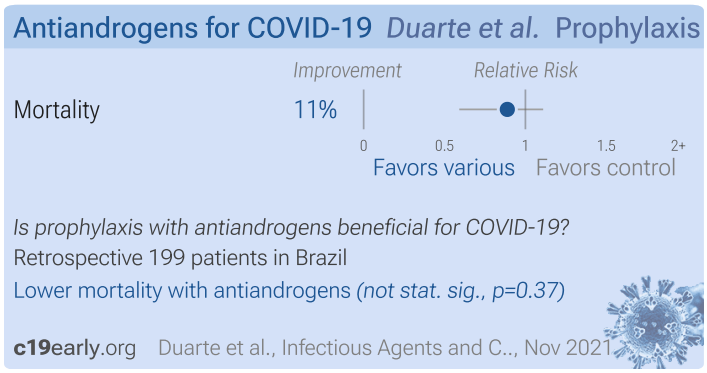
Davarpanah: Prospective study of 206 outpatients in Iran, 103 treated with spironolactone and sitagliptin, showing lower hospitalization and faster recovery with treatment. spironolactone 100mg and sitagliptin 100mg daily.

Davidsson



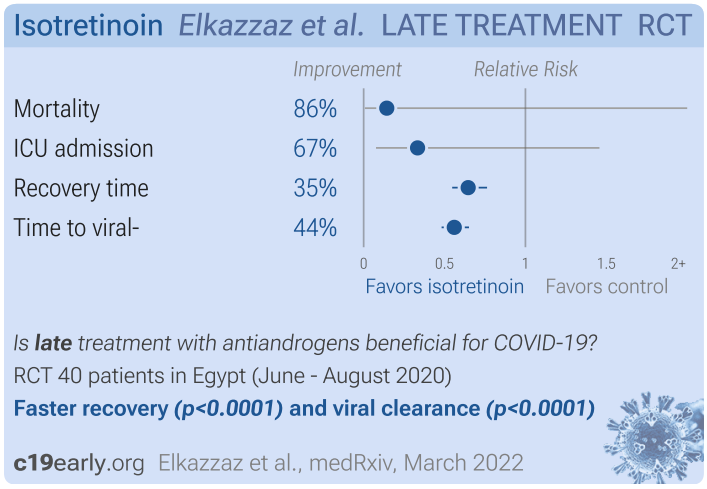
Davidsson: Retrospective 655 prostate cancer patients in Sweden, showing no significant difference in seropositivity with ADT.

Duarte



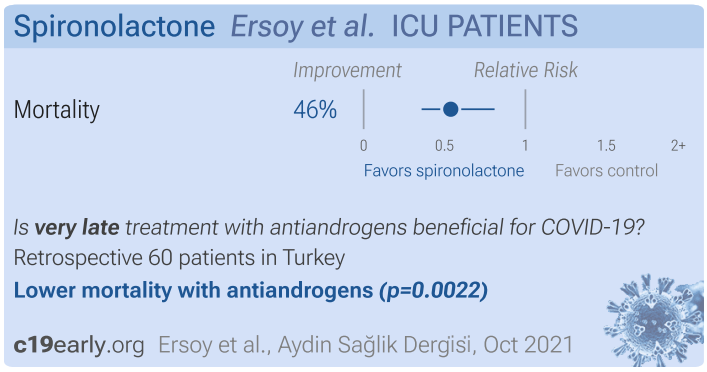
Duarte: Retrospective 199 prostate cancer patients hospitalized with COVID-19 in Brazil, showing no significant difference in mortality with active ADT.

Elkazzaz



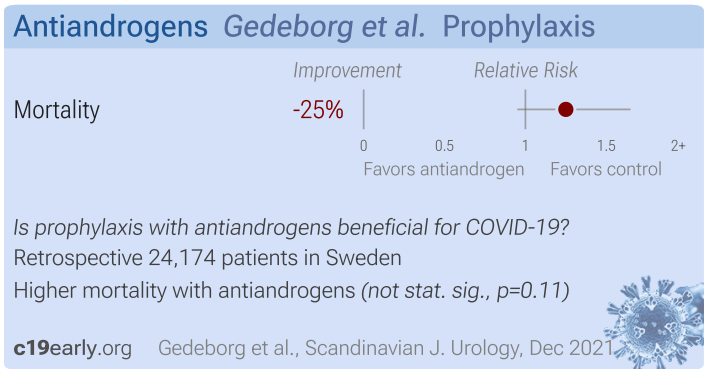
Elkazzaz: RCT with 20 13-cis-retinoic acid patients and 20 control patients, showing faster recovery and viral clearance with treatment. Aerosolized 13-cis-retinoic acid with increasing dose from 0.2 mg/kg/day to 4 mg/kg/day for 14 days, plus oral 13-cis-retinoic acid 20 mg/day. 13-cis retinoic acid, also known as isotretinoin, is a synthetic vitamin A derivative that has been shown to have antiandrogenic effects .

Ersoy



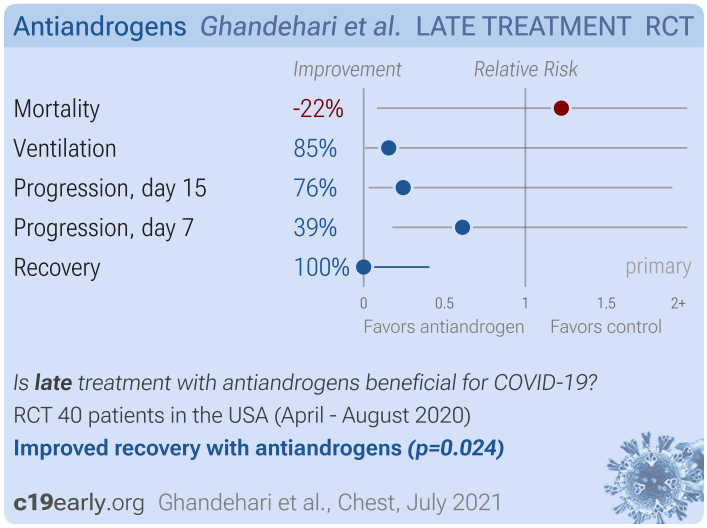
Ersoy: Retrospective 30 COVID-19 ARDS ICU patients and 30 control patients, showing lower mortality with treatment.

Gedeborg



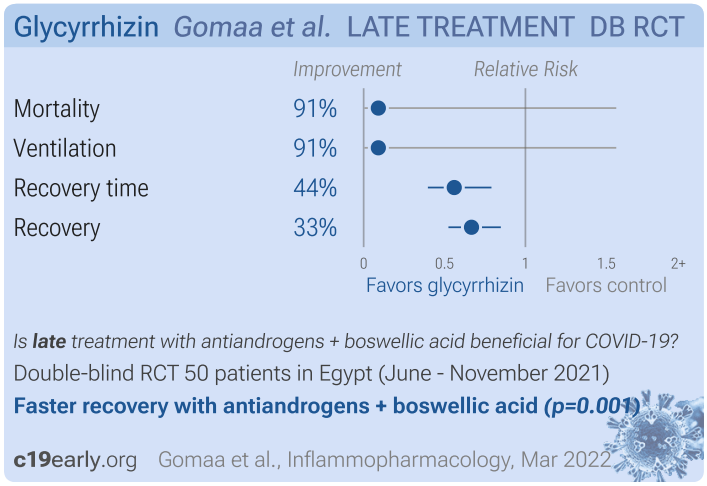
Gedeborg: Case control study with 474 patients that died of COVID-19 in Sweden, showing higher risk with ADT, without statistical significance.

Ghandehari



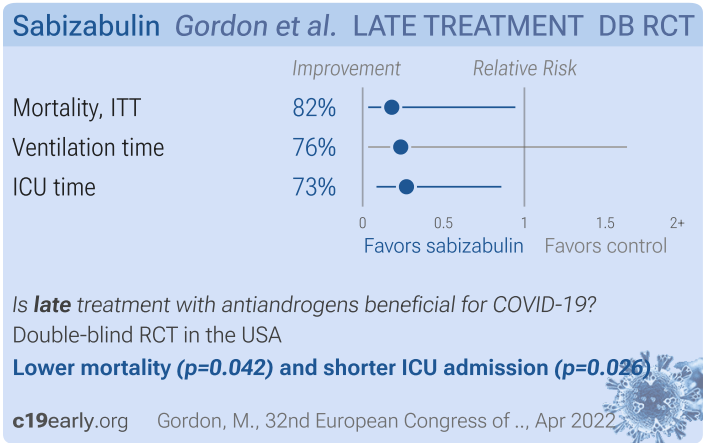
Ghandehari: RCT 42 hospitalized patients in the USA, showing improved recovery and lower progression with progesterone treatment.

Gomaa



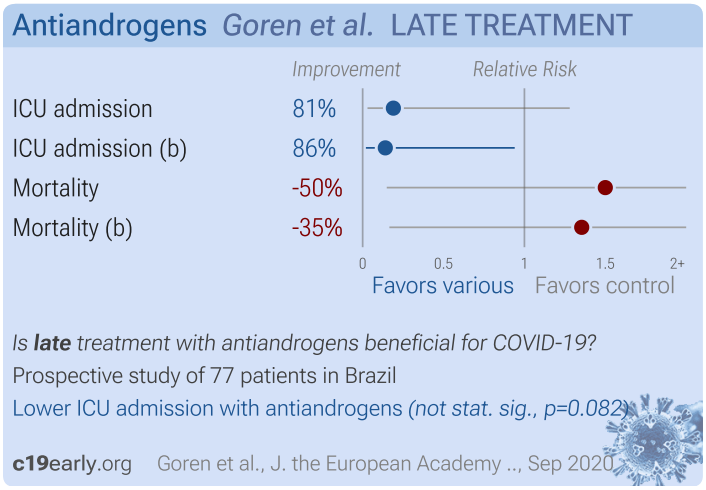
Gomaa: RCT with 50 hospitalized COVID+ patients in Egypt, 25 treated with glycyrrhizin and boswellic acid, showing improved recovery with treatment. Glycyrrhizin 60mg and boswellic acid 200mg bid for 2 weeks. NCT04487964.

Gordon



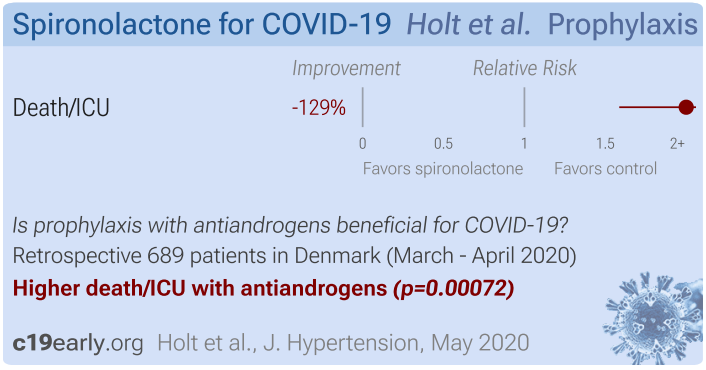
Gordon: Phase 2 RCT of sabizabulin showing lower mortality with treatment. For more discussion see *twitter.com (D)*.

Goren



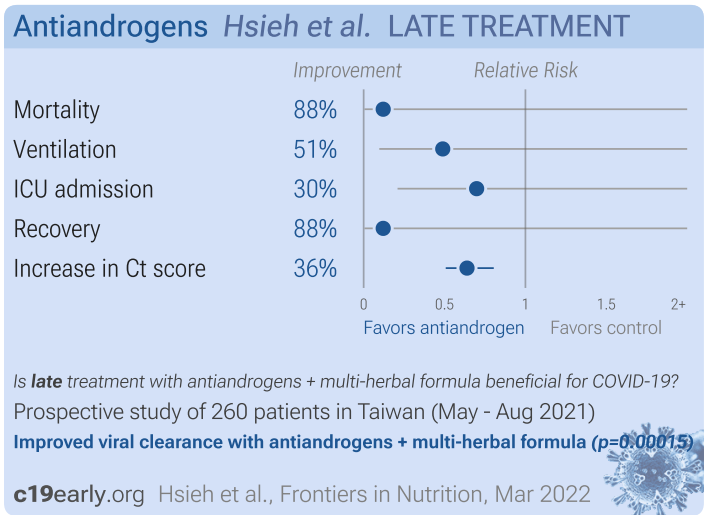
Goren: Prospective study of 77 men hospitalized with COVID-19, 12 taking antiandrogens (9 dutasteride, 2 finasteride, 1 spironolactone), showing lower ICU admission with treatment (statistically significant with age-matched controls only when excluding the spironolactone patient). NCT04368897.

Holt



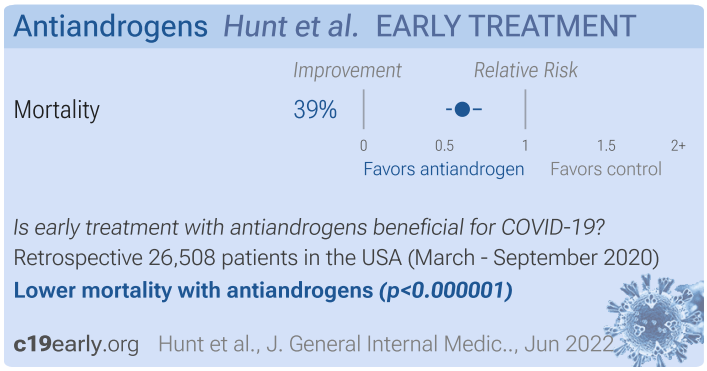
Holt: Retrospective 689 hospitalized COVID-19 patients in Denmark, showing higher risk of ICU/death with spironolactone use in unadjusted results subject to confounding by indication.

Hsieh



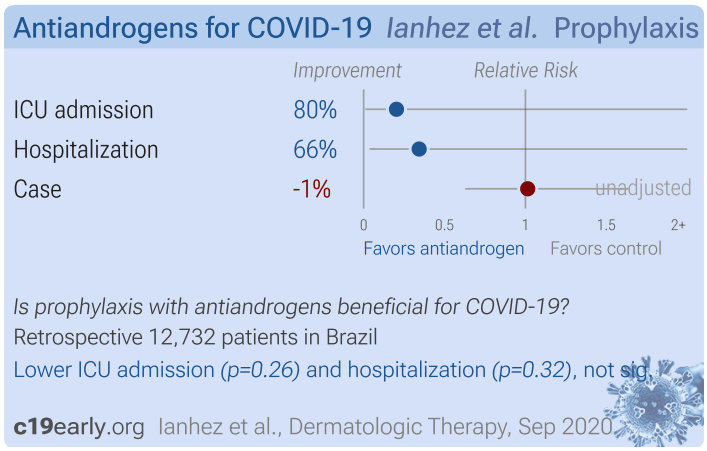
Hsieh: Prospective study of 260 hospitalized patients in Taiwan, 117 treated with herbal formula Jing Si Herbal Tea which includes antiandrogen glycyrrhiza glabra, showing improved recovery with treatment, with statistical significance for SpO2, Ct score, CRP, and Brixia score.

Hunt



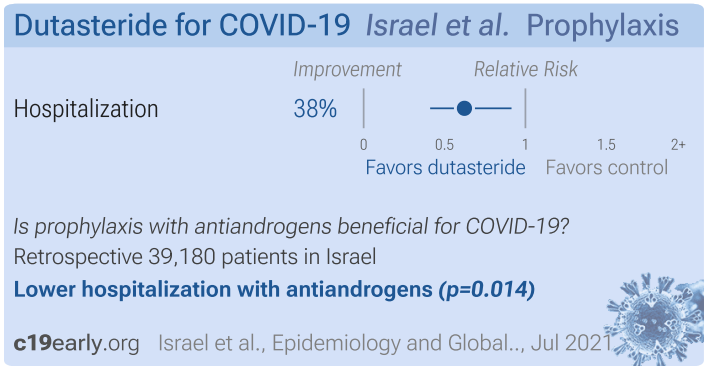
Hunt: Retrospective 26,508 consecutive COVID+ veterans in the USA, showing lower mortality with multiple treatments including anti-androgens. Treatment was defined as drugs administered ≥50% of the time within 2 weeks post-COVID+, and may be a continuation of prophylactic treatment in some cases, and may be early or late treatment in other cases. Further reduction in mortality was seen with combinations of treatments.

Ianhez



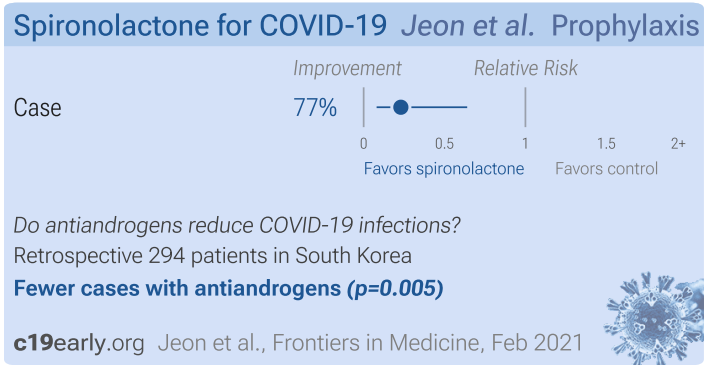
Ianhez: Retrospective survey of 41,529 participants, including 571 on antiandrogen therapy, showing no significant association between antiandrogen use and COVID-19 incidence, hospitalization, or ICU admission/mechanical ventilation.

Israel



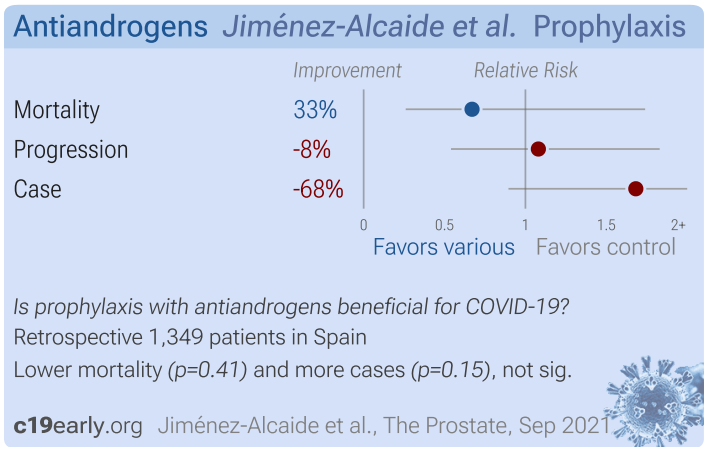
Israel: Case control study examining medication usage with a healthcare database in Israel, showing lower risk of hospitalization with dutasteride.

Jeon



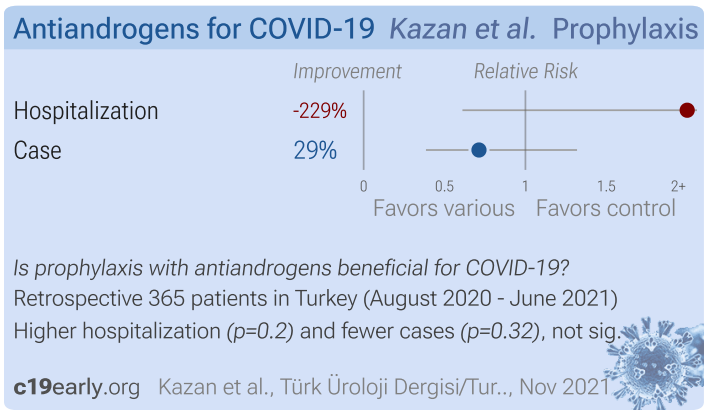
Jeon: Retrospective 6,462 liver cirrhosis patients in South Korea, with 67 COVID+ cases, showing significantly lower cases with spironolactone treatment. Death and ICU results per group are not provided.

Jiménez-Alcaide



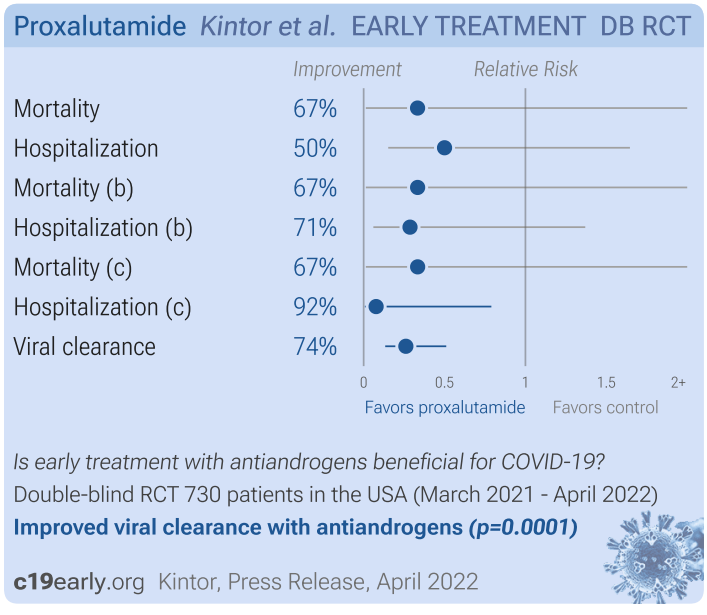
Jiménez-Alcaide: Retrospective 1,349 prostate cancer patients in Spain, 156 on ADT, showing no significant differences in COVID-19 outcomes with treatment.

Kazan



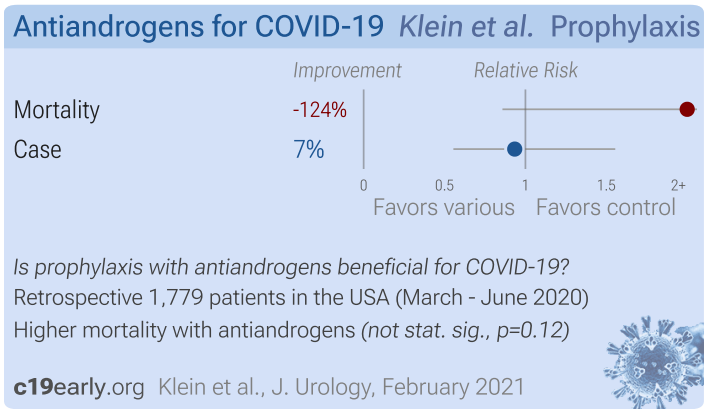
Kazan: Retrospective 365 prostate cancer patients in Turkey, 138 treated with ADT, showing no significant differences with treatment.

Kintor



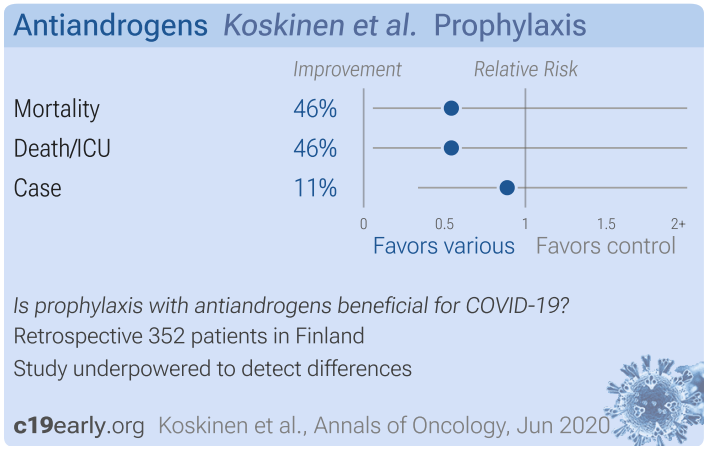
Kintor: RCT 733 outpatients, 99% in the USA, showing lower hospitalization/death, and significantly reduced viral load with proxalutamide treatment. The viral clearance result is from *Ma et al.*.

Klein



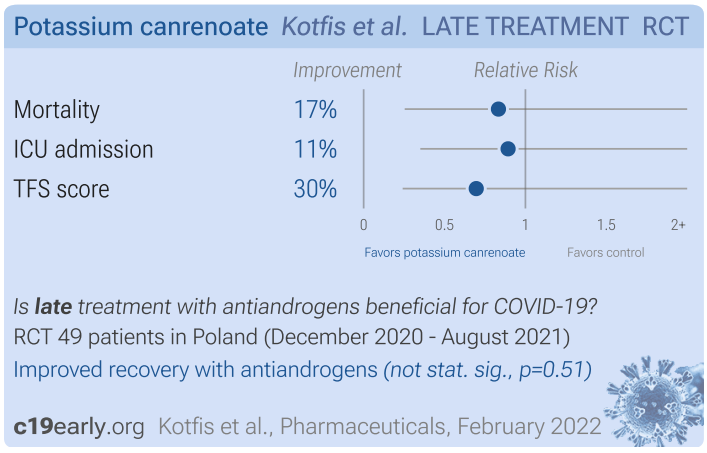
Klein: Retrospective 1,779 prostate cancer patients, showing no significant differences in COVID-19 outcomes with ADT.

Koskinen



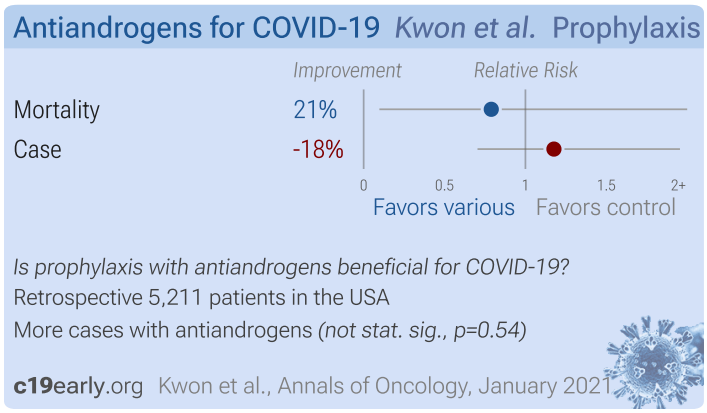
Koskinen: Retrospective 352 prostate cancer patients in Finland, showing no significant differences in COVID-19 with ADT.

Kotfis



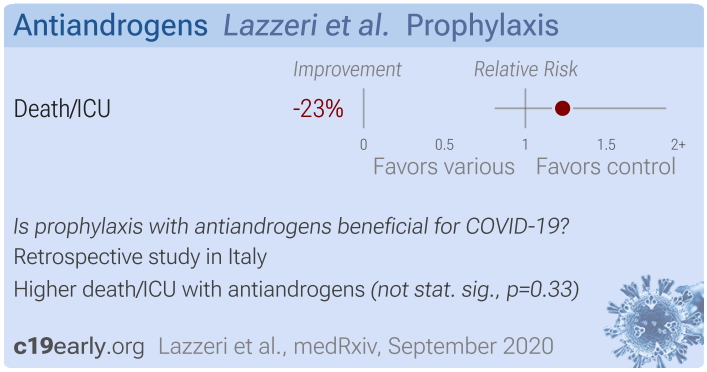
Kotfis: RCT with 24 patients treated with potassium canrenoate and 25 placebo patients in Poland, showing no significant differences.

Kwon



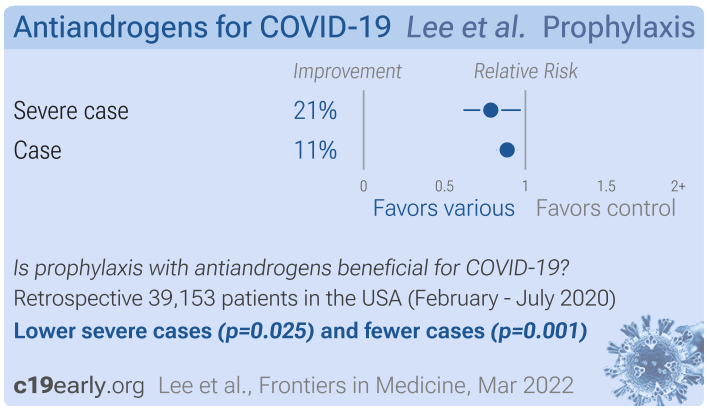
Kwon: Retrospective 5,211 prostate cancer patients, 799 on ADT, showing no significant differences in COVID-19 outcomes with treatment.

Lazzeri



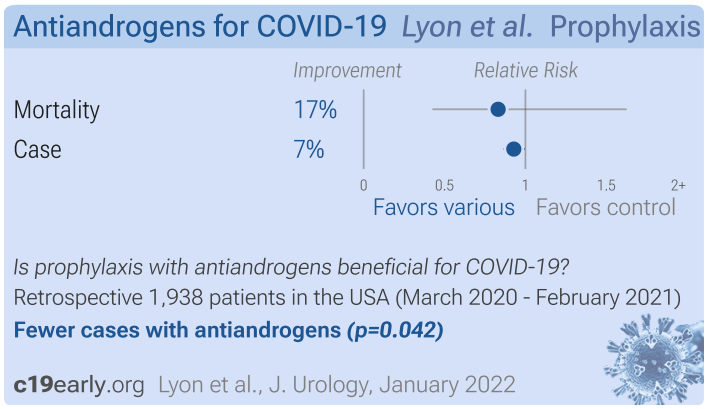
Lazzeri: Retrospective case-control study in Italy with 943 male COVID-19 patients, 45 on chronic 5ARI treatment (finasteride/dutasteride). There was significantly fewer COVID-19 patients >55 on 5ARI treatment compared to age-matched controls (5.57 vs. 8.14%, p=0.0083). The difference was greater for men aged >65 (7.14 vs. 12.31%, p=0.0001). There was no significant difference for ICU admission or death.

Lee



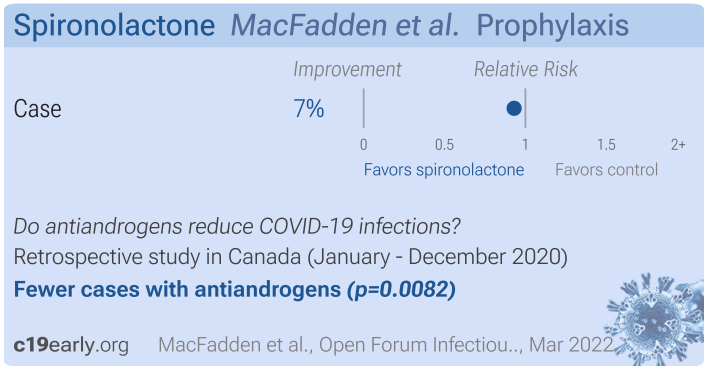
Lee (B): Retrospective 3,057 androgen deprivation therapy patients in the USA, and 36,096 control patients with cancer, showing lower risk of cases and severity with ADT.

Lyon



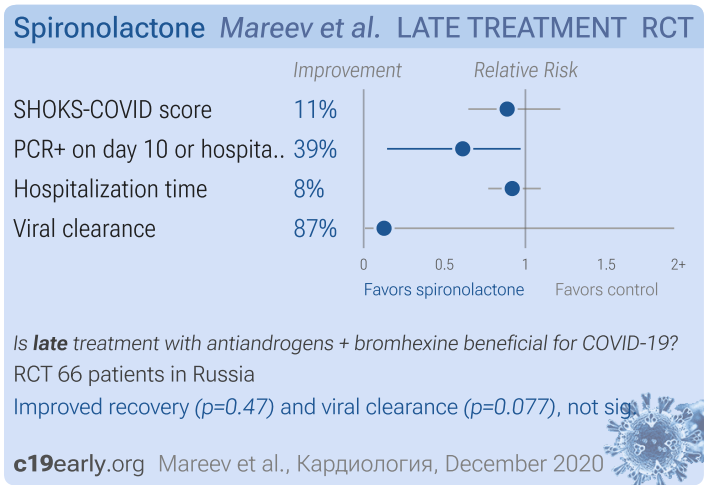
Lyon: Retrospective 944 5ARI users in the USA and 944 matched controls, showing lower risk of COVID-19 cases with treatment.

MacFadden



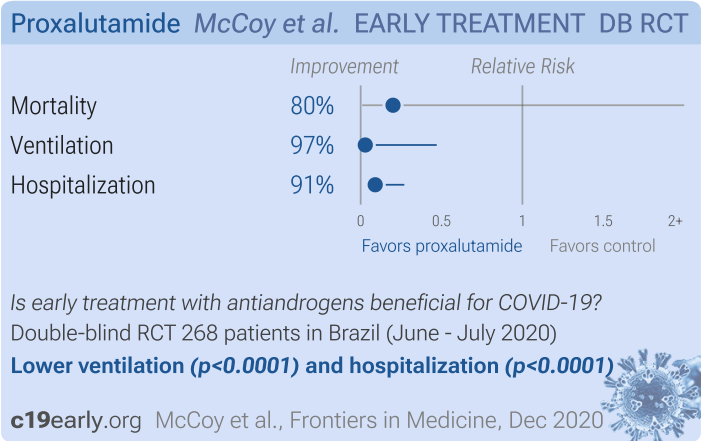
MacFadden: Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing lower cases with chronic use of spironolactone.

Mareev



Mareev: Prospective 103 PCR+ patients in Russia, 33 treated with bromexhine+spironolactone, showing lower PCR+ at day 10 or hospitalization >10 days with treatment. Bromhexine 8mg 4 times daily, spironolactone 25-50 mg/day for 10 days.

McCoy

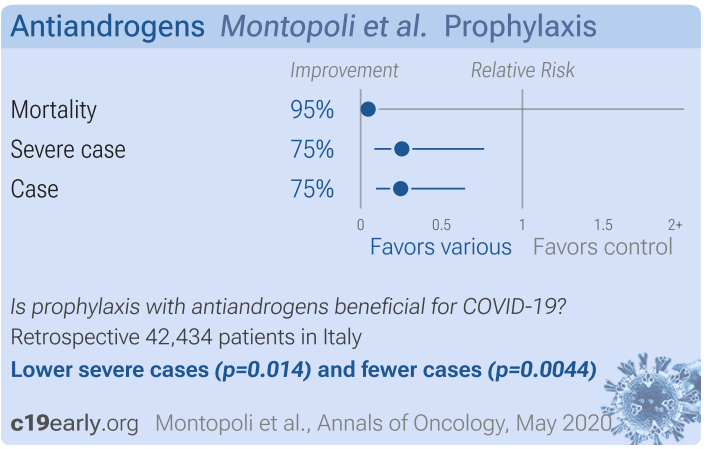


SEE ALSO
The High-Impact Medical Journal Editors Harassment Of The World's Leading Clinical Researcher of Repurposed Dr...

McCoy: RCT 268 male patients in Brazil, 134 treated with proxalutamide, showing significantly lower hospitalization and mechanical ventilation. NCT04446429.

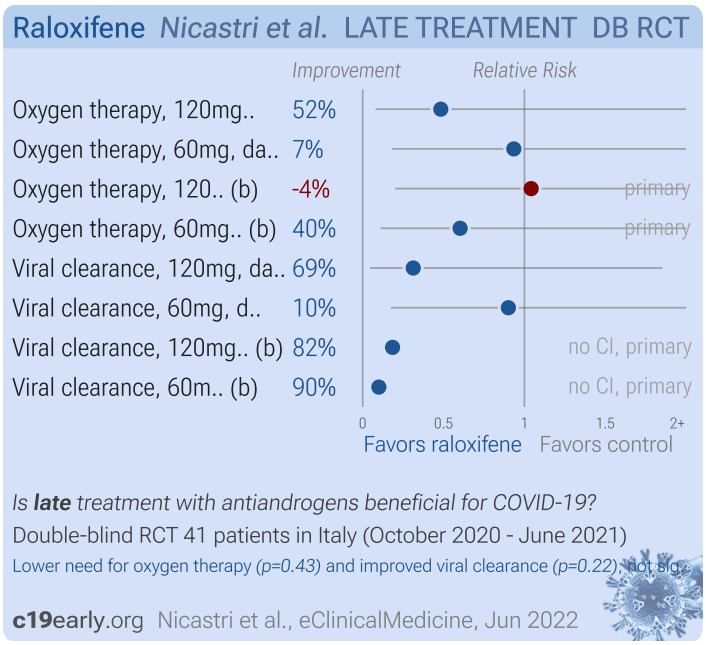
This paper was censored without details or author response, and the editors have ignored the authors, see *twitter.com (E)*.

Montopoli



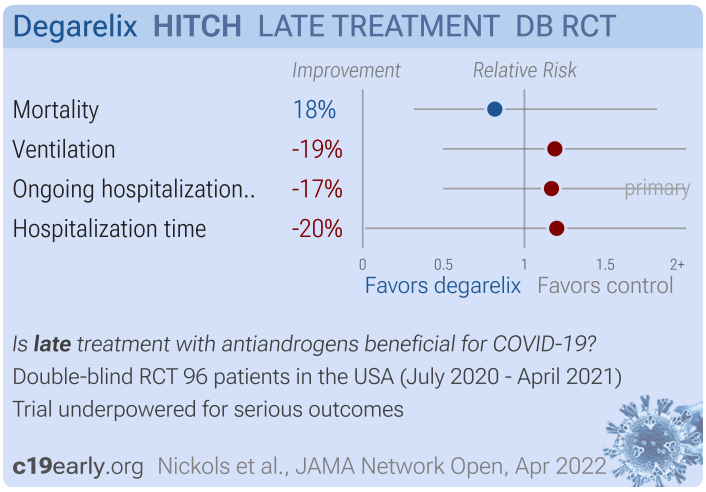
Montopoli: Retrospective 5,273 prostate cancer patients on androgen-deprivation therapy (ADT), and 37,161 not on ADT, showing lower risk of cases with treatment.

Nicastri



Nicastri: RCT 68 patients in Italy showing improved viral clearance with raloxifene.

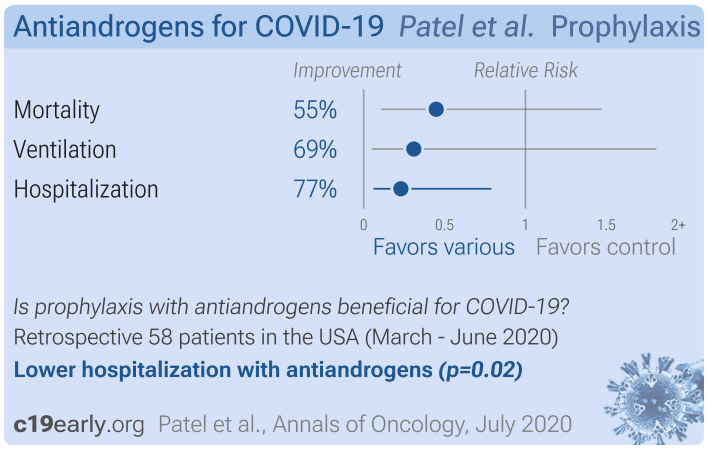
Nickols



Nickols: Early terminated RCT with 62 very late stage (79% on oxygen) degarelix patients and 34 placebo patients, showing no significant differences with treatment.

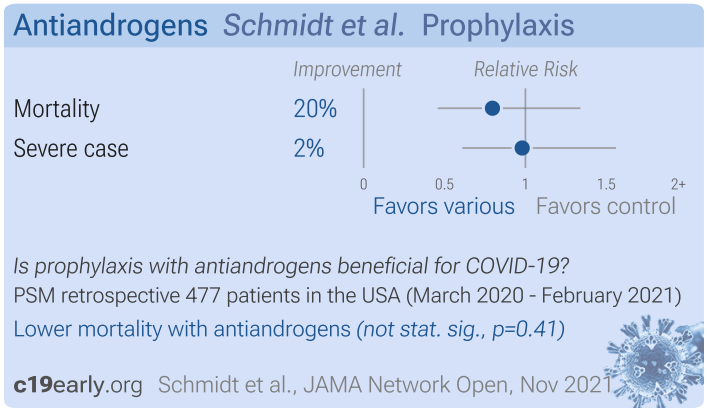
For discussion of many issues with this study see *twitter.com (F)*.

Patel



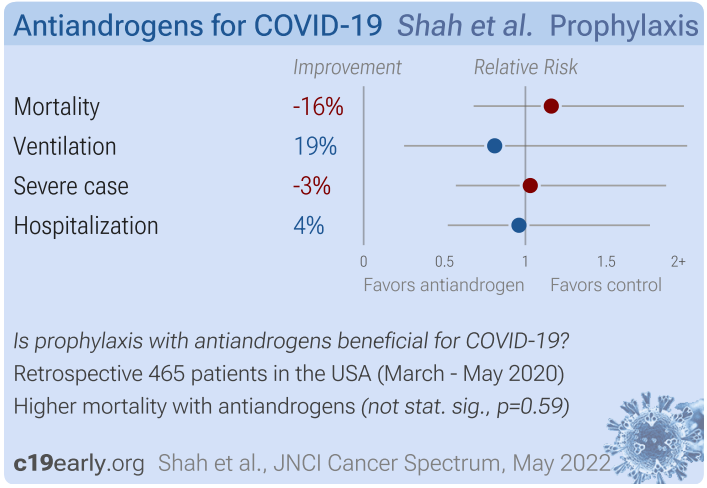
Patel: Retrospective 58 prostate cancer patients in the USA, showing lower risk of hospitalization with ADT.

Schmidt



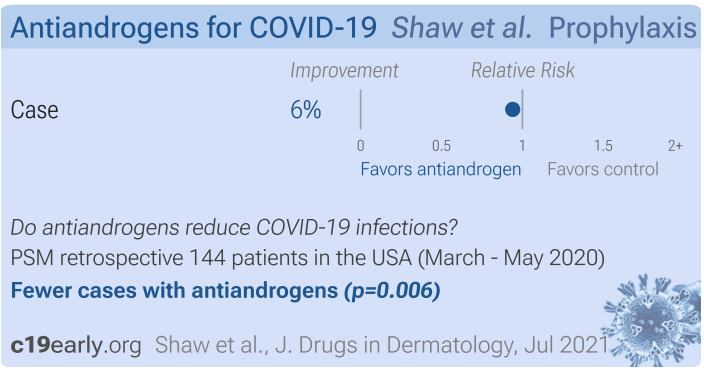
Schmidt: Retrospective 1,106 prostate cancer patients, showing no significant differences in COVID-19 outcomes with ADT.

Shah



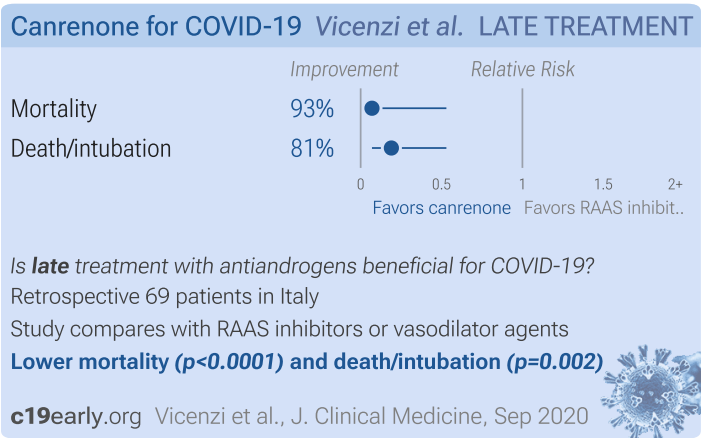
Shah: Retrospective 465 prostate cancer patients, showing no significant difference in COVID-19 outcomes with ADT.

Shaw



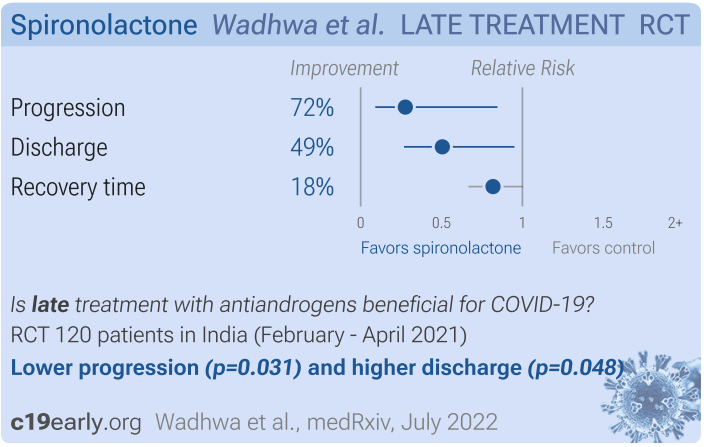
Shaw: PSM retrospective 144 alopecia patients in the USA, showing no significant difference in COVID-19 cases with anti-androgen use. The supplemental appendix is not available.

Vicenzi



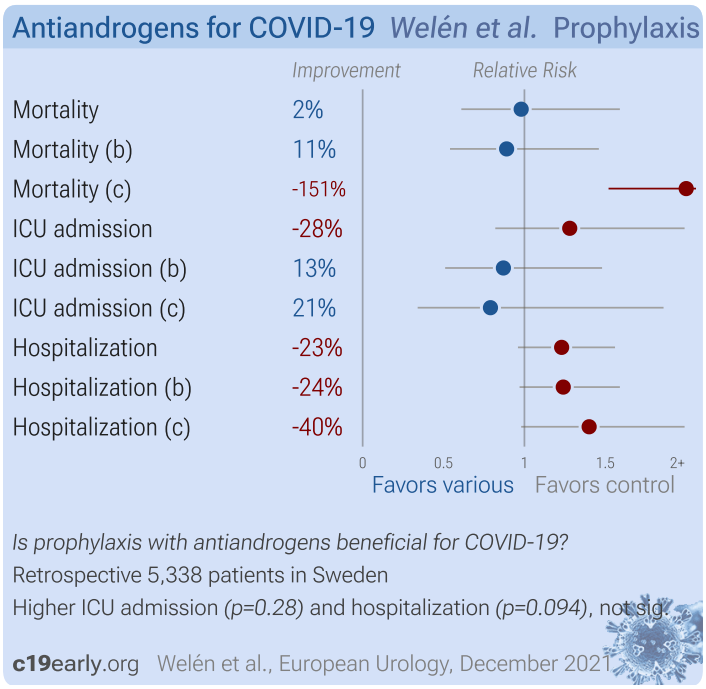
Vicenzi: Retrospective 69 consecutive hospitalized COVID-19 patients in Italy, 30 patients receiving canrenone, and 39 treated with vasodilator agents or renin–angiotensin–aldosterone system (RAAS) inhibitors, showing lower mortality with canrenone.

Wadhwa



Wadhwa: RCT 120 hospitalized patients in India, 74 treated with spironolactone and dexamethasone, and 46 with dexamethasone, showing lower progression with treatment. Spironolactone 50mg once daily day 1, 25mg once daily until day 21.

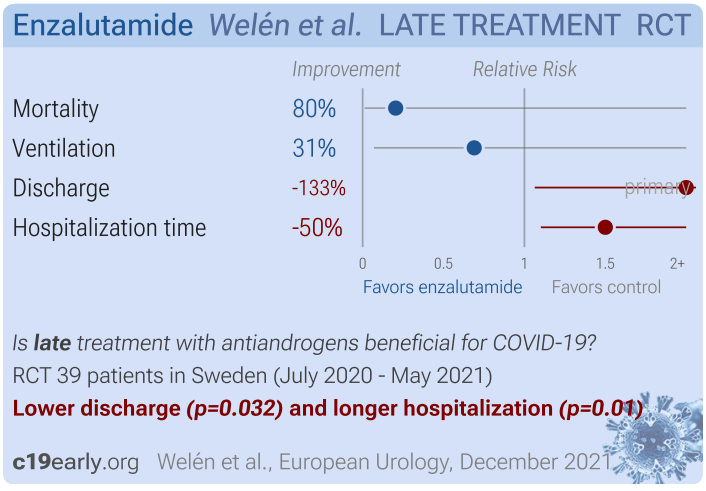
Welén



Welén (B): Retrospective 7,894 COVID+ prostate cancer patients, analyzing patients on antiandrogen treatment, ADT, and ADT + abiraterone acetate or enzalutamide, showing mixed results and higher mortality for ADT + abiraterone acetate or enzalutamide.
This paper also includes a small RCT which is listed separately, and an In Vitro HBEC study showing no significant differences (p = 0.084). The supplementary data is not currently available. NCT04475601.

For discussion of issues with this study see *sciencedirect.com, sciencedirect.com (B), sciencedirect.com (C), sciencedirect.com (D)*.

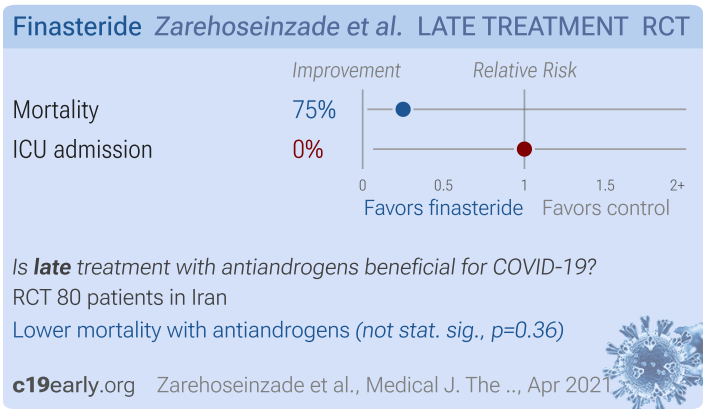
Welén



Welén: Very small late stage RCT with 10 control patients and 29 enzalutamide patients, showing mixed results. Discharge and hospitalization time favored the control group, while viral load reduction was better with treatment on days 4&6 (day 4 ΔCt −5.6 p = 0.084), and the only death occurred in the control group. 27% of enzalutamide patients had diabetes compared to 0% of the control group. This paper also includes a retrospective study which is listed separately, and an In Vitro HBEC study showing no significant differences (p = 0.084). The supplementary data is not currently available. NCT04475601.

For discussion of issues with this study see *sciencedirect.com, sciencedirect.com (B), sciencedirect.com (C), sciencedirect.com (D)*.

Zarehoseinzade



Zarehoseinzade: RCT 80 hospitalized COVID-19 patients in Iran, 40 treated with finasteride, showing no significant differences other than improved oxygen saturation on the 5th day with treatment. There was significantly more patients with diabetes in the control group. 5mg finasteride for 7 days. IRCT20200505047318N1.

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 antiandrogen 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 antiandrogen 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].

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

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

Cadegiani (C), 7/10/2021, Double Blind Randomized Controlled Trial, Brazil, preprint, 7 authors, study period 4 January, 2021 - 28 February, 2021.	**risk of death, 63.4% lower, RR 0.37, p = 1.00**, treatment 0 of 75 (0.0%), control 1 of 102 (1.0%), NNT 102, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 89.7% lower, RR 0.10, p = 0.07, treatment 0 of 75 (0.0%), control 5 of 102 (4.9%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 85.7% lower, RR 0.14, p < 0.001, treatment 2 of 75 (2.7%), control 19 of 102 (18.6%), NNT 6.3.
Cadegiani, 2/1/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 4 authors, excluded in exclusion analyses: potential randomization failure.	**risk of no recovery, 62.0% lower, RR 0.38, p = 0.009**, treatment 7 of 44 (15.9%), control 18 of 43 (41.9%), NNT 3.9.
	recovery time, 43.6% lower, relative time 0.56, p < 0.001, treatment 44, control 43, all symptoms.
	recovery time, 40.2% lower, relative time 0.60, p < 0.001, treatment 44, control 43, all symptoms except loss of smell or taste.
Cadegiani (B), 10/6/2020, prospective, Brazil, preprint, 4 authors, average treatment delay 3.0 days, excluded in exclusion analyses: significant unadjusted differences between groups.	**recovery time, 76.7% lower, relative time 0.23, p = 0.006**, treatment 8, control 262, excluding anosmia.
	recovery time, 82.8% lower, relative time 0.17, p = 0.002, treatment 8, control 262, including anosmia.

	time to viral-, 37.9% lower, relative time 0.62, $p = 0.02$, treatment 8, control 262.
Hunt, 6/29/2022, retrospective, USA, peer-reviewed, 8 authors, study period 1 March, 2020 - 10 September, 2020.	risk of death, 39.0% lower, RR 0.61, $p < 0.001$, treatment 167 of 1,788 (9.3%), control 1,445 of 24,720 (5.8%), adjusted per study, day 30.
Kintor, 4/5/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, study period 5 March, 2021 - 1 April, 2022, trial NCT04870606 (history).	risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 365 (0.0%), control 1 of 365 (0.3%), NNT 365, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), 1+ days of treatment, group size approximated.
	risk of hospitalization, 50.0% lower, RR 0.50, $p = 0.38$, treatment 4 of 365 (1.1%), control 8 of 365 (2.2%), NNT 91, 1+ days of treatment, group size approximated.
	risk of death, 66.6% lower, RR 0.33, $p = 1.00$, treatment 0 of 360 (0.0%), control 1 of 361 (0.3%), NNT 361, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), >1 day of treatment, group size approximated.
	risk of hospitalization, 71.3% lower, RR 0.29, $p = 0.18$, treatment 2 of 360 (0.6%), control 7 of 361 (1.9%), NNT 72, >1 day of treatment, group size approximated.
	risk of death, 66.6% lower, RR 0.33, $p = 1.00$, treatment 0 of 346 (0.0%), control 1 of 347 (0.3%), NNT 347, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), >7 days of treatment, group size approximated.
	risk of hospitalization, 92.3% lower, RR 0.08, $p = 0.03$, treatment 0 of 346 (0.0%), control 6 of 347 (1.7%), NNT 58, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), >7 days of treatment, group size approximated.
	risk of no viral clearance, 73.9% lower, RR 0.26, $p < 0.001$, day 7.
McCoy, 12/30/2020, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 15 authors, study period 15 June, 2020 - 28 July, 2020, trial NCT04446429 (history).	risk of death, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 134 (0.0%), control 2 of 134 (1.5%), NNT 67, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 97.1% lower, RR 0.03, $p < 0.001$, treatment 0 of 134 (0.0%), control 17 of 134 (12.7%), NNT 7.9, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 91.0% lower, RR 0.09, $p < 0.001$, treatment 3 of 134 (2.2%), control 35 of 134 (26.1%), NNT 4.2.

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.

Abbasi, 2/7/2022, Single Blind Randomized Controlled Trial, Iran, peer-reviewed, 11 authors, study period December 2020 - April 2021.	risk of death, 55.1% lower, RR 0.45, $p = 0.10$, treatment 5 of 51 (9.8%), control 19 of 87 (21.8%), NNT 8.3, day 5.
	risk of mechanical ventilation, 33.7% lower, RR 0.66, $p = 0.36$, treatment 7 of 51 (13.7%), control 18 of 87 (20.7%), NNT 14, day 5.
	risk of ICU admission, 18.8% lower, RR 0.81, $p = 0.67$, treatment 10 of 51 (19.6%), control 21 of 87 (24.1%), NNT 22, day 5.
	risk of no recovery, 47.3% lower, RR 0.53, $p < 0.001$, treatment mean 1.64 (±0.81) n=51, control mean 3.11 (±2.45) n=87, relative clinical score, day 5.
Barnette, 7/6/2022, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, 12 authors, study period 18 May, 2021 - 31 January, 2022.	risk of death, 55.2% lower, RR 0.45, $p = 0.002$, treatment 19 of 94 (20.2%), control 23 of 51 (45.1%), NNT 4.0.
	ventilation time, 49.5% lower, relative time 0.51, $p = 0.001$, treatment 98, control 52.
	ICU time, 43.5% lower, relative time 0.56, $p = 0.001$, treatment 98, control 52.
	hospitalization time, 26.0% lower, relative time 0.74, $p = 0.03$, treatment 98, control 52.
Cadegiani (D), 12/25/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 15 authors, study period 1 February, 2021 - 15 April, 2021, trial NCT04728802 (history).	risk of death, 78.0% lower, RR 0.22, $p < 0.001$, treatment 45 of 423 (10.6%), control 171 of 355 (48.2%), NNT 2.7, adjusted per study, 28 days, Cox proportional hazards.
	risk of death, 79.0% lower, RR 0.21, $p < 0.001$, treatment 34 of 423 (8.0%), control 138 of 355 (38.9%), NNT 3.2, adjusted per study, 14 days, Cox proportional hazards.
	recovery rate, RR 0.55, $p < 0.001$, treatment 423, control 355, adjusted per study, inverted to make RR<1 favor treatment, 28 days, Cox proportional hazards.
	recovery rate, RR 0.45, $p < 0.001$, treatment 423, control 355, adjusted per study, inverted to make RR<1 favor treatment, 14 days, Cox proportional hazards, primary outcome.
	hospitalization time, 33.3% lower, relative time 0.67, $p < 0.001$, treatment 423, control 355.
Davarpanah, 1/21/2022, prospective, Iran, preprint, 9 authors, study period July 2021 - September 2021, average treatment delay 5.74 days, this trial	risk of hospitalization, 78.3% lower, RR 0.22, $p < 0.001$, treatment 6 of 103 (5.8%), control 23 of 103 (22.3%), NNT 6.1, odds ratio converted to relative risk.

uses multiple treatments in the treatment arm (combined with sitagliptin) - results of individual treatments may vary.	recovery time, 64.4% lower, relative time 0.36, $p < 0.001$, treatment 103, control 103.
Elkazzaz, 3/8/2022, Randomized Controlled Trial, Egypt, preprint, 4 authors, study period June 2020 - August 2020, trial NCT04353180 (history).	risk of death, 85.7% lower, RR 0.14, $p = 0.23$, treatment 0 of 20 (0.0%), control 3 of 20 (15.0%), NNT 6.7, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 66.7% lower, RR 0.33, $p = 0.24$, treatment 2 of 20 (10.0%), control 6 of 20 (30.0%), NNT 5.0.
	recovery time, 35.4% lower, relative time 0.65, $p < 0.001$, treatment mean 16.3 (±4.5) n=20, control mean 25.23 (±4.72) n=20.
	time to viral-, 44.0% lower, relative time 0.56, $p < 0.001$, treatment mean 13.36 (±1.49) n=20, control mean 23.85 (±4.0) n=20.
Ersoy, 10/13/2021, retrospective, Turkey, peer-reviewed, 7 authors.	risk of death, 46.2% lower, RR 0.54, $p = 0.002$, treatment 14 of 30 (46.7%), control 26 of 30 (86.7%), NNT 2.5.
Ghandehari, 7/31/2021, Randomized Controlled Trial, USA, peer-reviewed, mean age 55.3, 14 authors, study period April 2020 - August 2020, trial NCT04365127 (history).	risk of death, 22.2% higher, RR 1.22, $p = 1.00$, treatment 1 of 18 (5.6%), control 1 of 22 (4.5%), day 15.
	risk of mechanical ventilation, 84.5% lower, RR 0.15, $p = 0.24$, treatment 0 of 18 (0.0%), control 3 of 22 (13.6%), NNT 7.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), peak value day 7 and 15.
	risk of progression, 75.6% lower, RR 0.24, $p = 0.20$, treatment 1 of 18 (5.6%), control 5 of 22 (22.7%), NNT 5.8, day 15.
	risk of progression, 38.9% lower, RR 0.61, $p = 0.48$, treatment 3 of 18 (16.7%), control 6 of 22 (27.3%), NNT 9.4, day 7.
Gomaa, 3/1/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Egypt, peer-reviewed, median age 60.0, 5 authors, study period June 2021 - November 2021, average treatment delay 6.0 days, this trial uses multiple treatments in the treatment arm (combined with boswellic acid) - results of individual treatments may vary, trial NCT04487964 (history).	risk of death, 90.9% lower, RR 0.09, $p = 0.05$, treatment 0 of 25 (0.0%), control 5 of 25 (20.0%), NNT 5.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of mechanical ventilation, 90.9% lower, RR 0.09, $p = 0.05$, treatment 0 of 25 (0.0%), control 5 of 25 (20.0%), NNT 5.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	recovery time, 44.0% lower, relative time 0.56, $p < 0.001$, treatment 25, control 25.
	risk of no recovery, 33.3% lower, RR 0.67, $p < 0.001$, treatment 25, control 25, relative clinical status, day 14.
Gordon, 4/25/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 1 author.	risk of death, 82.0% lower, RR 0.18, $p = 0.04$, ITT.
	ventilation time, 76.5% lower, relative time 0.24, $p = 0.14$.

	ICU time, 72.9% lower, relative time 0.27, $p = 0.03$.
Goren, 9/25/2020, prospective, Brazil, peer-reviewed, 15 authors, trial NCT04368897 (history).	**risk of ICU admission, 81.0% lower, RR 0.19, $p = 0.08$**, treatment 1 of 12 (8.3%), control 17 of 36 (47.2%), NNT 2.6, adjusted per study, age-matched controls.
	risk of ICU admission, 86.0% lower, RR 0.14, $p = 0.04$, treatment 1 of 12 (8.3%), control 38 of 65 (58.5%), NNT 2.0, adjusted per study, all controls.
	risk of death, 50.0% higher, RR 1.50, $p = 1.00$, treatment 1 of 12 (8.3%), control 2 of 36 (5.6%), age-matched controls.
	risk of death, 35.4% higher, RR 1.35, $p = 0.58$, treatment 1 of 12 (8.3%), control 4 of 65 (6.2%), all controls.
Hsieh, 3/14/2022, prospective, Taiwan, peer-reviewed, 7 authors, study period 1 May, 2021 - 31 August, 2021, this trial uses multiple treatments in the treatment arm (combined with multi-herbal formula) - results of individual treatments may vary.	**risk of death, 87.9% lower, RR 0.12, $p = 0.13$**, treatment 0 of 117 (0.0%), control 4 of 143 (2.8%), NNT 36, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 51.1% lower, RR 0.49, $p = 0.46$, treatment 2 of 117 (1.7%), control 5 of 143 (3.5%), NNT 56.
	risk of ICU admission, 30.2% lower, RR 0.70, $p = 0.76$, treatment 4 of 117 (3.4%), control 7 of 143 (4.9%), NNT 68.
	risk of no recovery, 87.9% lower, RR 0.12, $p = 0.13$, treatment 0 of 117 (0.0%), control 4 of 143 (2.8%), NNT 36, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	relative increase in Ct score, 36.1% better, RR 0.64, $p < 0.001$, treatment mean 8.14 (±4.9) n=117, control mean 5.2 (±6.99) n=143.
Kotfis, 2/5/2022, Randomized Controlled Trial, placebo-controlled, Poland, peer-reviewed, 10 authors, study period December 2020 - August 2021, trial NCT04912011 (history).	**risk of death, 16.7% lower, RR 0.83, $p = 1.00$**, treatment 4 of 24 (16.7%), control 5 of 25 (20.0%), NNT 30.
	risk of ICU admission, 10.7% lower, RR 0.89, $p = 1.00$, treatment 6 of 24 (25.0%), control 7 of 25 (28.0%), NNT 33.
	relative TFS score, 30.4% better, RR 0.70, $p = 0.51$, treatment 24, control 25.
Mareev, 12/3/2020, Randomized Controlled Trial, Russia, peer-reviewed, 20 authors, this trial uses multiple treatments in the treatment arm (combined with bromhexine) - results of individual treatments may vary, trial NCT04424134 (history).	**relative SHOKS-COVID score, 11.3% better, RR 0.89, $p = 0.47$**, treatment mean 2.12 (±1.39) n=33, control mean 2.39 (±1.59) n=33.
	risk of PCR+ on day 10 or hospitalization >10 days, 38.8% lower, RR 0.61, $p = 0.02$, treatment 14 of 24 (58.3%), control 20 of 21 (95.2%), NNT 2.7, odds ratio converted to relative risk.
	hospitalization time, 8.2% lower, relative time 0.92, $p = 0.35$, treatment 33, control 33.

	risk of no viral clearance, 87.4% lower, RR 0.13, *p* = 0.08, treatment 0 of 17 (0.0%), control 3 of 13 (23.1%), NNT 4.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 10.
Nicastri, 6/30/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Italy, peer-reviewed, 17 authors, study period October 2020 - June 2021, trial NCT05172050 (history).	**risk of oxygen therapy, 51.7% lower, OR 0.48, *p* = 0.43**, treatment 20, control 19, inverted to make OR<1 favor treatment, oxygen supplementation or mechanical ventilation, day 28, 120mg, RR approximated with OR.
	risk of oxygen therapy, 6.5% lower, OR 0.93, *p* = 0.94, treatment 22, control 19, inverted to make OR<1 favor treatment, oxygen supplementation or mechanical ventilation, day 28, 60mg, RR approximated with OR.
	risk of oxygen therapy, 4.2% higher, OR 1.04, *p* = 0.96, treatment 20, control 19, inverted to make OR<1 favor treatment, oxygen supplementation or mechanical ventilation, day 14, 120mg, primary outcome, RR approximated with OR.
	risk of oxygen therapy, 39.8% lower, OR 0.60, *p* = 0.56, treatment 22, control 19, inverted to make OR<1 favor treatment, oxygen supplementation or mechanical ventilation, day 14, 60mg, primary outcome, RR approximated with OR.
	risk of no viral clearance, 68.8% lower, OR 0.31, *p* = 0.22, treatment 20, control 19, inverted to make OR<1 favor treatment, mid-recovery, day 14, 120mg, RR approximated with OR.
	risk of no viral clearance, 9.9% lower, OR 0.90, *p* = 0.91, treatment 22, control 19, inverted to make OR<1 favor treatment, mid-recovery, day 14, 60mg, RR approximated with OR.
Nickols, 4/19/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 34 authors, study period 22 July, 2020 - 8 April, 2021, trial NCT04397718 (history) (HITCH).	**risk of death, 18.3% lower, RR 0.82, *p* = 0.66**, treatment 11 of 62 (17.7%), control 7 of 34 (20.6%), NNT 35, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of mechanical ventilation, 18.8% higher, RR 1.19, *p* = 0.70, treatment 13 of 62 (21.0%), control 6 of 34 (17.6%).
	risk of ongoing hospitalization, mortality, or mechanical ventilation, 16.7% higher, RR 1.17, *p* = 0.70, treatment 15 of 62 (24.2%), control 7 of 34 (20.6%), adjusted per study, odds ratio converted to relative risk, multivariable, primary outcome.
	hospitalization time, 20.0% higher, relative time 1.20, *p* = 0.94, treatment 62, control 34.
Vicenzi, 9/11/2020, retrospective, Italy, peer-reviewed, 10 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 93.0% lower, HR 0.07, *p* < 0.001**, treatment 30, control 39, adjusted per study, model 2, multivariable.
	risk of death/intubation, 81.0% lower, HR 0.19, *p* = 0.002, treatment 30, control 39, adjusted per study, model 2, multivariable.

Wadhwa, 7/2/2022, Randomized Controlled Trial, placebo-controlled, India, preprint, 18 authors, study period 1 February, 2021 - 30 April, 2021, trial CTRI/2021/03/031721.	risk of progression, 72.4% lower, RR 0.28, $p = 0.03$, treatment 4 of 74 (5.4%), control 9 of 46 (19.6%), NNT 7.1, progression to WHO >4.
	risk of no hospital discharge, 49.5% lower, RR 0.51, $p = 0.048$, treatment 13 of 74 (17.6%), control 16 of 46 (34.8%), NNT 5.8.
	recovery time, 18.2% lower, relative time 0.82, $p = 0.06$, treatment 74, control 46.
Welén, 12/14/2021, Randomized Controlled Trial, Sweden, peer-reviewed, 27 authors, study period 15 July, 2020 - 29 May, 2021, average treatment delay 9.5 days, trial NCT04475601 (history).	risk of death, 79.6% lower, RR 0.20, $p = 0.26$, treatment 0 of 29 (0.0%), control 1 of 10 (10.0%), NNT 10.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 31.0% lower, RR 0.69, $p = 1.00$, treatment 2 of 29 (6.9%), control 1 of 10 (10.0%), NNT 32.
	risk of no hospital discharge, 132.6% higher, RR 2.33, $p = 0.03$, treatment 29, control 10, inverted to make RR<1 favor treatment, primary outcome.
	hospitalization time, 50.0% higher, relative time 1.50, $p = 0.01$, treatment 29, control 10.
Zarehoseinzade, 4/30/2021, Randomized Controlled Trial, Iran, peer-reviewed, 5 authors.	risk of death, 75.0% lower, RR 0.25, $p = 0.36$, treatment 1 of 40 (2.5%), control 4 of 40 (10.0%), NNT 13.
	risk of ICU admission, no change, RR 1.00, $p = 1.00$, treatment 1 of 40 (2.5%), control 1 of 40 (2.5%).

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.

Bennani, 8/17/2020, retrospective, Italy, peer-reviewed, 2 authors.	risk of death, 94.9% lower, RR 0.05, $p = 1.00$, treatment 0 of 4 (0.0%), control 18 of 114 (15.8%), NNT 6.3, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 119.2% higher, RR 2.19, $p = 0.40$, treatment 1 of 4 (25.0%), control 13 of 114 (11.4%).
	risk of hospitalization, 25.0% lower, RR 0.75, $p = 0.60$, treatment 2 of 4 (50.0%), control 76 of 114 (66.7%), NNT 6.0.
	risk of severe case, 8.1% lower, RR 0.92, $p = 1.00$, treatment 1 of 4 (25.0%), control 31 of 114 (27.2%), NNT 46.
Cousins, 3/2/2023, retrospective, propensity score matching, USA, peer-reviewed, 2 authors.	risk of death, 18.4% lower, RR 0.82, $p = 0.004$, treatment 390 of 12,504 (3.1%), control 479 of 12,504 (3.8%), NNT 140, odds ratio converted to relative risk, 90 day exposure window, propensity score matching.

	risk of death, 11.6% lower, RR 0.88, $p = 0.04$, treatment 521 of 16,324 (3.2%), control 592 of 16,324 (3.6%), NNT 230, odds ratio converted to relative risk, 180 day exposure window, propensity score matching, primary outcome.
	risk of death, 14.5% lower, RR 0.85, $p = 0.003$, treatment 671 of 20,690 (3.2%), control 783 of 20,690 (3.8%), NNT 185, odds ratio converted to relative risk, 360 day exposure window, propensity score matching.
	risk of mechanical ventilation, 16.7% lower, RR 0.83, $p < 0.001$, treatment 936 of 12,504 (7.5%), control 1,118 of 12,504 (8.9%), NNT 69, odds ratio converted to relative risk, 90 day exposure window, propensity score matching.
	risk of mechanical ventilation, 16.7% lower, RR 0.83, $p < 0.001$, treatment 1,212 of 16,324 (7.4%), control 1,459 of 16,324 (8.9%), NNT 66, odds ratio converted to relative risk, 180 day exposure window, propensity score matching, primary outcome.
	risk of mechanical ventilation, 10.2% lower, RR 0.90, $p < 0.001$, treatment 1,524 of 20,690 (7.4%), control 1,701 of 20,690 (8.2%), NNT 117, odds ratio converted to relative risk, 360 day exposure window, propensity score matching.
Cousins (B), 7/6/2022, retrospective, propensity score matching, USA, peer-reviewed, 10 authors.	risk of mechanical ventilation, 81.0% lower, OR 0.19, $p = 0.006$, treatment 731, control 731, propensity score matching, RR approximated with OR.
	risk of ICU admission, 66.0% lower, OR 0.34, $p = 0.002$, treatment 731, control 731, propensity score matching, RR approximated with OR.
Davidsson, 1/19/2023, retrospective, Sweden, peer-reviewed, 10 authors.	risk of IgG positive, 1.8% lower, RR 0.98, $p = 0.95$, treatment 30 of 224 (13.4%), control 45 of 431 (10.4%), adjusted per study, odds ratio converted to relative risk, multivariable.
Duarte, 11/25/2021, retrospective, Brazil, peer-reviewed, 4 authors.	risk of death, 11.2% lower, RR 0.89, $p = 0.37$, treatment 100 of 156 (64.1%), control 32 of 43 (74.4%), NNT 9.7, adjusted per study, odds ratio converted to relative risk.
Gedeborg, 12/23/2021, retrospective, Sweden, peer-reviewed, 6 authors.	risk of death, 25.0% higher, OR 1.25, $p = 0.11$, treatment 271 of 474 (57.2%) cases, 5,181 of 23,700 (21.9%) controls, case control OR.
Holt, 5/7/2020, retrospective, Denmark, peer-reviewed, median age 70.0, 4 authors, study period 1 March, 2020 - 1 April, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death/ICU, 129.5% higher, RR 2.29, $p < 0.001$, treatment 16 of 31 (51.6%), control 148 of 658 (22.5%).
Ianhez, 9/3/2020, retrospective, Brazil, peer-reviewed, 4 authors.	risk of ICU admission, 79.7% lower, RR 0.20, $p = 0.26$, treatment 1 of 17 (5.9%), control 28 of 357 (7.8%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of hospitalization, 65.7% lower, RR 0.34, $p = 0.32$, treatment 2 of 17 (11.8%), control 64 of 357 (17.9%), adjusted per study,

	odds ratio converted to relative risk, multivariable.
	risk of case, 1.4% higher, RR 1.01, $p = 0.90$, treatment 17 of 571 (3.0%), control 357 of 12,161 (2.9%), unadjusted, total count not provided, estimated from percentage.
Israel, 7/27/2021, retrospective, Israel, peer-reviewed, 10 authors.	**risk of hospitalization, 37.7% lower, OR 0.62, $p = 0.01$**, treatment 30 of 6,530 (0.5%) cases, 240 of 32,650 (0.7%) controls, NNT 18, case control OR.
Jeon, 2/23/2021, retrospective, South Korea, peer-reviewed, 3 authors.	**risk of case, 77.0% lower, OR 0.23, $p = 0.005$**, treatment 6 of 49 (12.2%) cases, 89 of 245 (36.3%) controls, NNT 6.5, case control OR, model 2, within 3 months.
Jiménez-Alcaide, 9/13/2021, retrospective, Spain, peer-reviewed, 9 authors.	**risk of death, 33.0% lower, RR 0.67, $p = 0.41$**, treatment 3 of 11 (27.3%), control 17 of 50 (34.0%), adjusted per study, multivariable.
	risk of progression, 8.0% higher, RR 1.08, $p = 0.77$, treatment 11, control 50, adjusted per study, multivariable.
	risk of case, 68.2% higher, RR 1.68, $p = 0.15$, treatment 11 of 156 (7.1%), control 50 of 1,193 (4.2%), excluded in exclusion analyses: excessive unadjusted differences between groups.
Kazan, 11/1/2021, retrospective, Turkey, peer-reviewed, 10 authors, study period August 2020 - June 2021, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of hospitalization, 229.0% higher, RR 3.29, $p = 0.20$**, treatment 4 of 138 (2.9%), control 2 of 227 (0.9%).
	risk of case, 28.7% lower, RR 0.71, $p = 0.32$, treatment 13 of 138 (9.4%), control 30 of 227 (13.2%), NNT 26.
Klein, 2/1/2021, retrospective, USA, peer-reviewed, 7 authors, study period 12 March, 2020 - 10 June, 2020.	**risk of death, 123.9% higher, RR 2.24, $p = 0.12$**, treatment 6 of 304 (2.0%), control 13 of 1,475 (0.9%).
	risk of case, 6.6% lower, RR 0.93, $p = 0.80$, treatment 17 of 304 (5.6%), control 85 of 1,475 (5.8%), NNT 586, adjusted per study, odds ratio converted to relative risk, multivariable.
Koskinen, 6/29/2020, retrospective, Finland, peer-reviewed, 7 authors.	**risk of death, 45.8% lower, RR 0.54, $p = 1.00$**, treatment 1 of 134 (0.7%), control 3 of 218 (1.4%), NNT 159.
	risk of death/ICU, 45.8% lower, RR 0.54, $p = 1.00$, treatment 1 of 134 (0.7%), control 3 of 218 (1.4%), NNT 159.
	risk of case, 11.3% lower, RR 0.89, $p = 1.00$, treatment 6 of 134 (4.5%), control 11 of 218 (5.0%), NNT 176.
Kwon, 1/29/2021, retrospective, USA, peer-reviewed, 7 authors.	**risk of death, 21.1% lower, RR 0.79, $p = 1.00$**, treatment 1 of 799 (0.1%), control 7 of 4,412 (0.2%), NNT 2985.
	risk of case, 17.6% higher, RR 1.18, $p = 0.54$, treatment 18 of 799 (2.3%), control 79 of 4,412 (1.8%), adjusted per study, odds ratio converted to relative risk, multivariable.
Lazzeri, 9/21/2020, retrospective, Italy, preprint, 11 authors.	**risk of death/ICU, 23.0% higher, OR 1.23, $p = 0.33$**, multivariable, RR approximated with OR.

Lee (B), 3/7/2022, retrospective, USA, peer-reviewed, 14 authors, study period 15 February, 2020 - 15 July, 2020.	**risk of severe case, 21.4% lower, RR 0.79, p = 0.03**, treatment 76 of 295 (25.8%), control 727 of 2,427 (30.0%), NNT 24, adjusted per study, odds ratio converted to relative risk, propensity score weighting, multivariable.
	risk of case, 11.3% lower, RR 0.89, p < 0.001, treatment 295 of 3,057 (9.6%), control 2,427 of 36,096 (6.7%), adjusted per study, odds ratio converted to relative risk, propensity score weighting, multivariable.
Lyon, 1/31/2022, retrospective, USA, peer-reviewed, 8 authors, study period 8 March, 2020 - 15 February, 2021.	**risk of death, 16.9% lower, RR 0.83, p = 0.61**, treatment 15 of 944 (1.6%), control 19 of 994 (1.9%), NNT 310.
	risk of case, 7.2% lower, RR 0.93, p = 0.04, treatment 399 of 944 (42.3%), control 446 of 994 (44.9%), NNT 38, adjusted per study, odds ratio converted to relative risk, multivariable.
MacFadden, 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	**risk of case, 7.0% lower, OR 0.93, p = 0.008**, RR approximated with OR.
Montopoli, 5/6/2020, retrospective, Italy, peer-reviewed, 12 authors.	**risk of death, 95.4% lower, RR 0.05, p = 0.15**, treatment 0 of 5,273 (0.0%), control 18 of 37,161 (0.0%), NNT 2064, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of severe case, 74.5% lower, RR 0.25, p = 0.01, treatment 1 of 5,273 (0.0%), control 31 of 37,161 (0.1%), NNT 1551, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
	risk of case, 75.3% lower, RR 0.25, p = 0.004, treatment 4 of 5,273 (0.1%), control 114 of 37,161 (0.3%), NNT 433, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
Patel, 7/9/2020, retrospective, USA, peer-reviewed, 7 authors, study period 1 March, 2020 - 4 June, 2020.	**risk of death, 55.2% lower, RR 0.45, p = 0.22**, treatment 4 of 22 (18.2%), control 10 of 36 (27.8%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of mechanical ventilation, 69.0% lower, OR 0.31, p = 0.19, treatment 22, control 36, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 77.0% lower, OR 0.23, p = 0.02, treatment 22, control 36, adjusted per study, multivariable, RR approximated with OR.
Schmidt, 11/12/2021, retrospective, USA, peer-reviewed, 42 authors, study period 17 March, 2020 - 11 February, 2021.	**risk of death, 20.4% lower, RR 0.80, p = 0.41**, treatment 25 of 169 (14.8%), control 44 of 308 (14.3%), adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable.
	risk of severe case, 2.0% lower, OR 0.98, p = 0.94, treatment 169, control 308, adjusted per study, propensity score matching, multivariable, RR approximated with OR.

Shah, 5/12/2022, retrospective, USA, peer-reviewed, median age 71.0, 22 authors, study period 1 March, 2020 - 31 May, 2020.	risk of death, 16.0% higher, HR 1.16, $p = 0.59$, treatment 148, control 317.
	risk of mechanical ventilation, 19.0% lower, HR 0.81, $p = 0.73$, treatment 148, control 317.
	risk of severe case, 3.0% higher, HR 1.03, $p = 0.91$, treatment 148, control 317.
	risk of hospitalization, 4.0% lower, HR 0.96, $p = 0.90$, treatment 148, control 317.
Shaw, 7/1/2021, retrospective, USA, peer-reviewed, 10 authors, study period 1 March, 2020 - 15 May, 2020.	risk of case, 6.0% lower, OR 0.94, $p = 0.006$, treatment 47, control 97, adjusted per study, propensity score matching, multivariable, RR approximated with OR.
Welén (B), 12/14/2021, retrospective, Sweden, peer-reviewed, 27 authors, trial NCT04475601 (history).	risk of death, 2.0% lower, HR 0.98, $p = 0.94$, treatment 21 of 358 (5.9%), control 167 of 4,980 (3.4%), adjusted per study, antiandrogen treatment.
	risk of death, 11.0% lower, HR 0.89, $p = 0.66$, treatment 20 of 334 (6.0%), control 167 of 4,980 (3.4%), adjusted per study, ADT.
	risk of death, 151.0% higher, HR 2.51, $p < 0.001$, treatment 24 of 152 (15.8%), control 167 of 4,980 (3.4%), adjusted per study, ADT and abiraterone acetate or enzalutamide.
	risk of ICU admission, 28.0% higher, HR 1.28, $p = 0.28$, treatment 24 of 358 (6.7%), control 216 of 4,980 (4.3%), adjusted per study, antiandrogen treatment.
	risk of ICU admission, 13.0% lower, HR 0.87, $p = 0.62$, treatment 16 of 334 (4.8%), control 216 of 4,980 (4.3%), adjusted per study, ADT.
	risk of ICU admission, 21.0% lower, HR 0.79, $p = 0.60$, treatment 6 of 152 (3.9%), control 216 of 4,980 (4.3%), adjusted per study, ADT and abiraterone acetate or enzalutamide.
	risk of hospitalization, 23.0% higher, HR 1.23, $p = 0.09$, treatment 126 of 358 (35.2%), control 1,108 of 4,980 (22.2%), adjusted per study, antiandrogen treatment.
	risk of hospitalization, 24.0% higher, HR 1.24, $p = 0.09$, treatment 126 of 334 (37.7%), control 1,108 of 4,980 (22.2%), adjusted per study, ADT.
	risk of hospitalization, 40.0% higher, HR 1.40, $p = 0.06$, treatment 66 of 152 (43.4%), control 1,108 of 4,980 (22.2%), adjusted per study, ADT and abiraterone acetate or enzalutamide.

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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