Aspirin for COVID-19: real-time meta analysis of 72 studies

@CovidAnalysis, April 2024, Version 61
https://c19early.org/emeta.html

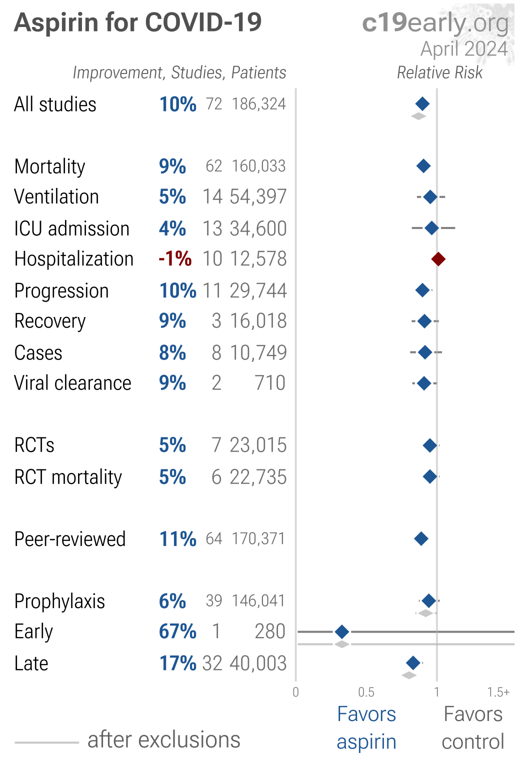
Abstract

Statistically significant lower risk is seen for mortality and progression. 28 studies from 26 independent teams in 11 countries show statistically significant improvements.

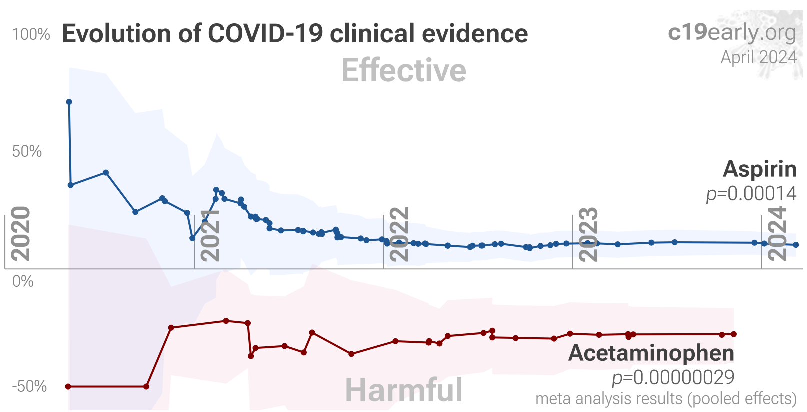
Meta analysis using the most serious outcome reported shows 10% [5-15%] lower risk. Results are similar for higher quality and peer-reviewed studies and worse for Randomized Controlled Trials. Early treatment is more effective than late treatment.

Studies to date do not show a significant benefit for mechanical ventilation and ICU admission. Benefit may be more likely without coadministered anticoagulants. The RECOVERY RCT shows 4% [-4-11%] lower mortality for all patients, however when restricting to non-LMWH patients there was 17% [-4-34%] improvement, comparable with the mortality results of all studies, 9% [4-15%], and the 16% improvement in the REMAP-CAP RCT.

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 are significantly more effective.



All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with aspirin for mortality Banaser, Baral, Srinivasan and mechanical ventilation Banaser.



HIGHLIGHTS

Aspirin reduces risk for COVID-19 with very high confidence for mortality, progression, and in pooled analysis, low confidence for recovery and viral clearance, and very low confidence for cases. Benefit may be more likely without coadministered anticoagulants.

19th treatment shown effective with ≥3 clinical studies in March 2021, now with p = 0.00014 from 72 studies, and recognized in 2 countries.

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

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 69 treatments.

72 aspirin COVID-19 studies

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Connors (DB RCT)	67%	0.33 [0.01-7.96]	hosp.	0/144	1/136
Early treatment	67%	0.33 [0.01-7.96]		0/144	1/136

Tau^2 = 0.00, I^2 = 0.0%, p = 0.5

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Goshua (PSM)	35%	0.65 [0.42-0.98]	death	319 (n)	319 (n)
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Mura (PSM)	15%	0.85 [0.69-1.01]	death	527 (n)	527 (n)
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Aidouni (ICU)	31%	0.69 [0.54-0.88]	death	202/712	165/412
Singla (RCT)	57%	0.43 [0.04-3.27]	death	3/49	5/49
Shamsi	96%	0.04 [0.00-7.20]	death	0/13	24/170
Mehrizi	16%	0.84 [0.82-0.86]	death	population-based cohort	
Lewandowski	-70%	1.70 [1.08-2.70]	death	430 (all patients)	
Late treatment	17%	0.83 [0.77-0.90]		1,202/16,729	1,907/22,844

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Reese (PSM)	-61%	1.61 [1.31-1.99]	death	4,921 (n)	4,921 (n)
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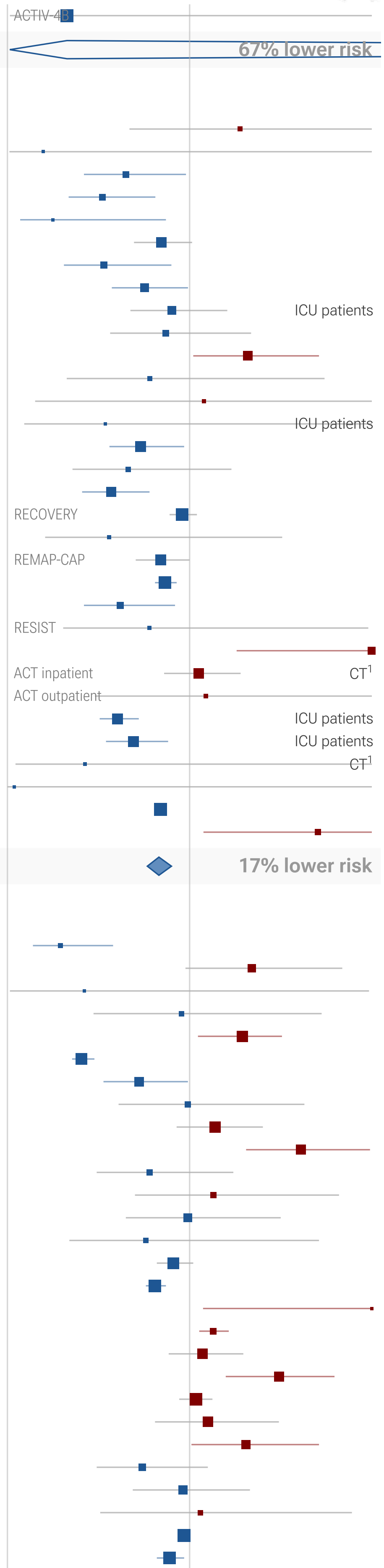

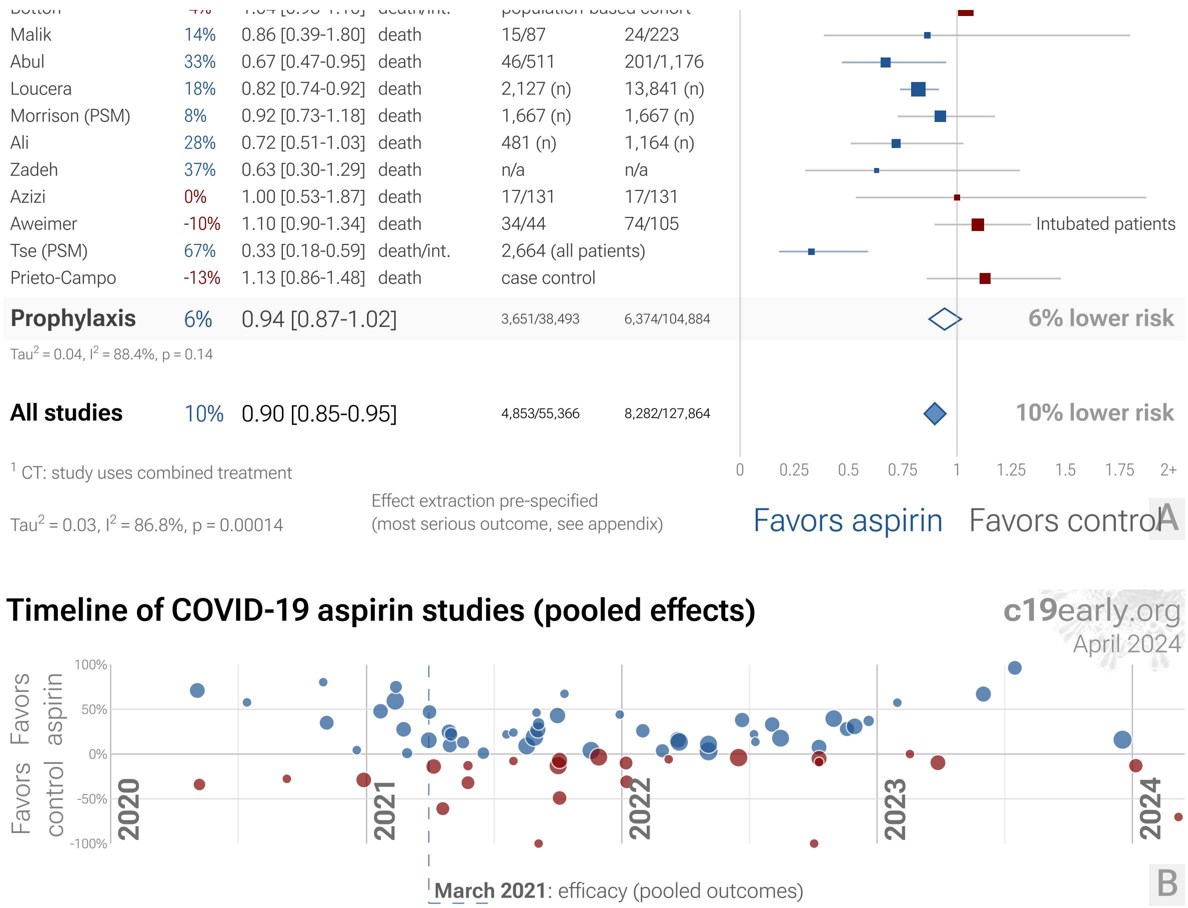

Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in aspirin studies.** The marked date indicates the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes.

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 *Duloquin, Hampshire, Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

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

Analysis. We analyze all significant controlled studies of aspirin 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.

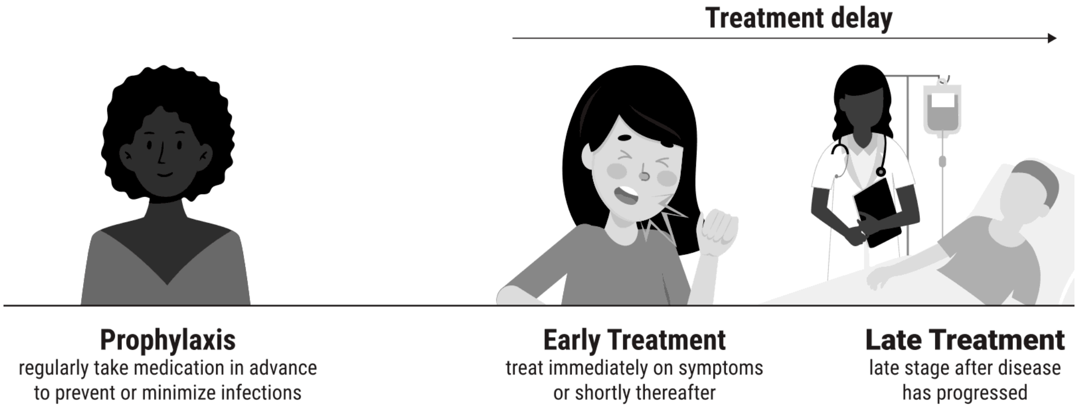

Figure 2. Treatment stages.

Preclinical Research

An *In Vitro* study supports the efficacy of aspirin [Geiger].

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 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 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	**10%** [5-15%] ***	72	186,324	1,037
After exclusions	**13%** [8-18%] ****	63	180,001	950
Peer-reviewed studies	**11%** [6-16%] ****	64	170,371	923
Randomized Controlled Trials	**5%** [-2-11%]	7	23,015	201
Mortality	**9%** [4-15%] ***	62	160,033	915
Ventilation	**5%** [-6-14%]	14	54,397	180
ICU admission	**4%** [-13-18%]	13	34,600	192
Hospitalization	**-1%** [-6-4%]	10	12,578	128
Recovery	**9%** [-1-18%]	3	16,018	78
Cases	**8%** [-4-19%]	8	10,749	75
Viral	**9%** [-0-17%]	2	710	16
RCT mortality	**5%** [-2-11%]	6	22,735	174

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. * $p<0.05$ **** $p<0.0001$.

	Early treatment	Late treatment	Prophylaxis
All studies	**67%** [-696-99%]	**17%** [10-23%] ****	**6%** [-2-13%]
After exclusions	**67%** [-696-99%]	**20%** [14-25%] ****	**8%** [0-15%] *
Peer-reviewed studies	**67%** [-696-99%]	**18%** [11-24%] ****	**6%** [-1-13%]
Randomized Controlled Trials	**67%** [-696-99%]	**5%** [-2-11%]	
Mortality		**17%** [10-23%] ****	**3%** [-7-11%]
Ventilation		**5%** [-19-24%]	**2%** [-2-7%]
ICU admission		**0%** [-65-40%]	**4%** [-15-19%]
Hospitalization	**67%** [-696-99%]	**17%** [-19-42%]	**-1%** [-7-4%]
Recovery		**9%** [-1-18%]	
Cases			**8%** [-4-19%]
Viral		**-2%** [-61-36%]	**10%** [0-18%] *
RCT mortality		**5%** [-2-11%]	

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. * $p<0.05$ **** $p<0.0001$.

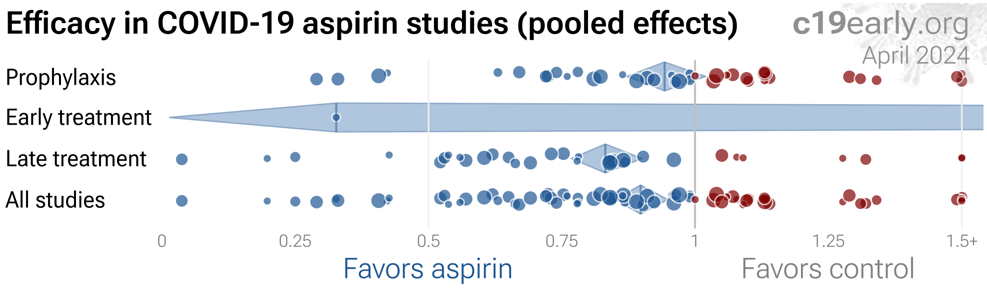

Figure 3. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

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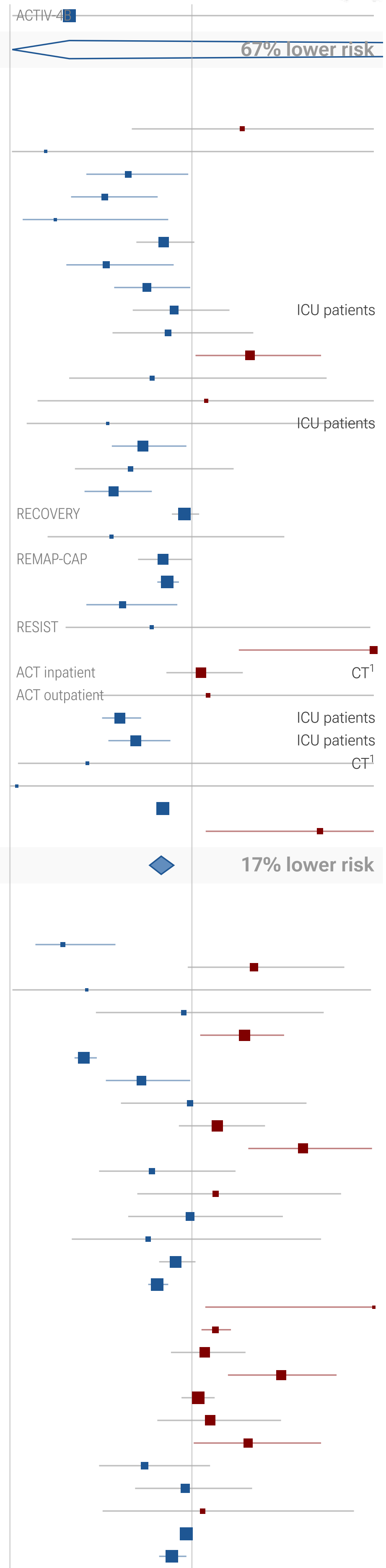

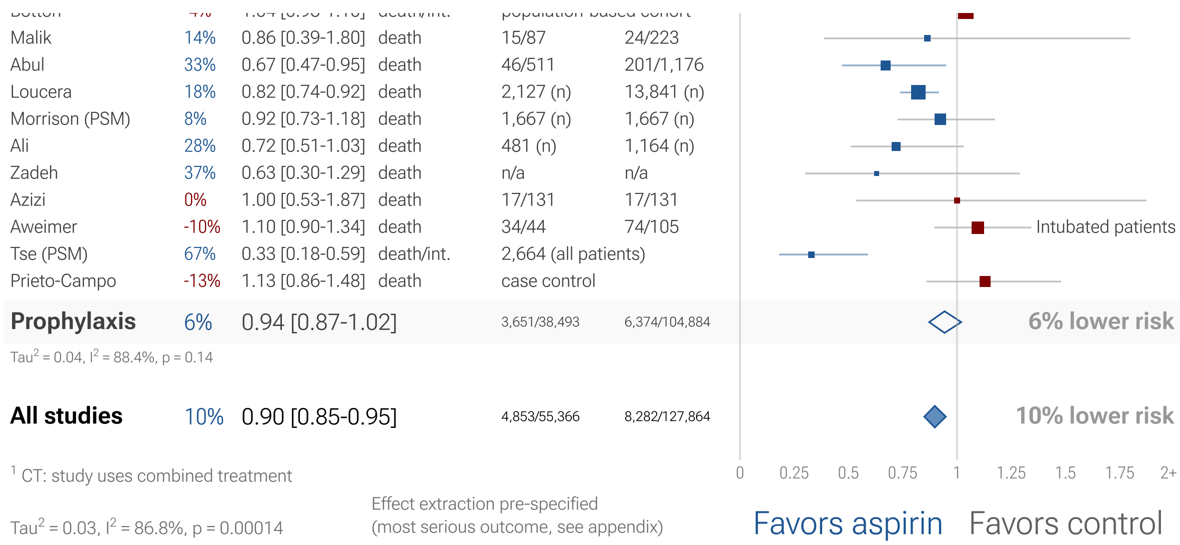

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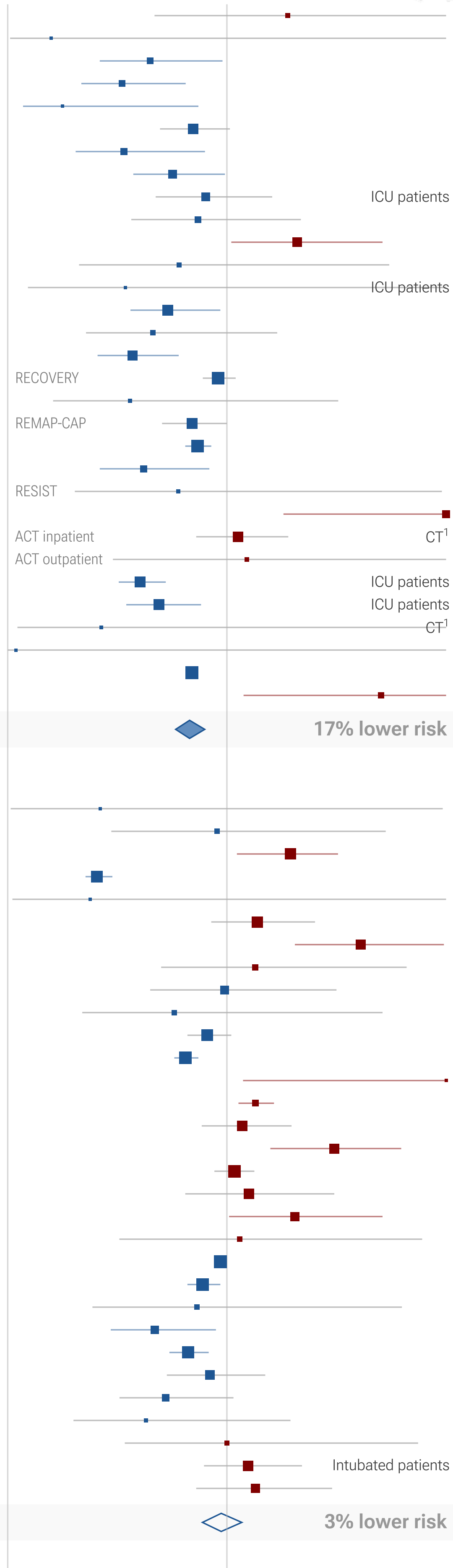
Bradbury (RCT)	16%	0.84 [0.70-1.00]	165/563	170/521
Chow (PSW)	13%	0.87 [0.81-0.93]	population-based cohort	
Santoro (PSM)	38%	0.62 [0.42-0.92]	360 (n)	2,949 (n)
Ghati (RCT)	22%	0.78 [0.31-1.98]	11/442	7/219
Karimpour-Razke..	-123%	2.23 [1.26-3.38]	39/90	64/363
Eikelboom (RCT)	-5%	1.05 [0.86-1.28]	193/1,063	186/1,056
Eikelboom (RCT)	-9%	1.09 [0.48-2.46]	12/1,945	11/1,936
Ali (ICU)	40%	0.60 [0.51-0.72]	152/660	202/530
Aidouni (ICU)	31%	0.69 [0.54-0.88]	202/712	165/412
Singla (RCT)	57%	0.43 [0.04-3.27]	3/49	5/49
Shamsi	96%	0.04 [0.00-7.20]	0/13	24/170
Mehrizi	16%	0.84 [0.82-0.86]	population-based cohort	
Lewandowski	-70%	1.70 [1.08-2.70]	430 (all patients)	
Late treatment	17%	0.83 [0.77-0.90]	1,191/16,698	1,901/22,808

Tau[2] = 0.02, I[2] = 78.1%, p < 0.0001

	Improvement, RR [CI]		Treatment	Control
Wang	58%	0.42 [0.01-1.98]	1/9	13/49
Yuan	4%	0.96 [0.47-1.72]	11/52	29/131
Ramos-Rincón	-29%	1.29 [1.05-1.51]	132/264	253/526
Osborne (PSM)	59%	0.41 [0.35-0.48]	272/6,300	661/6,300
Merzon	62%	0.38 [0.02-4.94]	1/21	6/91
Mulhem	-14%	1.14 [0.93-1.40]	300/1,354	216/1,865
Reese (PSM)	-61%	1.61 [1.31-1.99]	4,921 (n)	4,921 (n)
Pan	-13%	1.13 [0.70-1.82]	239 (n)	523 (n)
Oh	1%	0.99 [0.65-1.50]	n/a	n/a
Son (PSM)	24%	0.76 [0.34-1.71]	case control	
Ma (PSM)	9%	0.91 [0.82-1.02]		
Chow (PSM)	19%	0.81 [0.76-0.87]	1,280/6,781	2,271/10,566
Kim (PSM)	-700%	8.00 [1.07-59.6]	6/15	1/20
Basheer	-13%	1.13 [1.05-1.21]	45/140	29/250
Sisinni	-7%	1.07 [0.89-1.29]	93/253	251/731
Pérez-Segura	-49%	1.49 [1.20-1.80]	66/155	183/608
Formiga (PSM)	-3%	1.03 [0.94-1.13]	1,000/3,291	874/2,885
Sullerot (PSW)	-10%	1.10 [0.81-1.49]	101/301	224/746
Monserrat .. (PSM)	-31%	1.31 [1.01-1.71]	n/a	n/a
Gogtay	-6%	1.06 [0.51-1.89]	12/38	21/87
Campbell (PSW)	3%	0.97 [0.95-1.00]	419 (n)	20,311 (n)
Lal	11%	0.89 [0.82-0.97]	4,691 (n)	16,888 (n)
Malik	14%	0.86 [0.39-1.80]	15/87	24/223
Abul	33%	0.67 [0.47-0.95]	46/511	201/1,176
Loucera	18%	0.82 [0.74-0.92]	2,127 (n)	13,841 (n)
Morrison (PSM)	8%	0.92 [0.73-1.18]	1,667 (n)	1,667 (n)
Ali	28%	0.72 [0.51-1.03]	481 (n)	1,164 (n)
Zadeh	37%	0.63 [0.30-1.29]	n/a	n/a
Azizi	0%	1.00 [0.53-1.87]	17/131	17/131
Aweimer	-10%	1.10 [0.90-1.34]	34/44	74/105
Prieto-Campo	-13%	1.13 [0.86-1.48]	case control	
Prophylaxis	3%	0.97 [0.89-1.07]	3,432/34,292	5,348/85,805

Tau[2] = 0.04, I[2] = 89.3%, p = 0.59



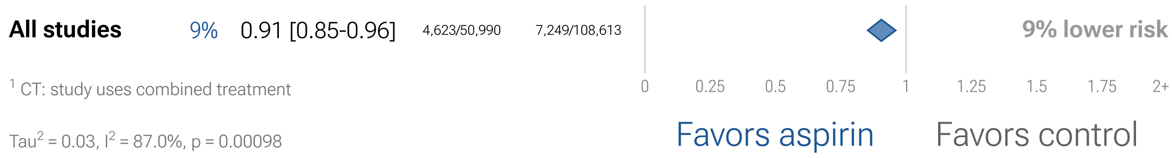


Figure 5. Random effects meta-analysis for mortality results.

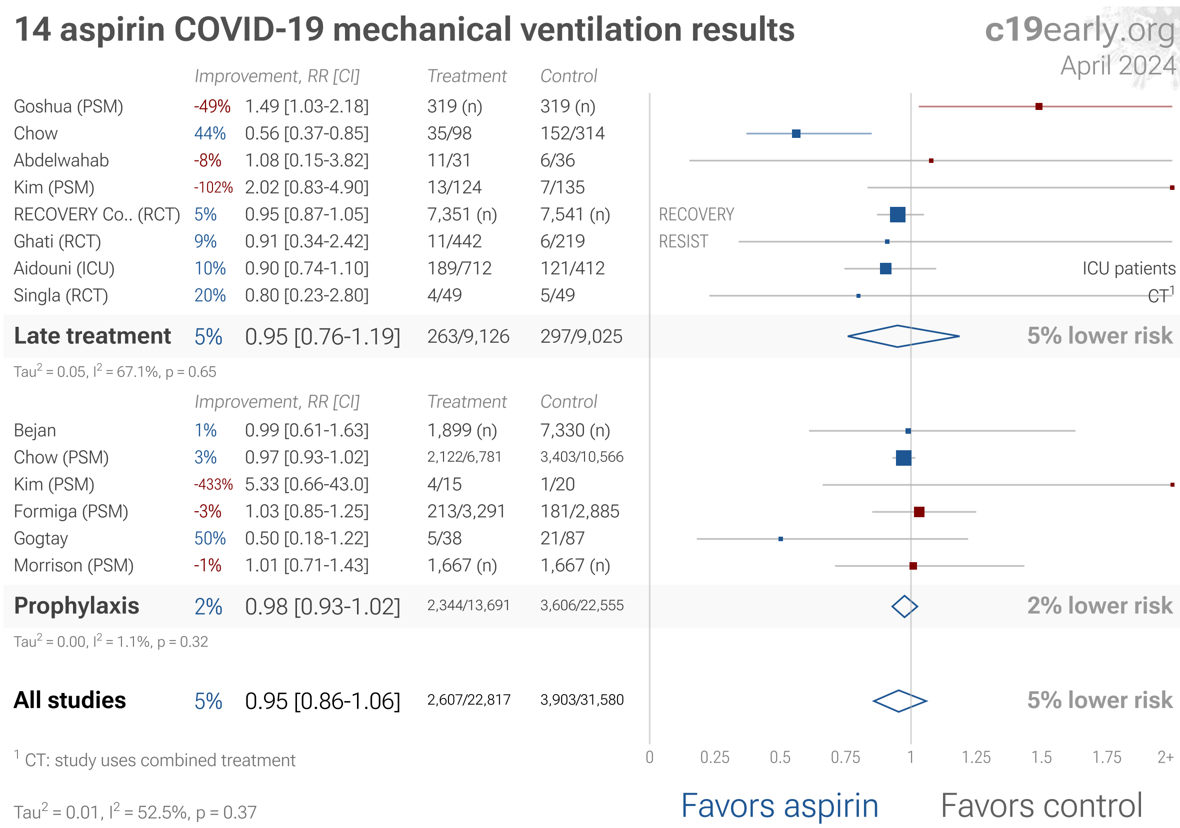


Figure 6. Random effects meta-analysis for ventilation.

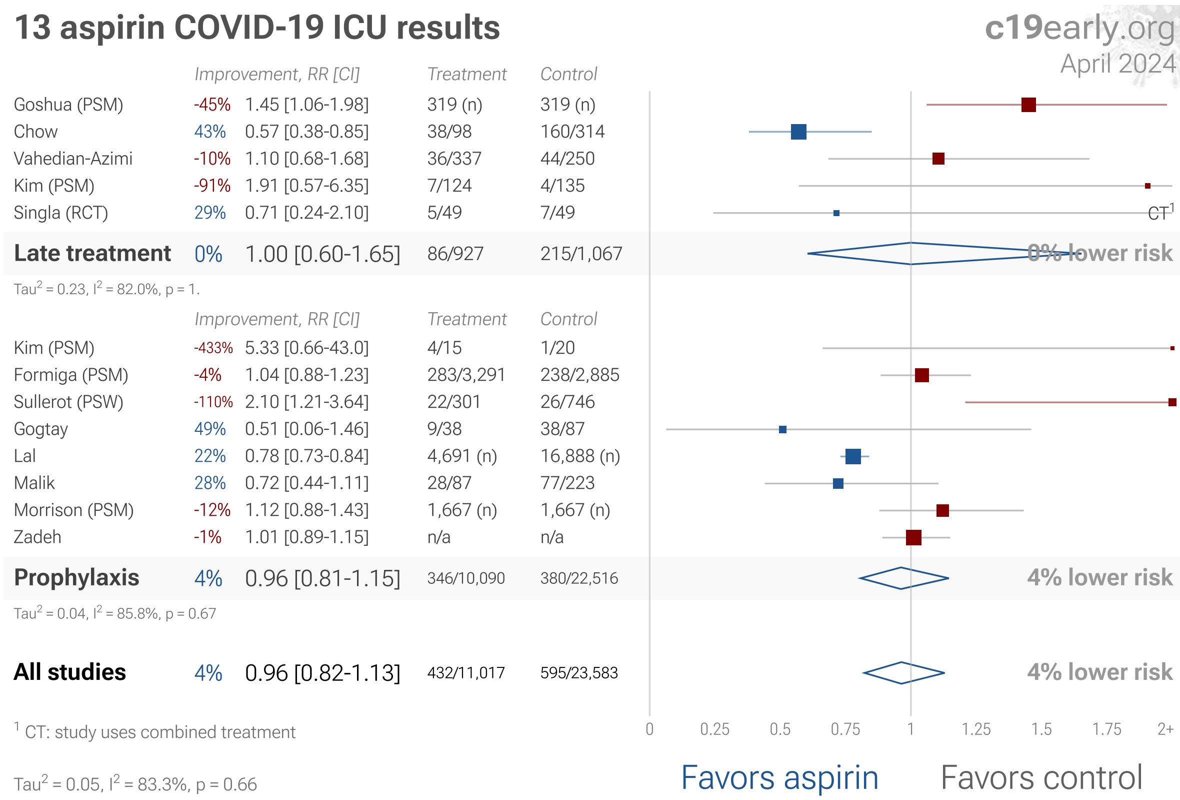


Figure 7. Random effects meta-analysis for ICU admission.

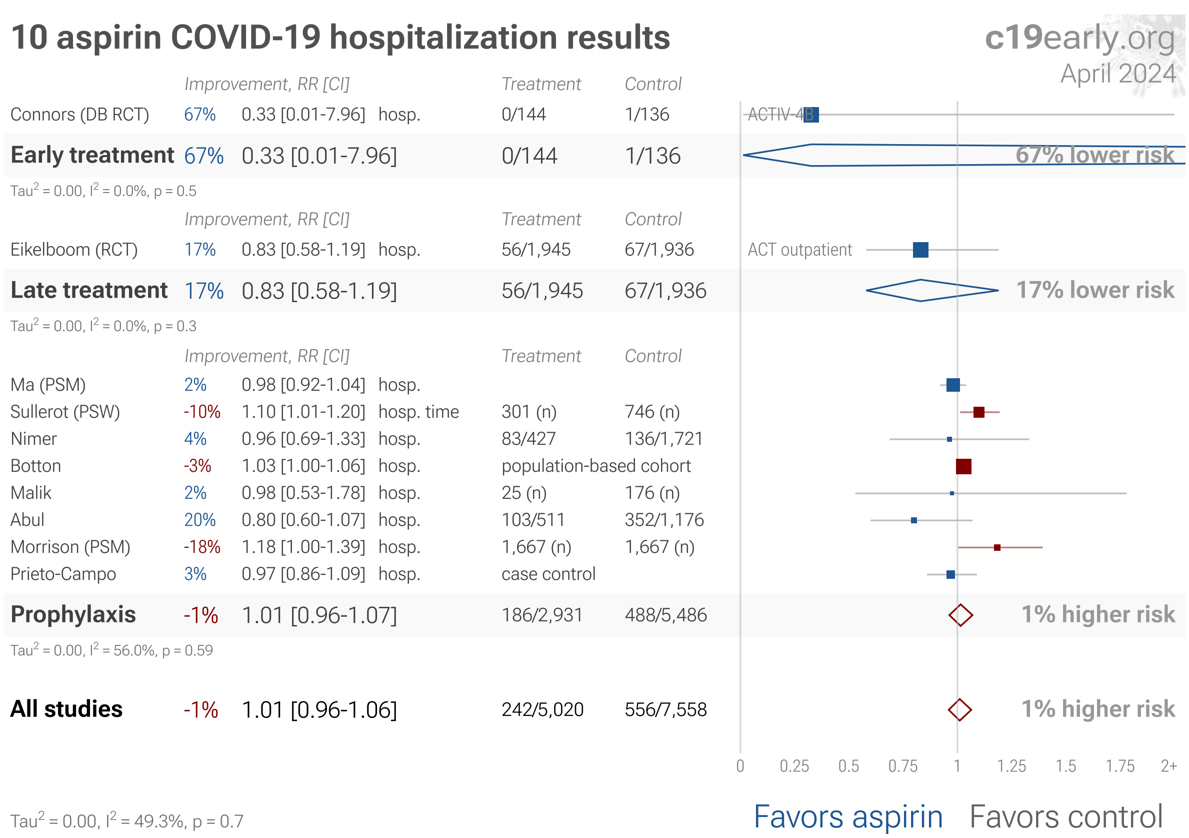


Figure 8. Random effects meta-analysis for hospitalization.

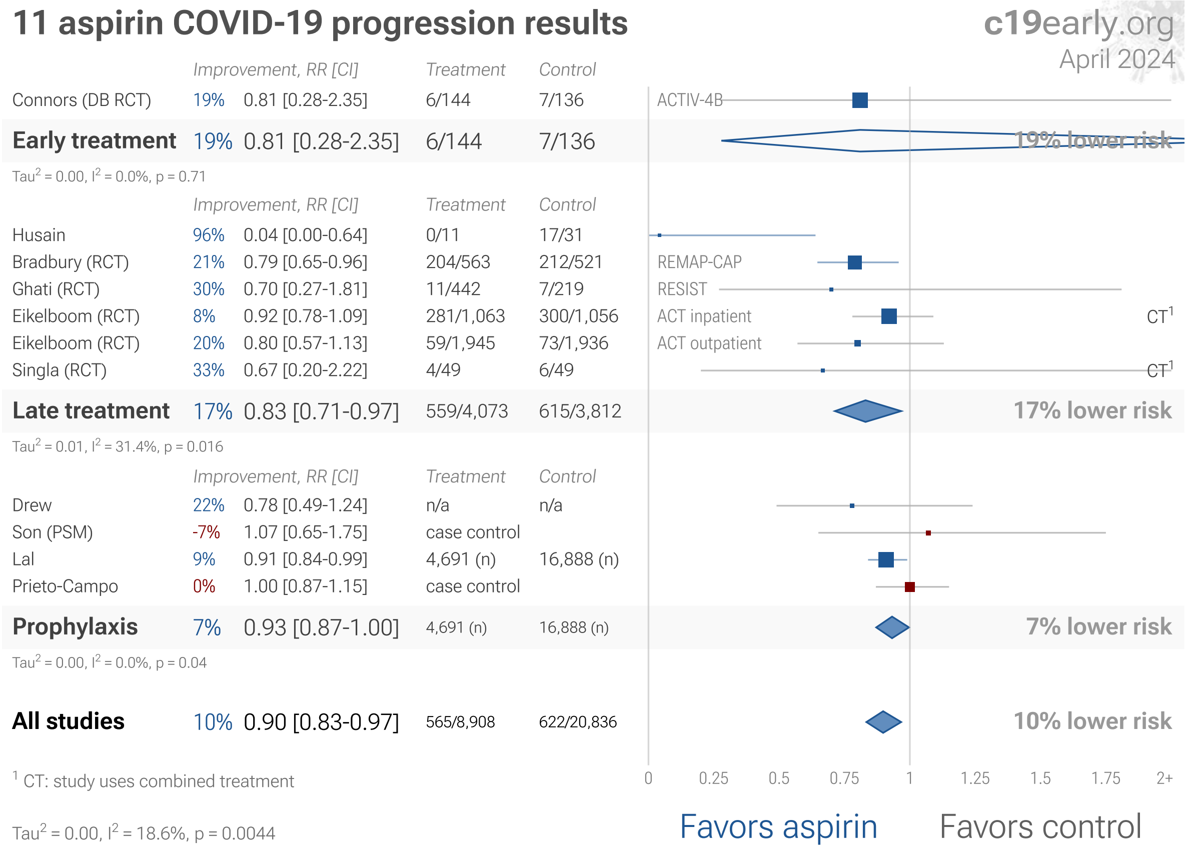


Figure 9. Random effects meta-analysis for progression.

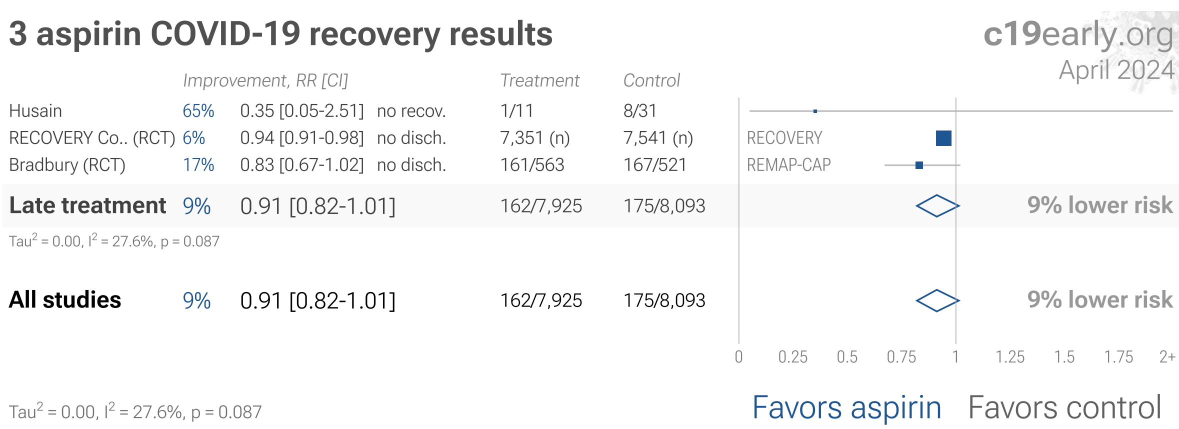


Figure 10. Random effects meta-analysis for recovery.

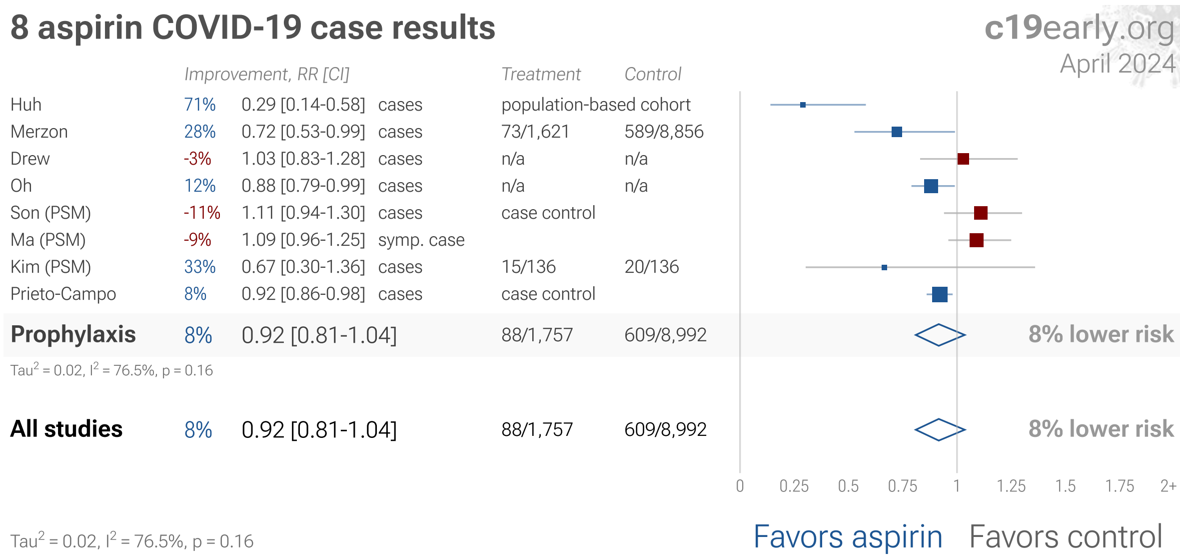


Figure 11. Random effects meta-analysis for cases.

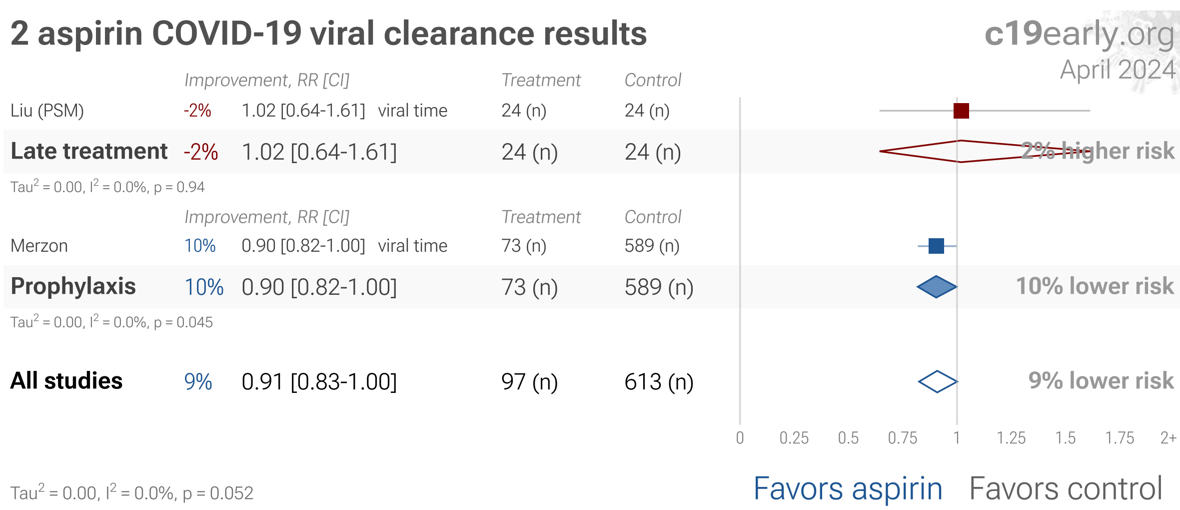


Figure 12. Random effects meta-analysis for viral clearance.

64 aspirin COVID-19 peer reviewed studies

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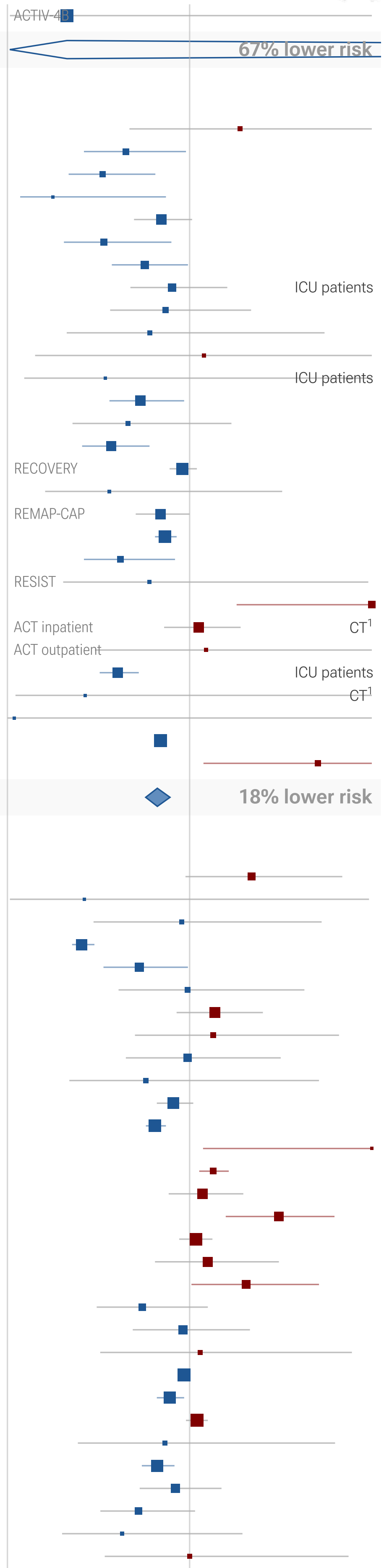
Study	Improvement	RR [CI]	Outcome	Treatment	Control	Notes
Connors (DB RCT)	67%	0.33 [0.01-7.96]	hosp.	0/144	1/136	ACTIV-4B
Early treatment	**67%**	**0.33 [0.01-7.96]**		**0/144**	**1/136**	**67% lower risk**
Tau^2 = 0.00, I^2 = 0.0%, p = 0.5						
	Improvement, RR [CI]			*Treatment*	*Control*	
Alamdari	-28%	1.28 [0.67-2.43]	death	9/53	54/406	
Goshua (PSM)	35%	0.65 [0.42-0.98]	death	319 (n)	319 (n)	
Meizlish (PSM)	48%	0.52 [0.34-0.81]	death	319 (n)	319 (n)	
Liu (PSM)	75%	0.25 [0.07-0.87]	death	2/28	11/204	
Mura (PSM)	15%	0.85 [0.69-1.01]	death	527 (n)	527 (n)	
Chow	47%	0.53 [0.31-0.90]	death	26/98	73/314	
Haji Aghajani	25%	0.75 [0.57-0.99]	death	336 (n)	655 (n)	
Elhadi (ICU)	10%	0.90 [0.67-1.21]	death	22/40	259/425	ICU patients
Sahai (PSM)	13%	0.87 [0.56-1.34]	death	33/248	38/248	
Vahedian-Azimi	22%	0.78 [0.33-1.74]	death	13/337	28/250	
Abdelwahab	-8%	1.08 [0.15-3.82]	ventilation	11/31	6/36	
Karruli (ICU)	46%	0.54 [0.09-3.13]	death	1/5	22/27	ICU patients
Al Harthi (PSM)	27%	0.73 [0.56-0.97]	death	98/176	107/173	
Kim (PSM)	34%	0.66 [0.36-1.23]	death	14/124	23/135	
Zhao	43%	0.57 [0.41-0.78]	death	121/473	140/473	
RECOVERY Co.. (RCT)	4%	0.96 [0.89-1.04]	death	7,351 (n)	7,541 (n)	RECOVERY
Mustafa	44%	0.56 [0.21-1.51]	death	4/66	41/378	
Bradbury (RCT)	16%	0.84 [0.70-1.00]	death	165/563	170/521	REMAP-CAP
Chow (PSW)	13%	0.87 [0.81-0.93]	death	population-based cohort		
Santoro (PSM)	38%	0.62 [0.42-0.92]	death	360 (n)	2,949 (n)	
Ghati (RCT)	22%	0.78 [0.31-1.98]	death	11/442	7/219	RESIST
Karimpour-Razke..	-123%	2.23 [1.26-3.38]	death	39/90	64/363	
Eikelboom (RCT)	-5%	1.05 [0.86-1.28]	death	193/1,063	186/1,056	ACT inpatient, CT[1]
Eikelboom (RCT)	-9%	1.09 [0.48-2.46]	death	12/1,945	11/1,936	ACT outpatient
Ali (ICU)	40%	0.60 [0.51-0.72]	death	152/660	202/530	ICU patients
Singla (RCT)	57%	0.43 [0.04-3.27]	death	3/49	5/49	CT[1]
Shamsi	96%	0.04 [0.00-7.20]	death	0/13	24/170	
Mehrizi	16%	0.84 [0.82-0.86]	death	population-based cohort		
Lewandowski	-70%	1.70 [1.08-2.70]	death	430 (all patients)		
Late treatment	**18%**	**0.82 [0.76-0.89]**		**929/15,716**	**1,471/20,223**	**18% lower risk**
Tau^2 = 0.02, I^2 = 75.9%, p < 0.0001						
	Improvement, RR [CI]			*Treatment*	*Control*	
Holt	-34%	1.34 [0.98-1.84]	death/ICU	35/116	129/573	
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49	
Yuan	4%	0.96 [0.47-1.72]	death	11/52	29/131	
Osborne (PSM)	59%	0.41 [0.35-0.48]	death	272/6,300	661/6,300	
Merzon	28%	0.72 [0.53-0.99]	cases	73/1,621	589/8,856	
Bejan	1%	0.99 [0.61-1.63]	ventilation	1,899 (n)	7,330 (n)	
Mulhem	-14%	1.14 [0.93-1.40]	death	300/1,354	216/1,865	
Pan	-13%	1.13 [0.70-1.82]	death	239 (n)	523 (n)	
Oh	1%	0.99 [0.65-1.50]	death	n/a	n/a	
Son (PSM)	24%	0.76 [0.34-1.71]	death	case control		
Ma (PSM)	9%	0.91 [0.82-1.02]	death			
Chow (PSM)	19%	0.81 [0.76-0.87]	death	1,280/6,781	2,271/10,566	
Kim (PSM)	-700%	8.00 [1.07-59.6]	death	6/15	1/20	
Basheer	-13%	1.13 [1.05-1.21]	death	45/140	29/250	
Sisinni	-7%	1.07 [0.89-1.29]	death	93/253	251/731	
Pérez-Segura	-49%	1.49 [1.20-1.80]	death	66/155	183/608	
Formiga (PSM)	-3%	1.03 [0.94-1.13]	death	1,000/3,291	874/2,885	
Sullerot (PSW)	-10%	1.10 [0.81-1.49]	death	101/301	224/746	
Monserrat .. (PSM)	-31%	1.31 [1.01-1.71]	death	n/a	n/a	
Levy	26%	0.74 [0.49-1.10]	death/hosp.	29/159	178/690	
Nimer	4%	0.96 [0.69-1.33]	hosp.	83/427	136/1,721	
Gogtay	-6%	1.06 [0.51-1.89]	death	12/38	21/87	
Campbell (PSW)	3%	0.97 [0.95-1.00]	death	419 (n)	20,311 (n)	
Lal	11%	0.89 [0.82-0.97]	death	4,691 (n)	16,888 (n)	
Botton	-4%	1.04 [0.98-1.10]	death/int.	population-based cohort		
Malik	14%	0.86 [0.39-1.80]	death	15/87	24/223	
Loucera	18%	0.82 [0.74-0.92]	death	2,127 (n)	13,841 (n)	
Morrison (PSM)	8%	0.92 [0.73-1.18]	death	1,667 (n)	1,667 (n)	
Ali	28%	0.72 [0.51-1.03]	death	481 (n)	1,164 (n)	
Zadeh	37%	0.63 [0.30-1.29]	death	n/a	n/a	
Azizi	0%	1.00 [0.53-1.87]	death	17/131	17/131	
Aweimer	-10%	1.10 [0.90-1.34]	death	34/44	74/105	Intubated patients



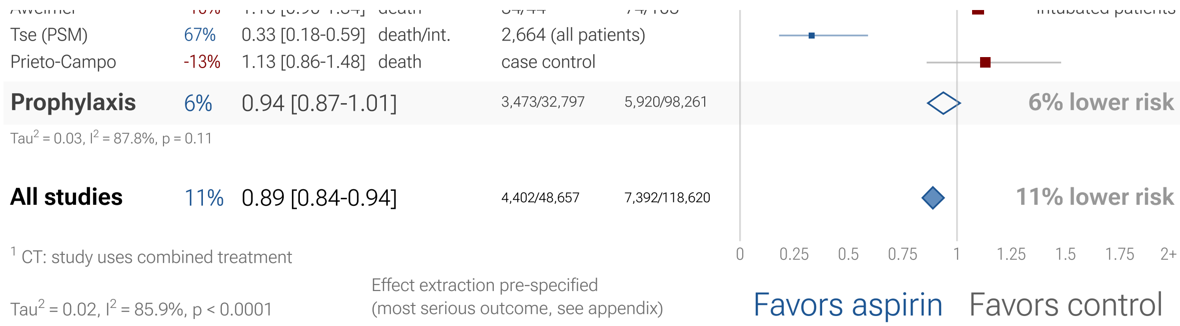


Figure 13. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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 14 shows a comparison of results for RCTs and non-RCT studies. Figure 15 and 16 show forest plots for random effects meta-analysis of all Randomized Controlled Trials and RCT mortality results. RCT results are included in Table 1 and Table 2.

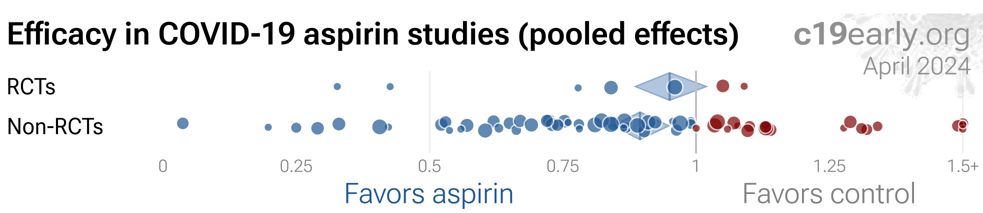


Figure 14. **Results for RCTs and non-RCT studies.**

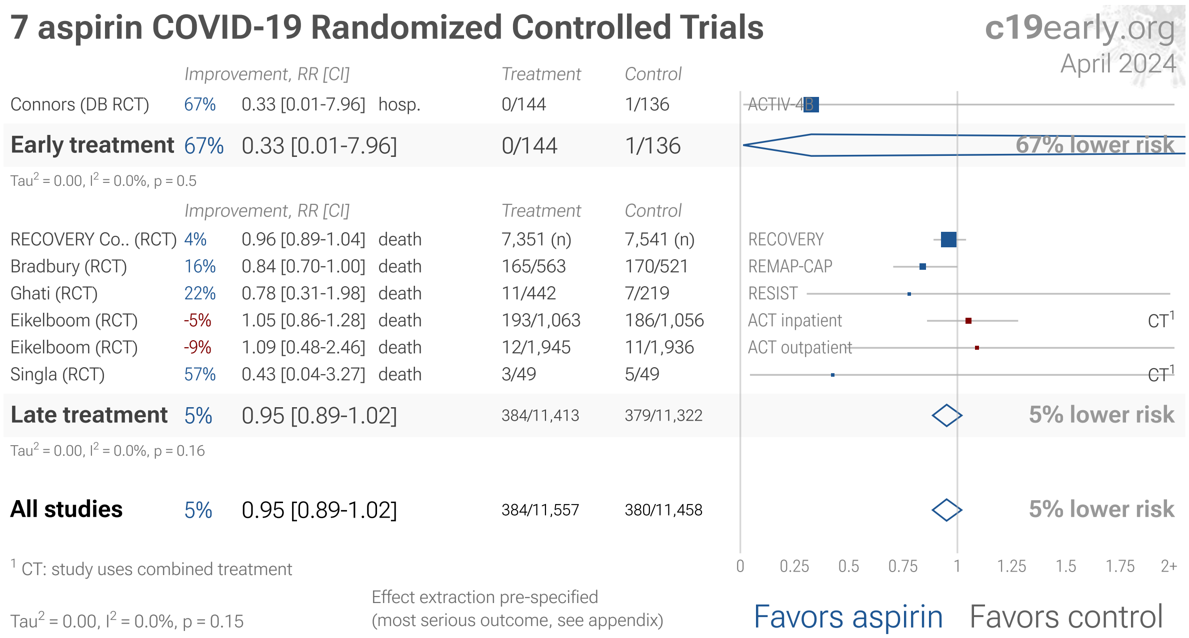


Figure 15. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

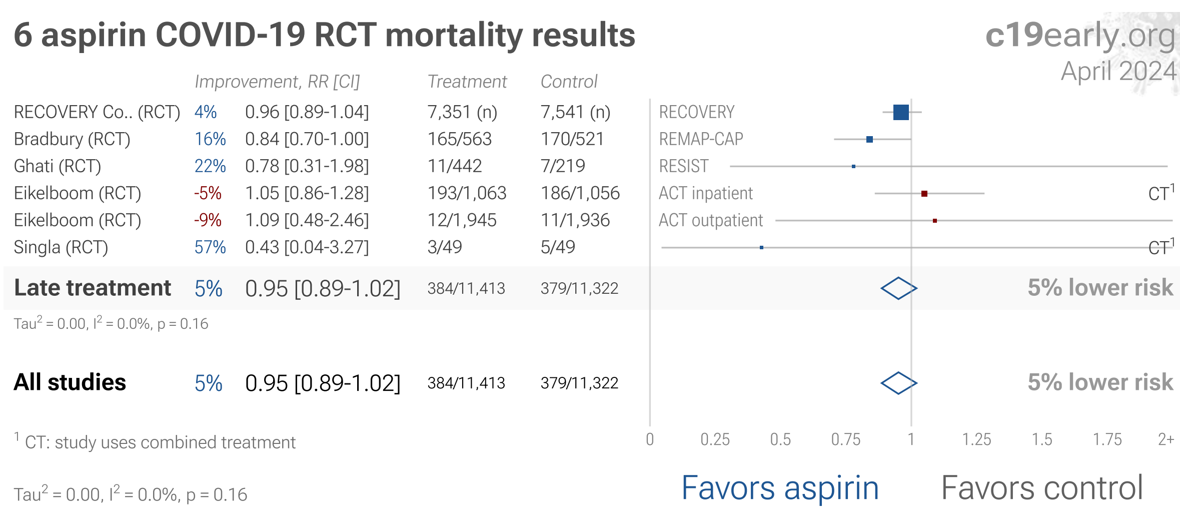


Figure 16. **Random effects meta-analysis for RCT mortality results.**

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

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

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 69 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.

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for aspirin are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

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

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

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

Exclusions

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

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

Alamdari, substantial unadjusted confounding by indication likely.

Aweimer, unadjusted results with no group details.

Azizi, age matching based on only two categories, matching may be very poor given the relationship between age and COVID-19 risk; inconsistent data.

Elhadi, unadjusted results with no group details.

Holt, unadjusted results with no group details.

Karimpour-Razkenari, substantial unadjusted confounding by indication likely.

Mulhem, substantial unadjusted confounding by indication likely; substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.

Mustafa, unadjusted results with no group details.

Shamsi, unadjusted results with no group details.

63 aspirin COVID-19 studies after exclusions

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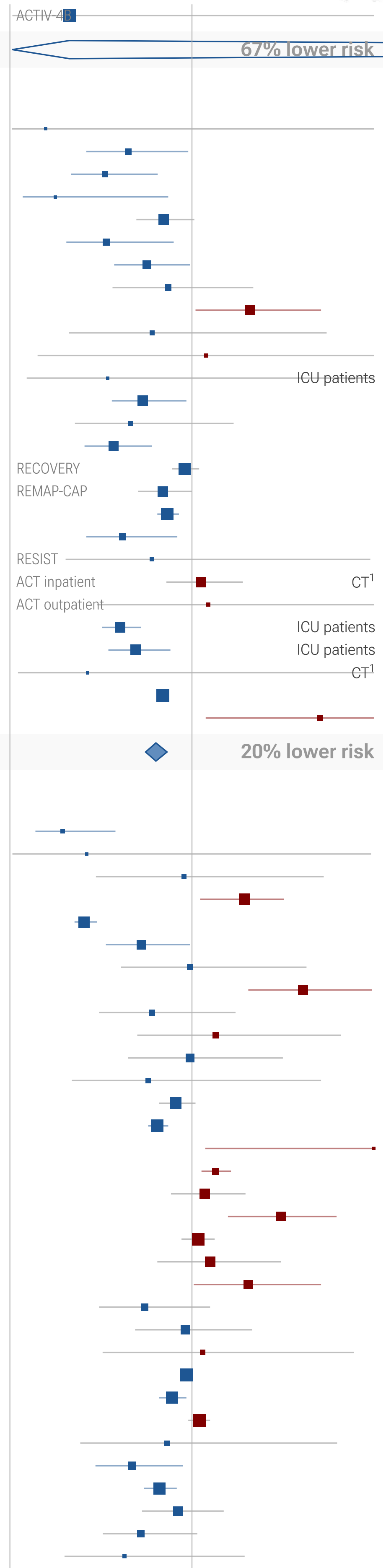
	Improvement, RR [CI]			Treatment	Control
Connors (DB RCT)	67%	0.33 [0.01-7.96]	hosp.	0/144	1/136
Early treatment	**67%**	**0.33 [0.01-7.96]**		**0/144**	**1/136**

Tau^2 = 0.00, I^2 = 0.0%, p = 0.5

	Improvement, RR [CI]			Treatment	Control
Husain	80%	0.20 [0.01-3.55]	death	0/11	3/31
Goshua (PSM)	35%	0.65 [0.42-0.98]	death	319 (n)	319 (n)
Meizlish (PSM)	48%	0.52 [0.34-0.81]	death	319 (n)	319 (n)
Liu (PSM)	75%	0.25 [0.07-0.87]	death	2/28	11/204
Mura (PSM)	15%	0.85 [0.69-1.01]	death	527 (n)	527 (n)
Chow	47%	0.53 [0.31-0.90]	death	26/98	73/314
Haji Aghajani	25%	0.75 [0.57-0.99]	death	336 (n)	655 (n)
Sahai (PSM)	13%	0.87 [0.56-1.34]	death	33/248	38/248
Pourhoseingholi	-32%	1.32 [1.02-1.71]	death	71/290	268/2,178
Vahedian-Azimi	22%	0.78 [0.33-1.74]	death	13/337	28/250
Abdelwahab	-8%	1.08 [0.15-3.82]	ventilation	11/31	6/36
Karruli (ICU)	46%	0.54 [0.09-3.13]	death	1/5	22/27
Al Harthi (PSM)	27%	0.73 [0.56-0.97]	death	98/176	107/173
Kim (PSM)	34%	0.66 [0.36-1.23]	death	14/124	23/135
Zhao	43%	0.57 [0.41-0.78]	death	121/473	140/473
RECOVERY Co.. (RCT)	4%	0.96 [0.89-1.04]	death	7,351 (n)	7,541 (n)
Bradbury (RCT)	16%	0.84 [0.70-1.00]	death	165/563	170/521
Chow (PSW)	13%	0.87 [0.81-0.93]	death	population-based cohort	
Santoro (PSM)	38%	0.62 [0.42-0.92]	death	360 (n)	2,949 (n)
Ghati (RCT)	22%	0.78 [0.31-1.98]	death	11/442	7/219
Eikelboom (RCT)	-5%	1.05 [0.86-1.28]	death	193/1,063	186/1,056
Eikelboom (RCT)	-9%	1.09 [0.48-2.46]	death	12/1,945	11/1,936
Ali (ICU)	40%	0.60 [0.51-0.72]	death	152/660	202/530
Aidouni (ICU)	31%	0.69 [0.54-0.88]	death	202/712	165/412
Singla (RCT)	57%	0.43 [0.04-3.27]	death	3/49	5/49
Mehrizi	16%	0.84 [0.82-0.86]	death	population-based cohort	
Lewandowski	-70%	1.70 [1.08-2.70]	death	430 (all patients)	
Late treatment	**20%**	**0.80 [0.75-0.86]**		**1,128/16,467**	**1,465/21,102**

Tau^2 = 0.01, I^2 = 72.7%, p < 0.0001

	Improvement, RR [CI]			Treatment	Control
Huh	71%	0.29 [0.14-0.58]	cases	population-based cohort	
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49
Yuan	4%	0.96 [0.47-1.72]	death	11/52	29/131
Ramos-Rincón	-29%	1.29 [1.05-1.51]	death	132/264	253/526
Osborne (PSM)	59%	0.41 [0.35-0.48]	death	272/6,300	661/6,300
Merzon	28%	0.72 [0.53-0.99]	cases	73/1,621	589/8,856
Bejan	1%	0.99 [0.61-1.63]	ventilation	1,899 (n)	7,330 (n)
Reese (PSM)	-61%	1.61 [1.31-1.99]	death	4,921 (n)	4,921 (n)
Drew	22%	0.78 [0.49-1.24]	progression	n/a	n/a
Pan	-13%	1.13 [0.70-1.82]	death	239 (n)	523 (n)
Oh	1%	0.99 [0.65-1.50]	death	n/a	n/a
Son (PSM)	24%	0.76 [0.34-1.71]	death	case control	
Ma (PSM)	9%	0.91 [0.82-1.02]	death		
Chow (PSM)	19%	0.81 [0.76-0.87]	death	1,280/6,781	2,271/10,566
Kim (PSM)	-700%	8.00 [1.07-59.6]	death	6/15	1/20
Basheer	-13%	1.13 [1.05-1.21]	death	45/140	29/250
Sisinni	-7%	1.07 [0.89-1.29]	death	93/253	251/731
Pérez-Segura	-49%	1.49 [1.20-1.80]	death	66/155	183/608
Formiga (PSM)	-3%	1.03 [0.94-1.13]	death	1,000/3,291	874/2,885
Sullerot (PSW)	-10%	1.10 [0.81-1.49]	death	101/301	224/746
Monserrat .. (PSM)	-31%	1.31 [1.01-1.71]	death	n/a	n/a
Levy	26%	0.74 [0.49-1.10]	death/hosp.	29/159	178/690
Nimer	4%	0.96 [0.69-1.33]	hosp.	83/427	136/1,721
Gogtay	-6%	1.06 [0.51-1.89]	death	12/38	21/87
Campbell (PSW)	3%	0.97 [0.95-1.00]	death	419 (n)	20,311 (n)
Lal	11%	0.89 [0.82-0.97]	death	4,691 (n)	16,888 (n)
Botton	-4%	1.04 [0.98-1.10]	death/int.	population-based cohort	
Malik	14%	0.86 [0.39-1.80]	death	15/87	24/223
Abul	33%	0.67 [0.47-0.95]	death	46/511	201/1,176
Loucera	18%	0.82 [0.74-0.92]	death	2,127 (n)	13,841 (n)
Morrison (PSM)	8%	0.92 [0.73-1.18]	death	1,667 (n)	1,667 (n)
Ali	28%	0.72 [0.51-1.03]	death	481 (n)	1,164 (n)
Zadeh	37%	0.63 [0.30-1.29]	death	n/a	n/a
Tse (PSM)	67%	0.33 [0.18-0.59]	death/int.	2,664 (all patients)	



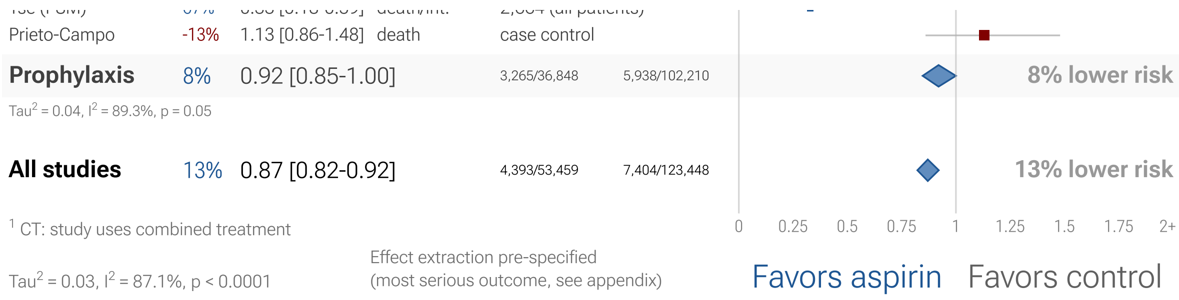


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

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

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

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

Table 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 69 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

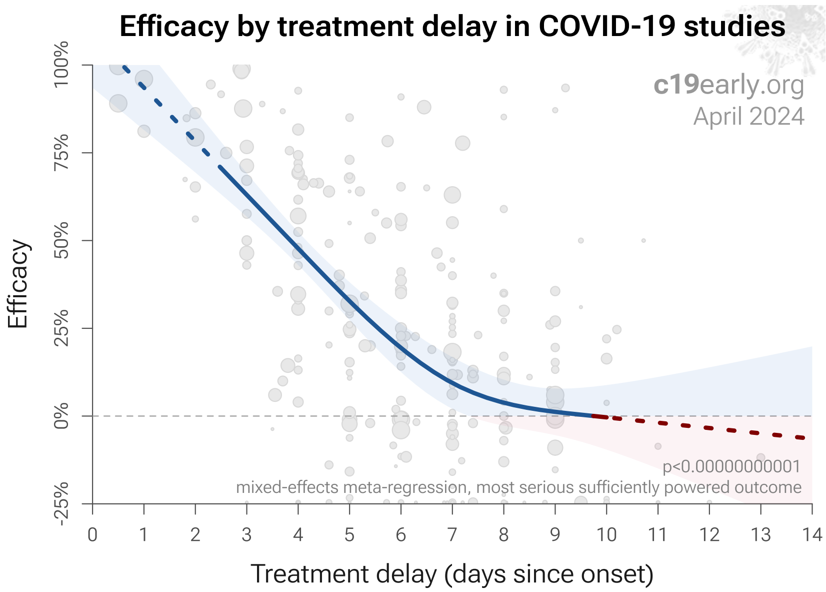


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 69 treatments.

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, for example as in *López-Medina et al.*

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [Korves], 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 degree to which TMPRSS2 contributes to viral entry can differ across variants [Peacock, Willett].

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

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

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

Effect measured. Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

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. 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.

Pooled Effects

Combining studies is required. For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results.

Specific outcome and pooled analyses. We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Using more information. Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Ethical and practical issues limit high-risk trials. Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster collection of evidence.

Improvement across outcomes. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 69 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 19 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 20 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 21 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.0000045$ to $p = 0.0000000067$.

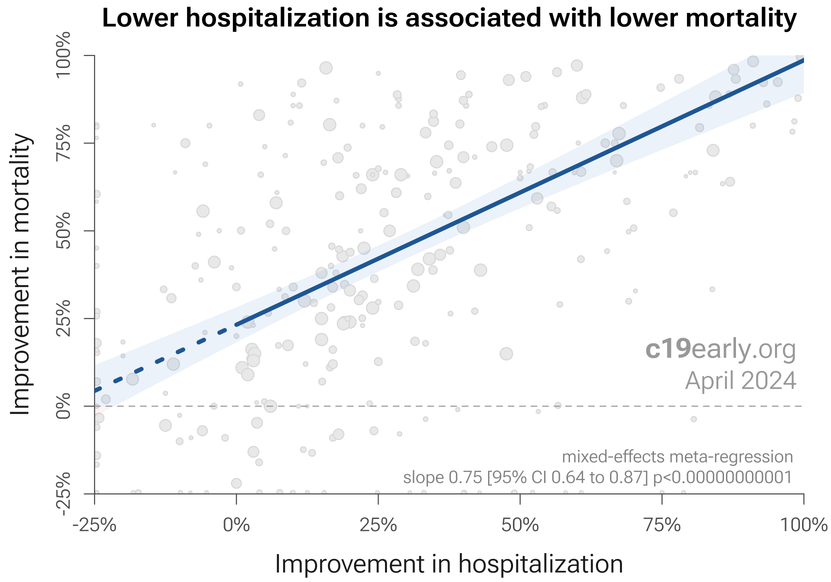


Figure 19. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

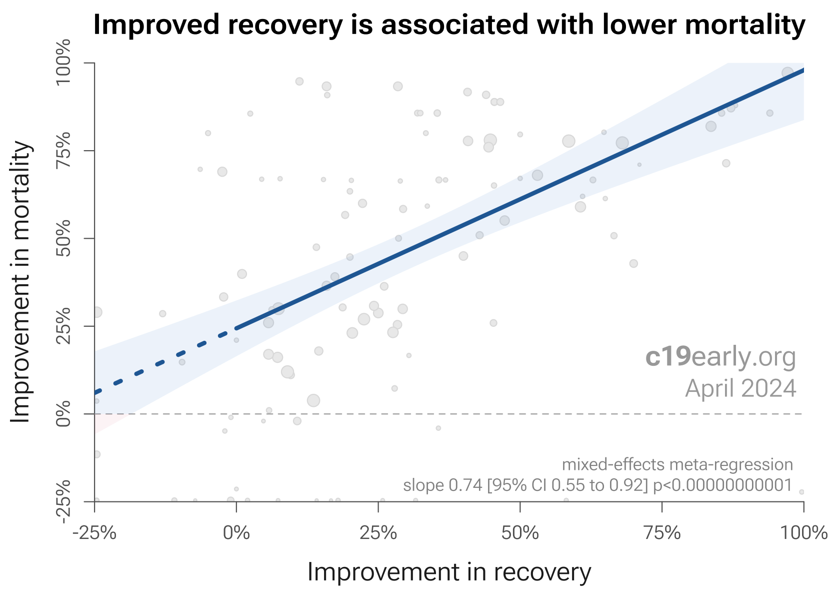


Figure 20. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

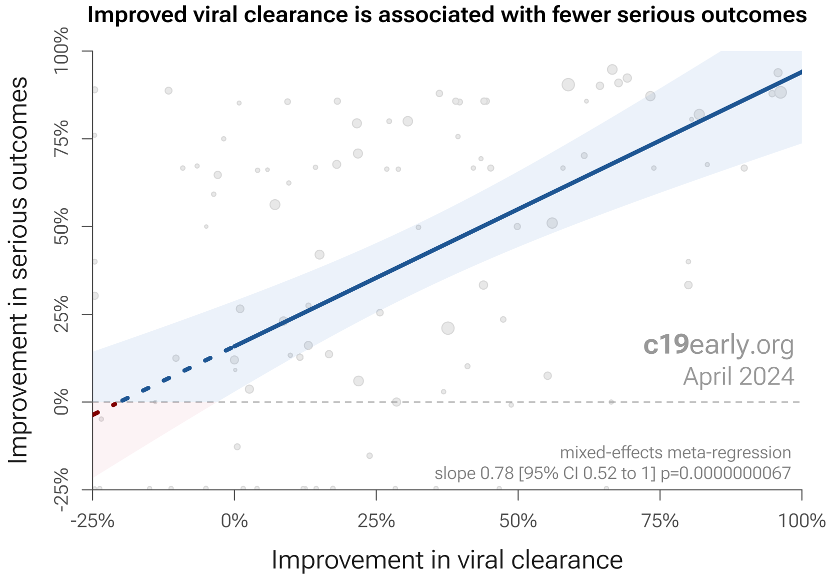


Figure 19. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 4 months faster (6 months for RCTs). Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 85% of these have been confirmed with one or more specific outcomes, with a mean delay of 3.7 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 5.8 months. Figure 22 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

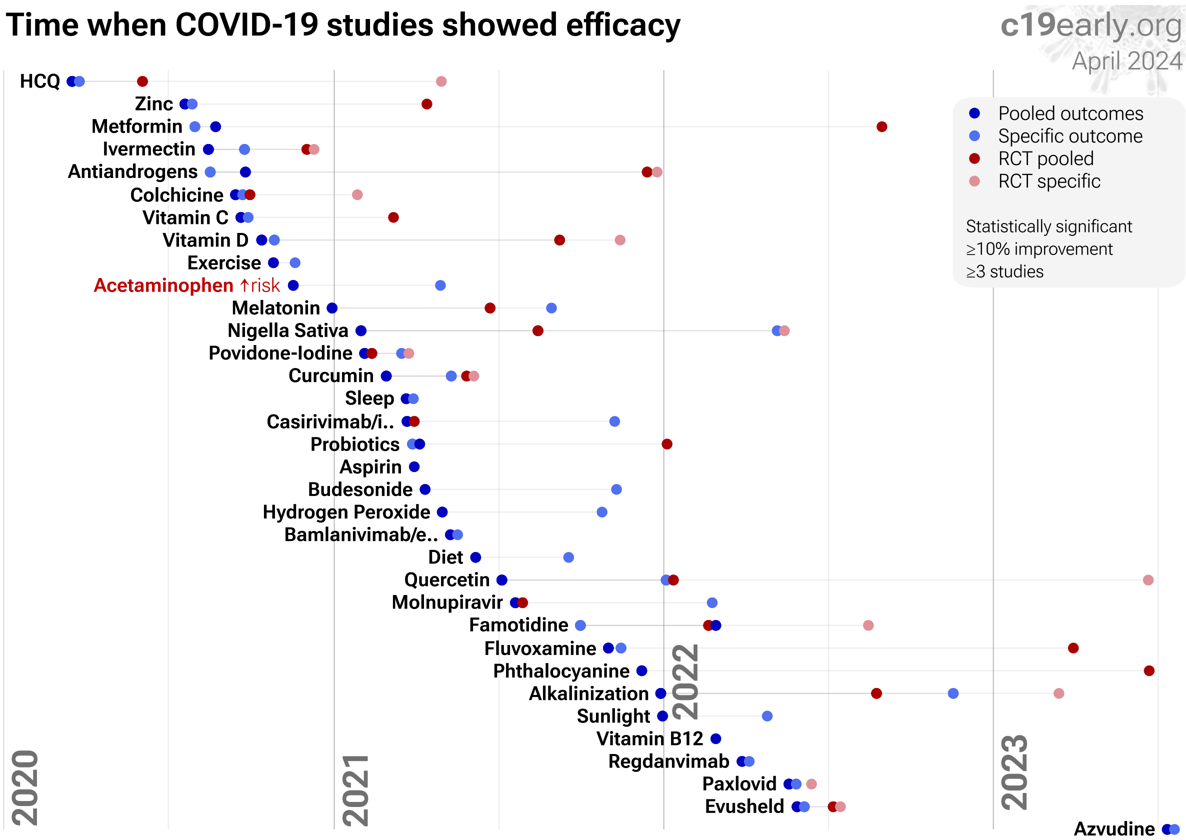


Figure 22. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations. Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary. Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present 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, twitter.com*.

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 23 shows a scatter plot of results for prospective and retrospective studies. 40% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 30% of prospective studies, consistent with a bias toward publishing positive results. The median effect size for retrospective studies is 14% improvement, compared to 13% for prospective studies, showing similar results.

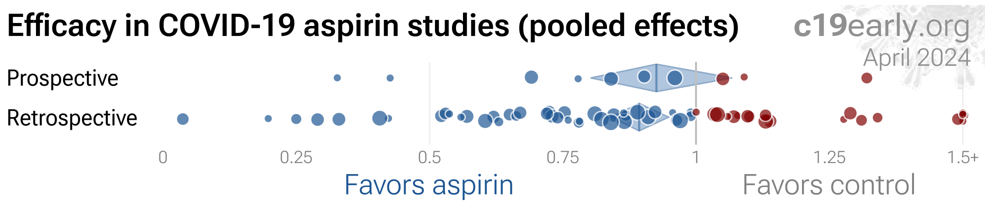


Figure 23. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 24 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.

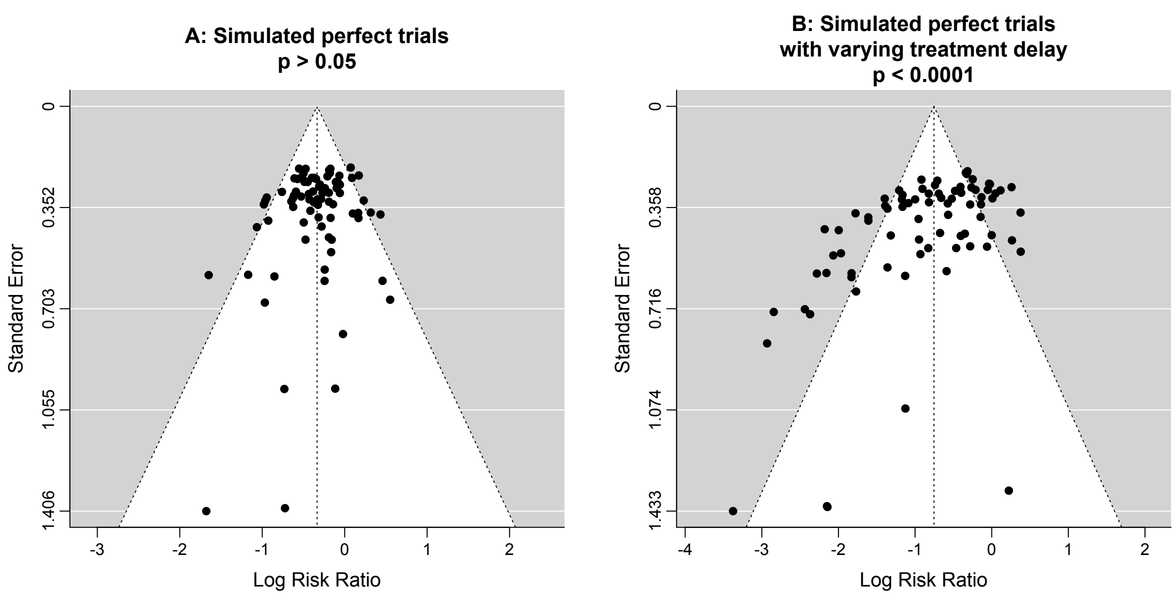


Figure 24. **Example funnel plot analysis for simulated perfect trials.**

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Aspirin for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 aspirin trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all aspirin trials represent the optimal conditions for efficacy.

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 for 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 with conflicts of interest 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 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. 2 of 72 studies combine treatments. The results of aspirin alone may differ. 2 of 7 RCTs use combined treatment. Other meta analyses show significant improvements with aspirin for mortality [Banaser, Baral, Srinivasan] and mechanical ventilation [Banaser].

Perspective

Results compared with other treatments. SARS-CoV-2 infection and replication involves a complex interplay of 50+ host and viral proteins and other factors [Lui, Lv, Malone, Murigneux, Niarakis], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk [c19early.org], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 25 shows an overview of the results for aspirin in the context of multiple COVID-19 treatments, and Figure 26 shows a plot of efficacy vs. cost for COVID-19 treatments.

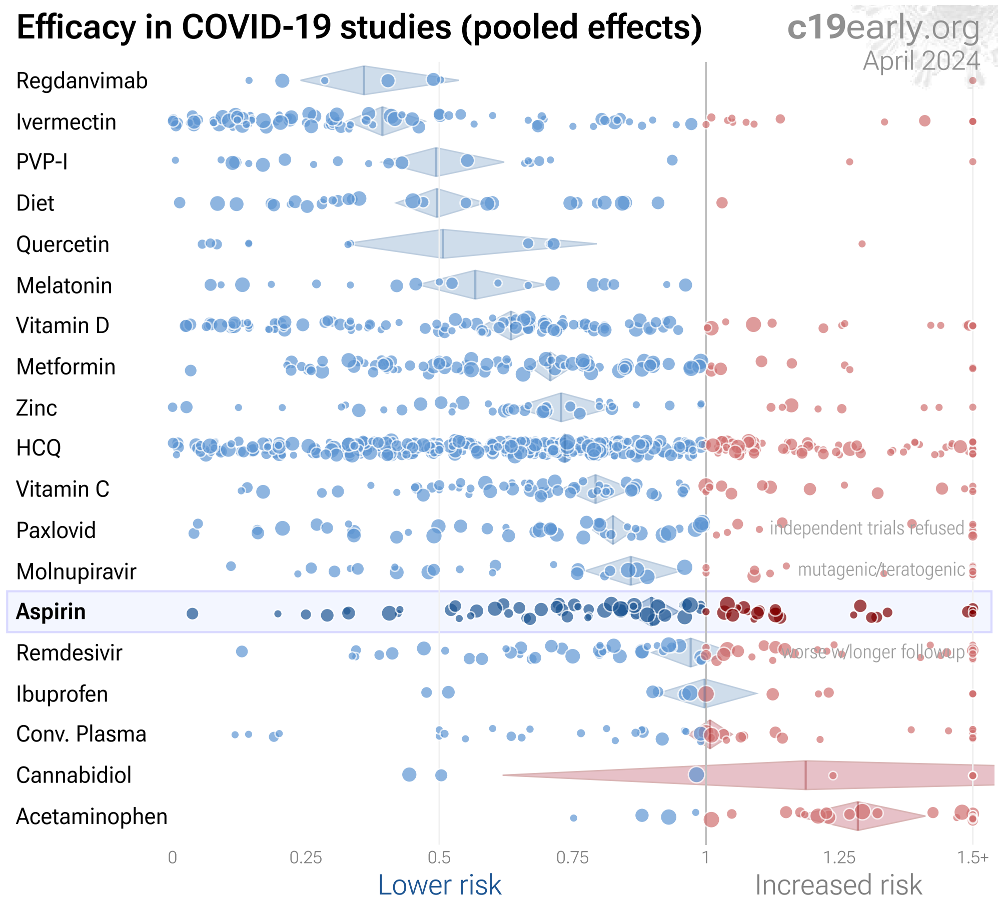


Figure 25. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,400 proposed treatments show efficacy *c19early.org (B)*.

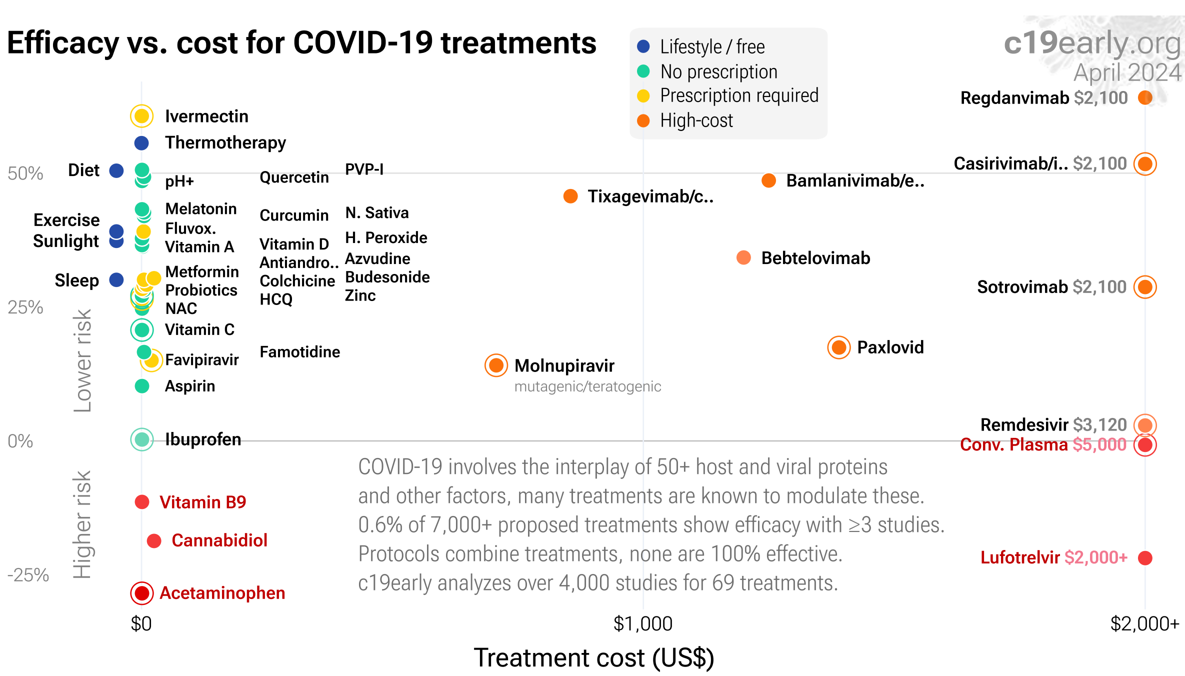


Figure 26. Efficacy vs. cost for COVID-19 treatments.

Conclusion

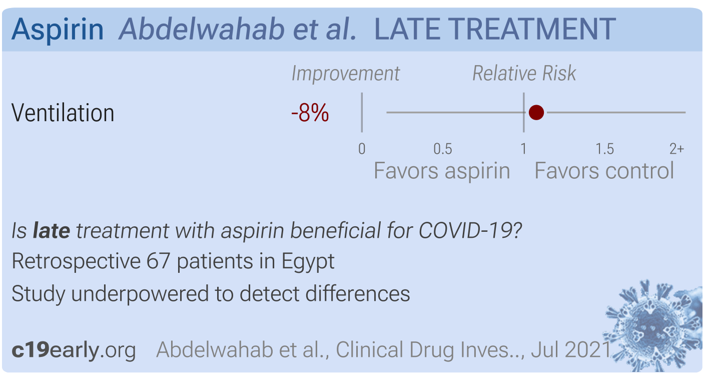
Aspirin is an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality and progression. 28 studies from 26 independent teams in 11 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 10% [5-15%] lower risk. Results are similar for higher quality and peer-reviewed studies and worse for Randomized Controlled Trials. Early treatment is more effective than late treatment.

Studies to date do not show a significant benefit for mechanical ventilation and ICU admission. Benefit may be more likely without coadministered anticoagulants. The RECOVERY RCT shows 4% [-4-11%] lower mortality for all patients, however when restricting to non-LMWH patients there was 17% [-4-34%] improvement, comparable with the mortality results of all studies, 9% [4-15%], and the 16% improvement in the REMAP-CAP RCT.

Other meta analyses show significant improvements with aspirin for mortality [Banaser, Baral, Srinivasan] and mechanical ventilation [Banaser].

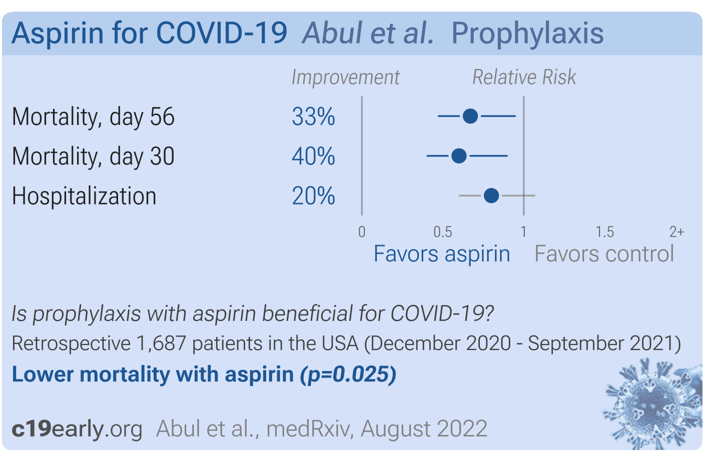
Study Notes

Abdelwahab



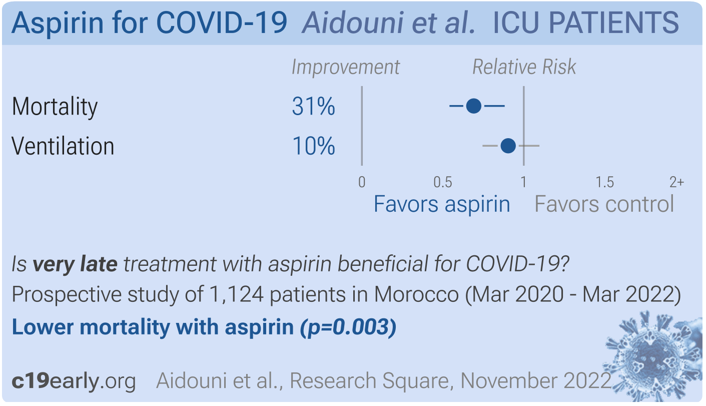
Abdelwahab: Retrospective 225 hospitalized patients in Egypt, showing significantly lower thromboembolic events with aspirin treatment, but no significant difference in the need for mechanical ventilation.

Abul



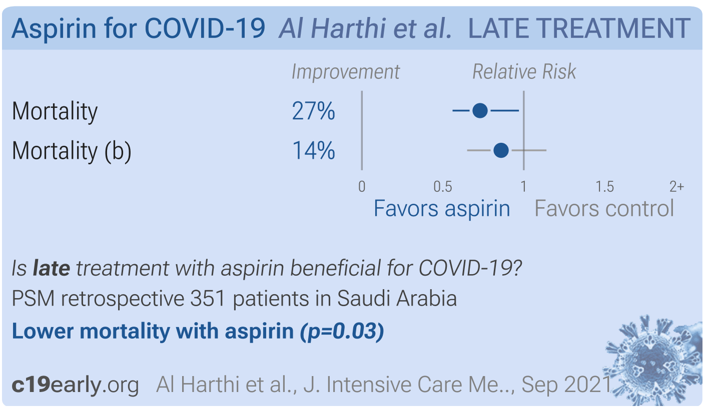
Abul: Retrospective 1,687 nursing home residents in the USA, showing significantly lower risk of mortality with chronic low-dose aspirin use. Low dose 81mg aspirin users had treatment ≥10 of 14 days prior to the positive COVID date, control patients had no aspirin use in the prior 14 days.

Aidouni



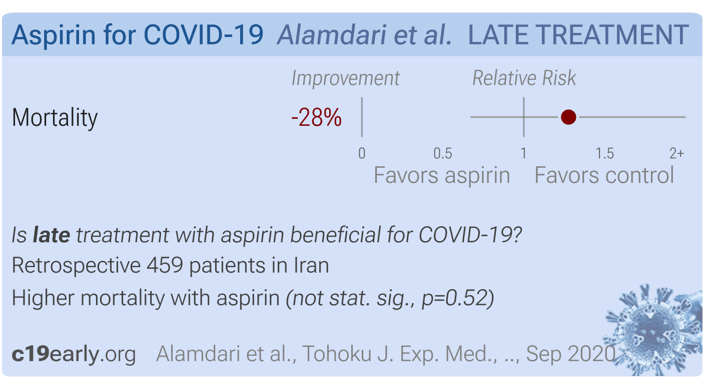
Aidouni: Prospective study of 1,124 COVID-19 ICU patients, showing lower mortality with aspirin treatment.

Al Harthi



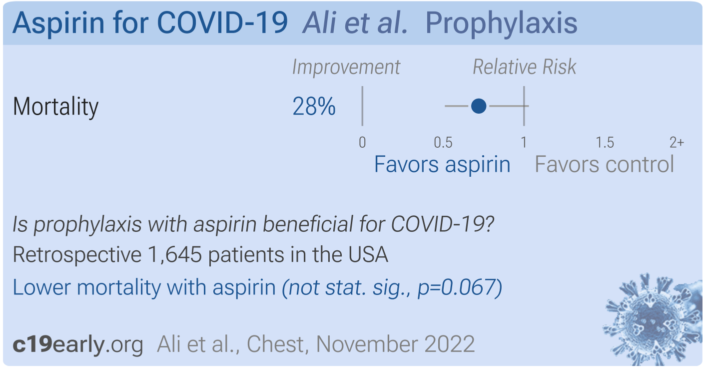
Al Harthi: Retrospective 1,033 critical condition patients, showing lower in-hospital mortality with aspirin in PSM analysis. Patients receiving aspirin also had a higher risk of significant bleeding, although not reaching statistical significance. Authors note that the use of aspirin during an ICU stay should be tailored to each patient.

Alamdari



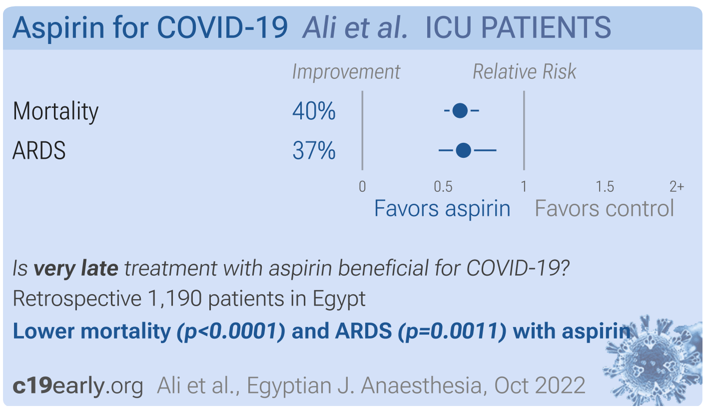
Alamdari: Retrospective 459 patients in Iran, 53 treated with aspirin, showing no significant difference with treatment.

Ali



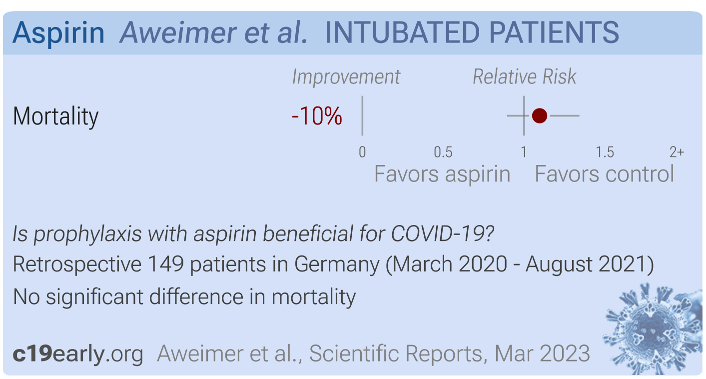
Ali (B): Retrospective 1,645 hospitalized patients in the USA, showing lower mortality with aspirin use, without statistical significance.

Ali



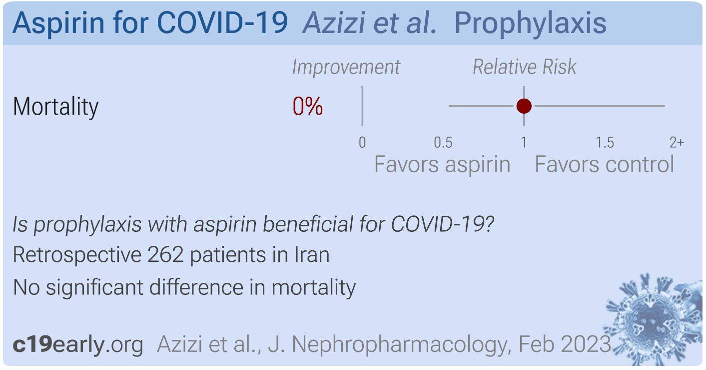
Ali: Retrospective 1,190 ICU patients in Egypt, showing lower mortality with aspirin treatment. 150mg daily.

Aweimer



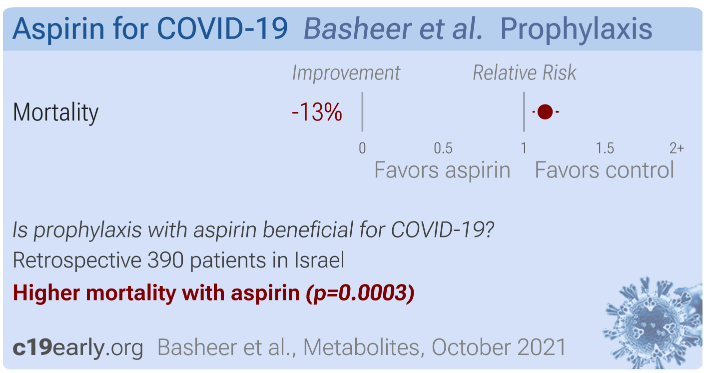
Aweimer: Retrospective 149 patients under invasive mechanical ventilation in Germany showing no significant difference in mortality with aspirin prophylaxis in unadjusted results.

Azizi



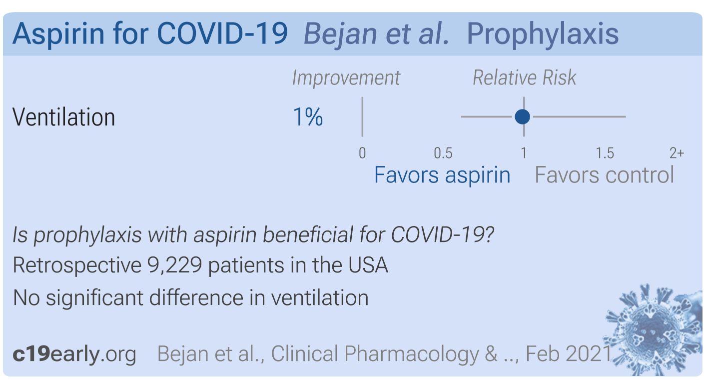
Azizi: Retrospective 131 COVID-19 patients with aspirin use and 131 matched controls in Iran, showing no significant difference in outcomes, however age matching used only two categories, 40-60 and 60+, therefore matching may be very poor given the relationship between age and COVID-19 risk. The percentages given for the control group death/recovery outcomes do not match the reported counts.

Basheer



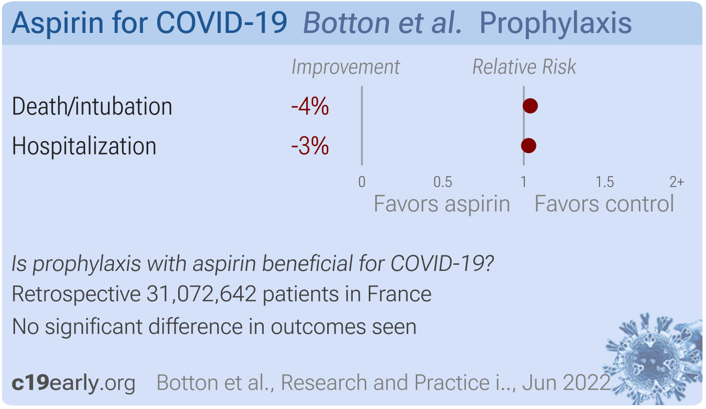
Basheer: Retrospective 390 hospitalized patients in Israel, showing higher risk of mortality with prior aspirin use. Details of the analysis are not provided.

Bejan



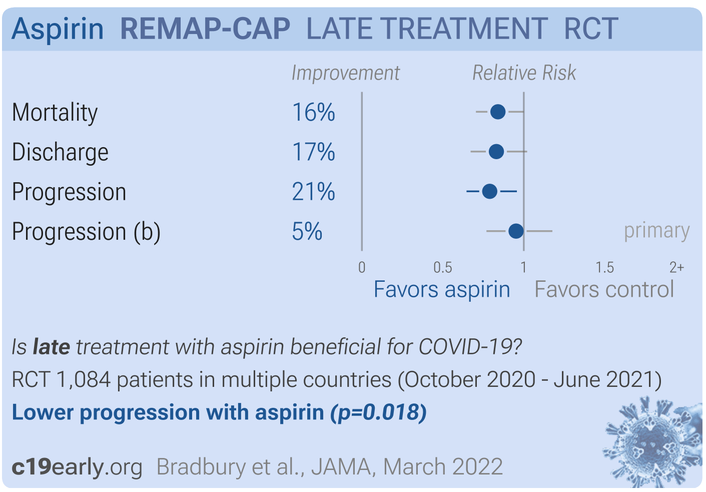
Bejan: Retrospective 9,748 COVID-19 patients in the USA showing no signficant difference with aspirin use.

Botton



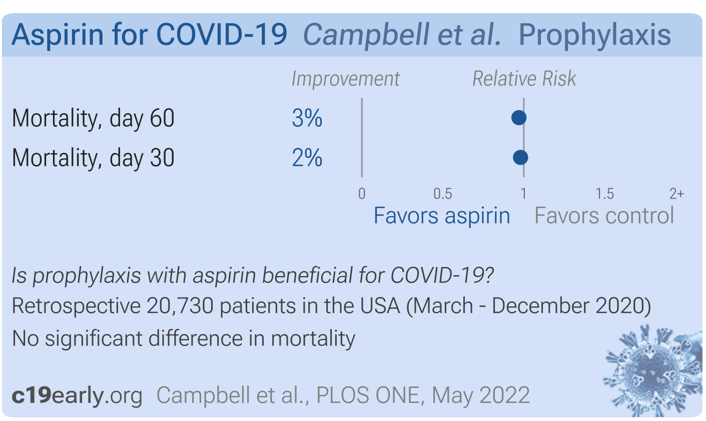
Botton: Retrospective 31 million people without cardiovascular disease in France, showing no significant difference in hospitalization or combined intubation/death with low dose aspirin prophylaxis.

Bradbury



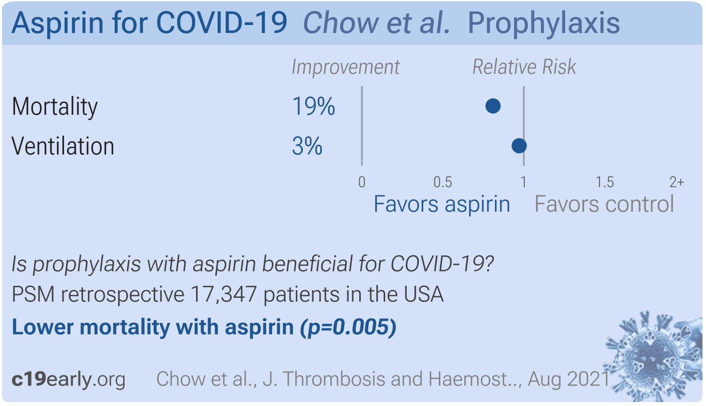
Bradbury: RCT 1,557 critical patients, showing significantly lower mortality with aspirin, with 97.5% posterior probability of efficacy.

Campbell



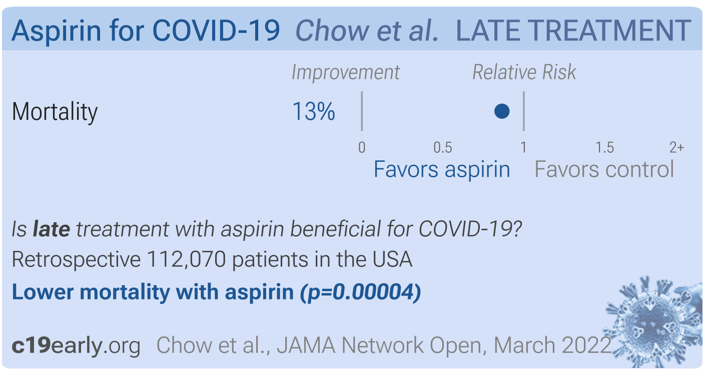
Campbell: Retrospective 28,856 COVID-19 patients in the USA, showing no significant difference in mortality for chronic aspirin use vs. sporadic NSAID use. Since aspirin is available OTC and authors only tracked prescriptions, many patients classified as sporadic users may have been chronic users.

Chow



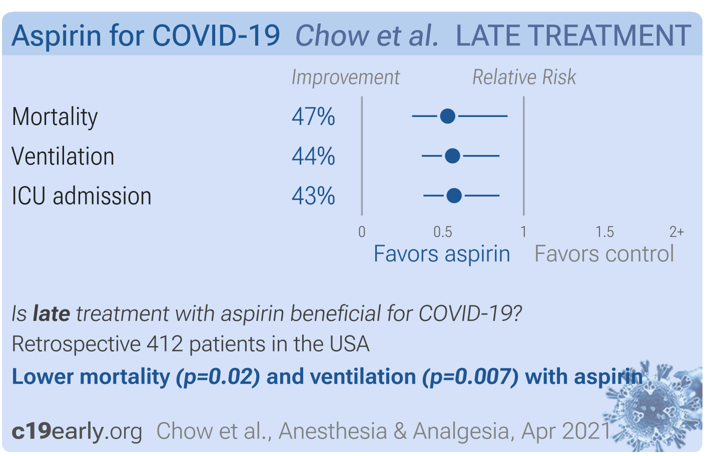
Chow (C): PSM retrospective 6,781 hospitalized patients ≥50 years old in the USA who were on pre-hospital antiplatelet therapy (84% aspirin), and 10,566 matched controls, showing lower mortality with treatment.

Chow



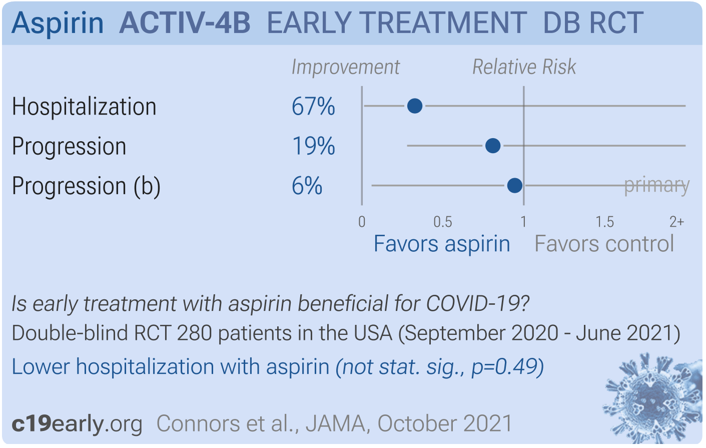
Chow: Retrospective 112,269 hospitalized COVID-19 patients in the USA, showing lower mortality with aspirin treatment.

Chow



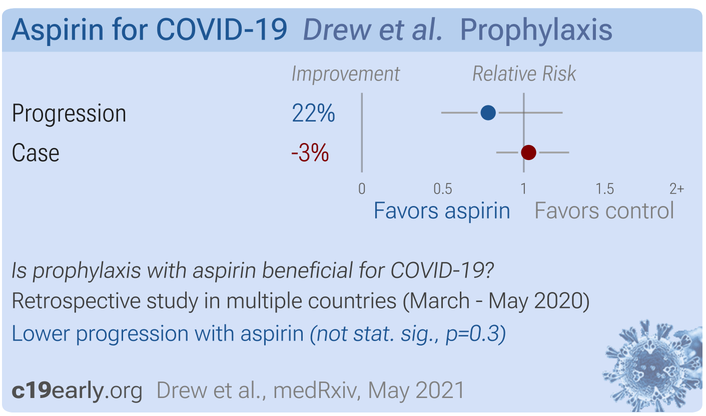
Chow (B): Retrospective 412 hospitalized patients, 98 treated with aspirin, showing lower mortality, ventilation, and ICU admission with treatment.

Connors



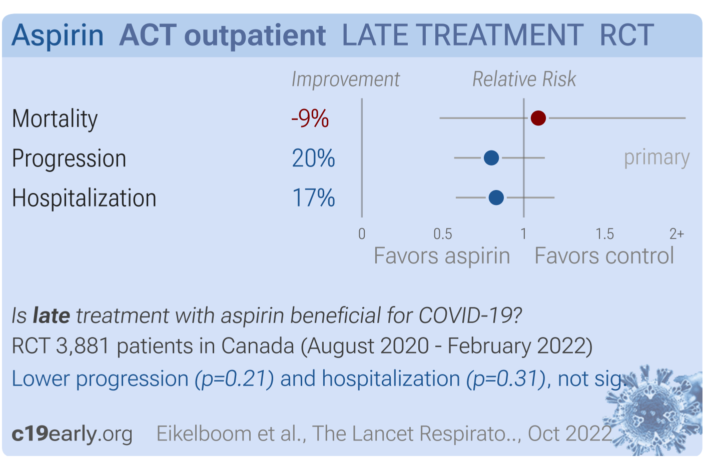
Connors: Early terminated RCT with 164 aspirin and 164 control patients in the USA with very few events, showing no significant difference with aspirin treatment for the combined endpoint of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, and hospitalization for cardiovascular or pulmonary indication. There was no mortality and no major bleeding events among participants that started treatment (there was one ITT placebo death).

Drew



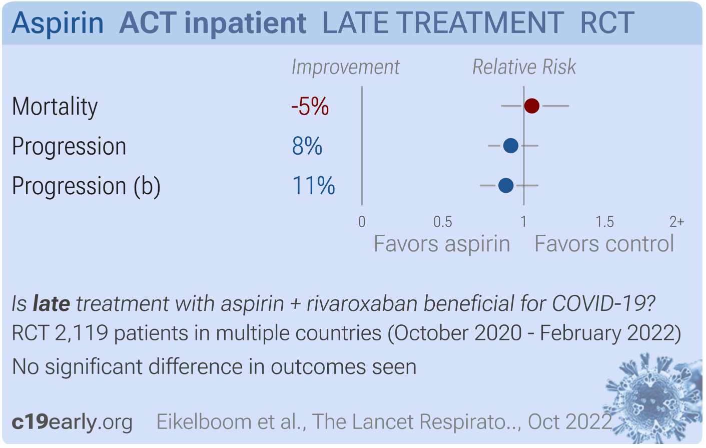
Drew: Retrospective 2,736,091 individuals in the U.S., U.K., and Sweden, showing lower risk of hospital/clinic visits with aspirin use.

Eikelboom



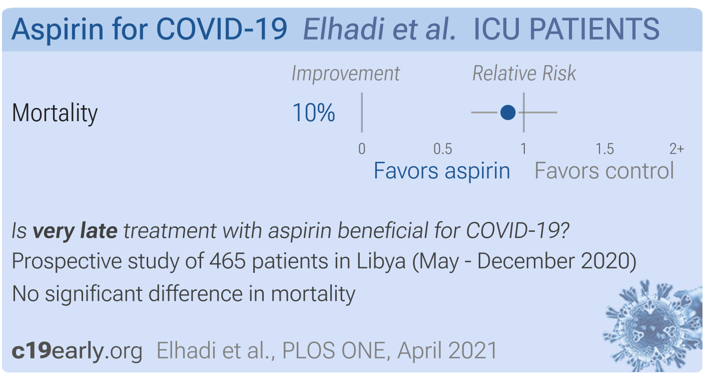
Eikelboom: Late (5.4 days) outpatient RCT showing no significant difference in outcomes with aspirin treatment.

Eikelboom



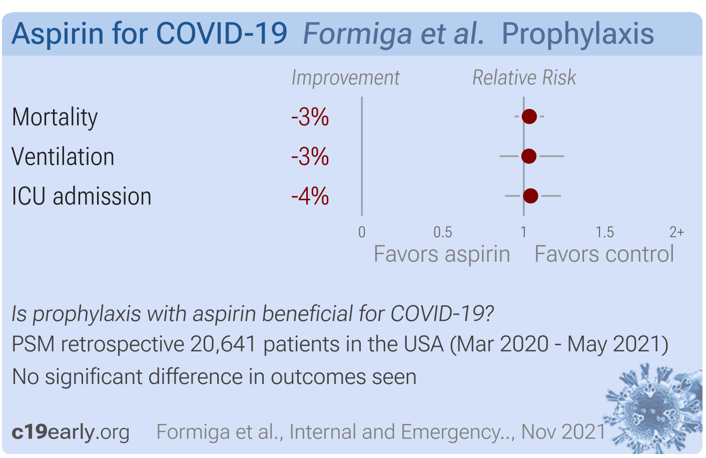
Eikelboom (B): RCT very late stage (baseline SpO2 77%) patients, showing no significant differences with rivaroxaban and aspirin treatment.

Elhadi



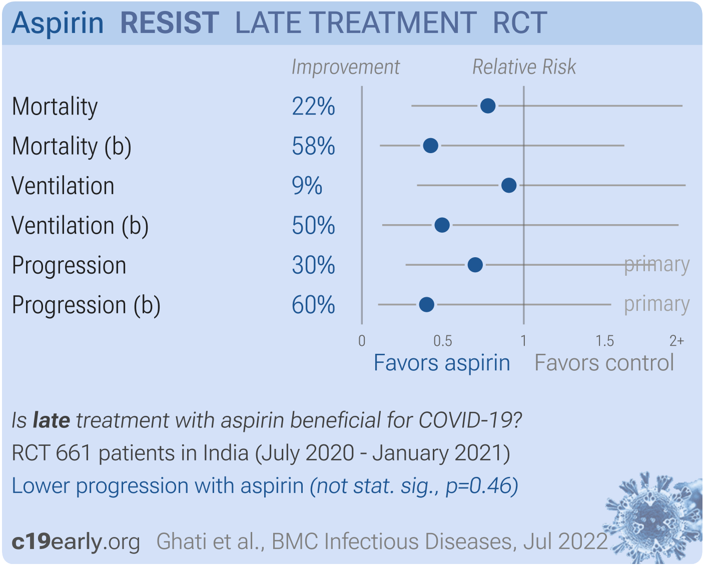
Elhadi: Prospective study of 465 COVID-19 ICU patients in Libya showing no significant differences with treatment.

Formiga



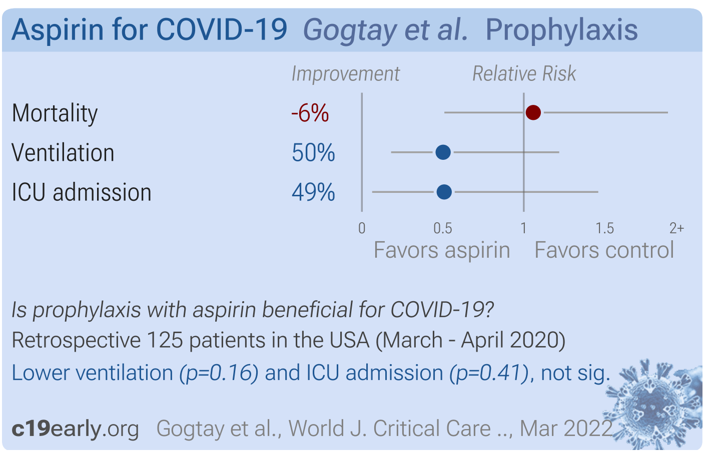
Formiga: Retrospective 20,641 hospitalized patients in Spain, showing no significant difference in outcomes with existing aspirin use.

Ghati



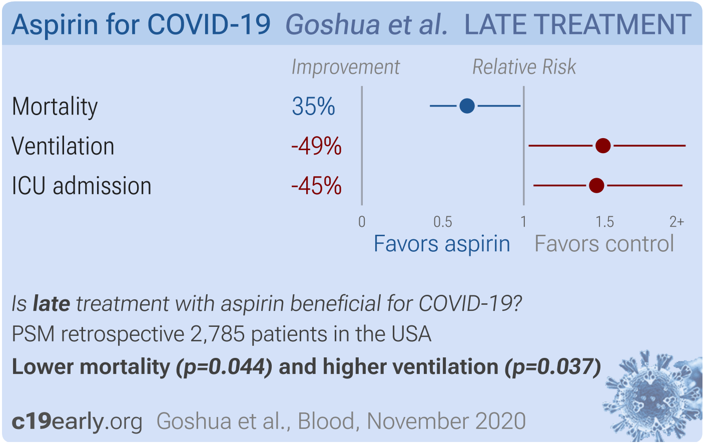
Ghati: RCT hospitalized patients in India, 224 treated with atorvastatin, 225 with aspirin, and 225 with both, showing lower serum interleukin-6 levels with aspirin, but no statistically significant changes in other outcomes. Low dose aspirin 75mg daily for 10 days.

Gogtay



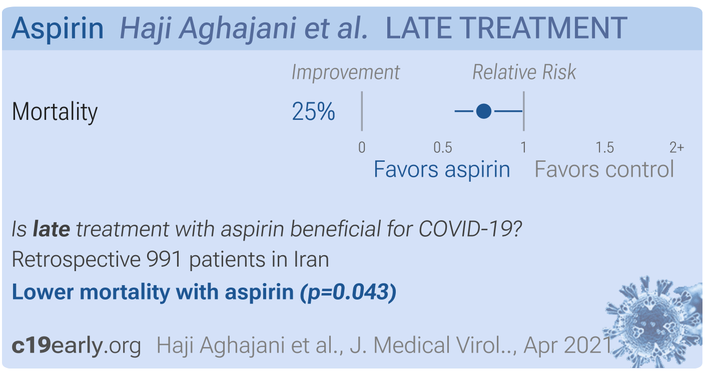
Gogtay: Retrospective 125 COVID+ hospitalized patients in the USA, showing no significant differences with aspirin prophylaxis.

Goshua



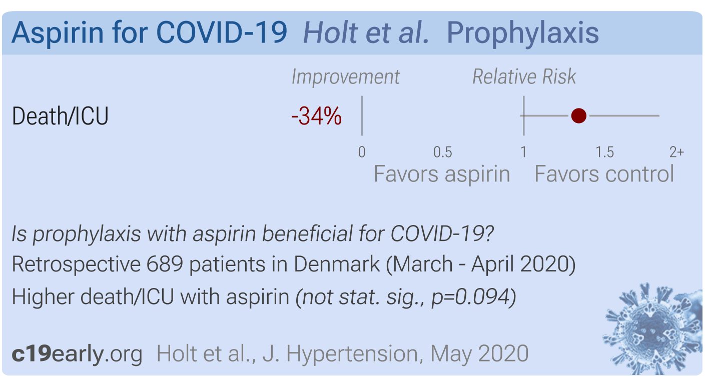
Goshua: PSM retrospective 2,785 hospitalized patients in the USA, showing lower mortality and higher ventilation and ICU admission with aspirin treatment.

Haji Aghajani



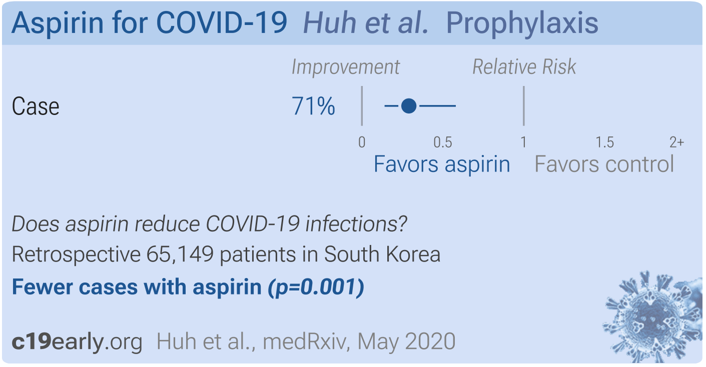
Haji Aghajani: Retrospective 991 hospitalized patients in Iran, showing lower mortality with aspirin treatment.

Holt



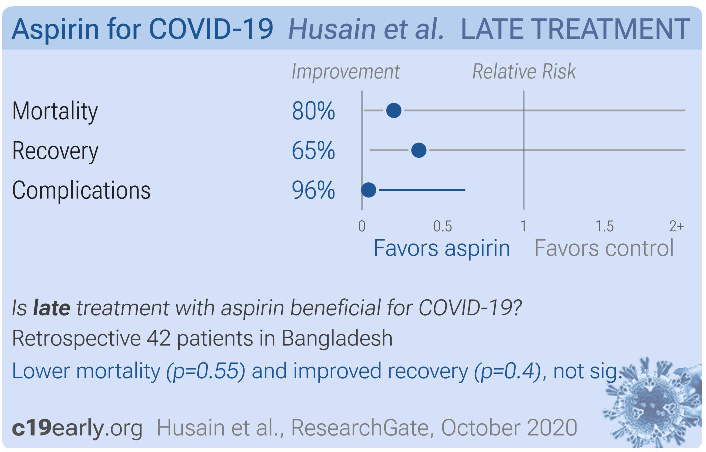
Holt: Retrospective 689 hospitalized COVID-19 patients in Denmark, showing higher risk of ICU/death with aspirin use in unadjusted results subject to confounding by indication.

Huh



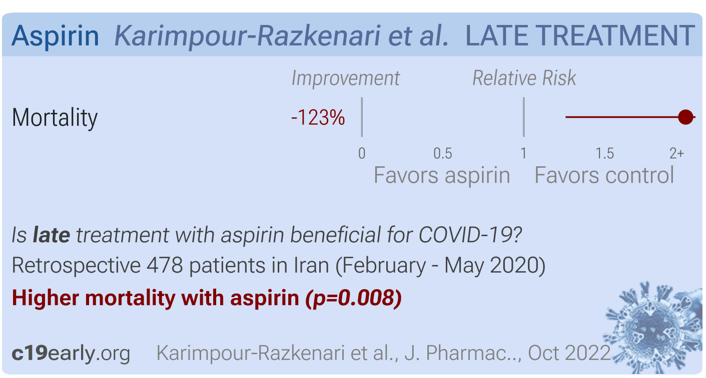
Huh: Retrospective database analysis of 65,149 in South Korea, showing significantly lower cases with existing aspirin treatment. The journal version of this paper does not present the aspirin results (only combined results for NSAIDs).

Husain



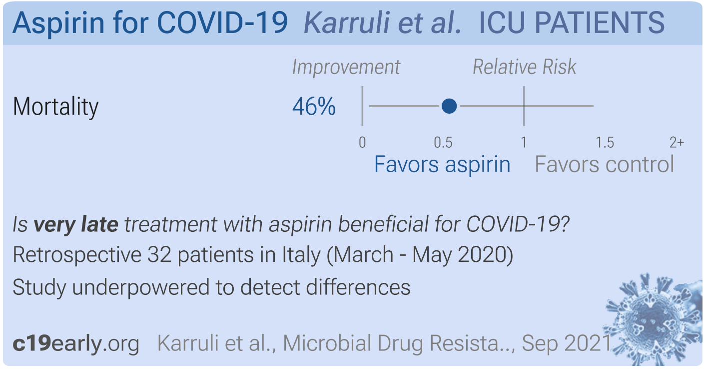
Husain: Retrospective 42 patients in Bangladesh, 11 treated with aspirin, showing fewer complications with treatment.

Karimpour-Razkenari



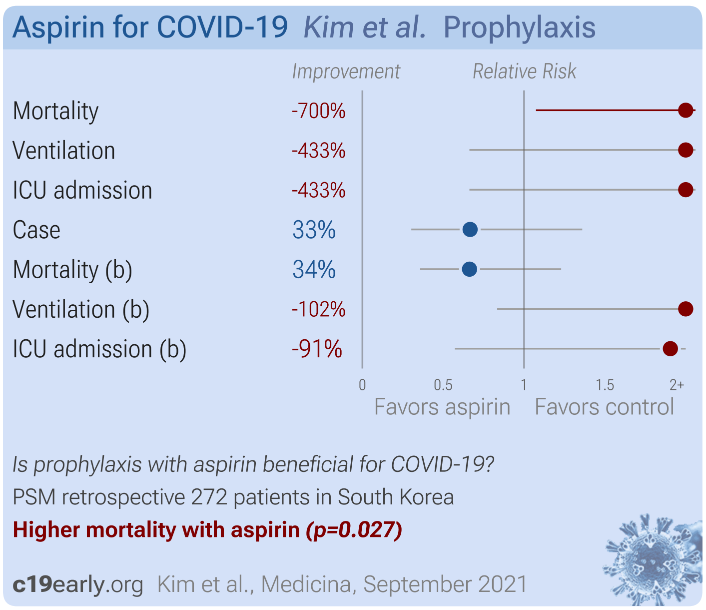
Karimpour-Razkenari: Retrospective 478 moderate to severe hospitalized patients in Iran, showing higher mortality with aspirin treatment. Authors note confounding by indication for aspirin treatment.

Karruli



Karruli: Retrospective 32 ICU patients showing lower mortality with aspirin treatment, without statistical significance.

Kim

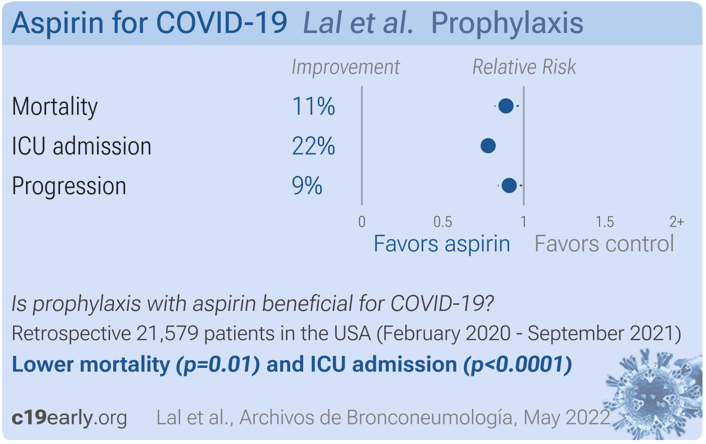


Kim (B): Retrospective database analysis of 22,660 patients tested for COVID-19 in South Korea. There was no significant difference in cases according to aspirin use. Aspirin use before COVID-19 was related to an increased death rate and aspirin use after COVID-19 was related to a higher risk of oxygen therapy.

Kim

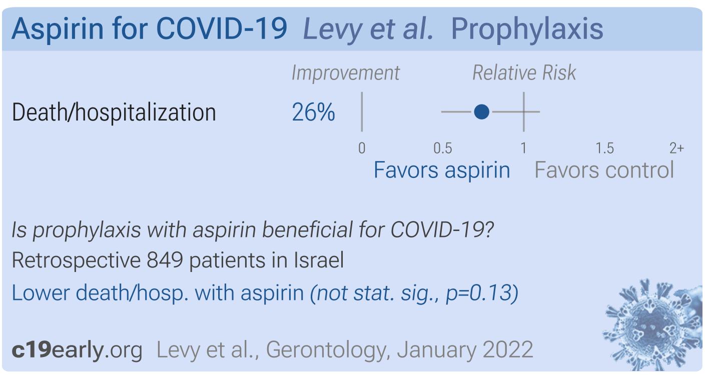
Kim: Retrospective database analysis of 22,660 patients tested for COVID-19 in South Korea. There was no significant difference in cases according to aspirin use. Aspirin use before COVID-19 was related to an increased death rate and aspirin use after COVID-19 was related to a higher risk of oxygen therapy.

Lal



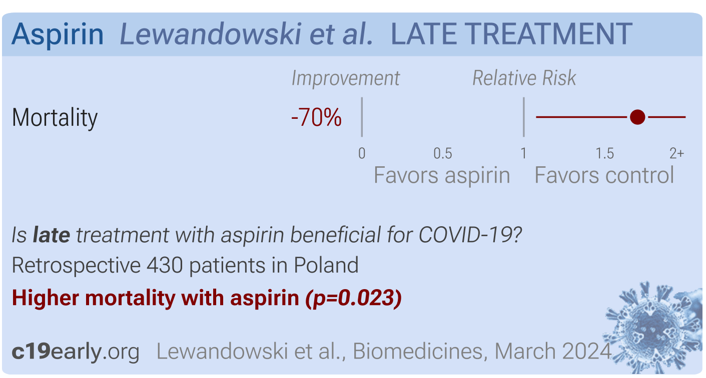
Lal: Retrospective 21,579 hospitalized COVID-19 patients mostly in the USA, showing lower risk of mortality and severity with existing aspirin use.

Levy



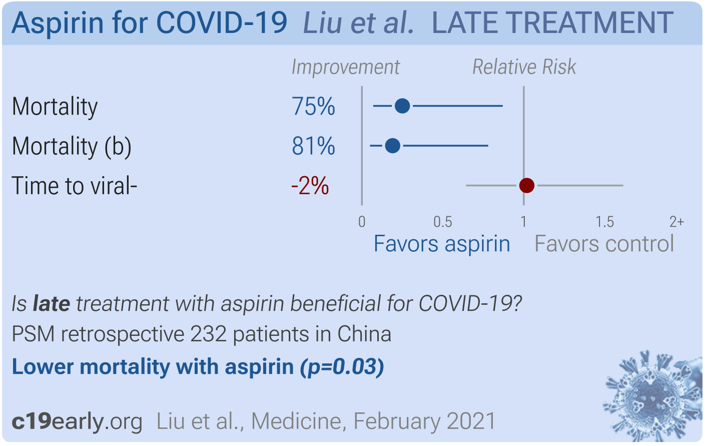
Levy: Retrospective 849 COVID-19+ patients in skilled nursing homes, showing lower risk of combined hospitalization/death with aspirin prophylaxis, not reaching statistical significance.

Lewandowski



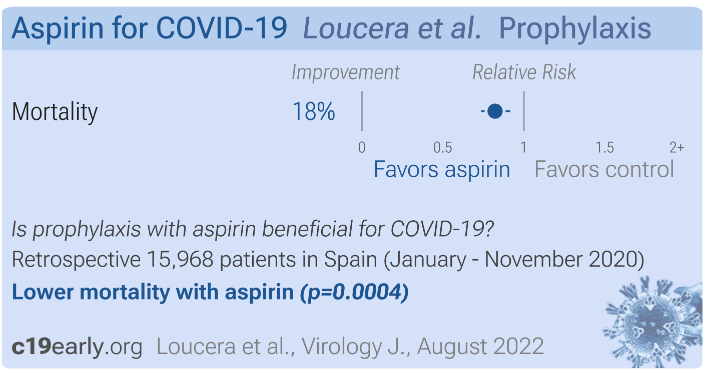
Lewandowski: Retrospective 430 hospitalized COVID-19 patients with type 2 diabetes in Poland showing lower mortality with metformin and higher mortality with remdesivir, convalescent plasma, and aspirin in univariable analysis. These results were not statistically significant except for aspirin, and no baseline information per treatment is provided to assess confounding.

Liu



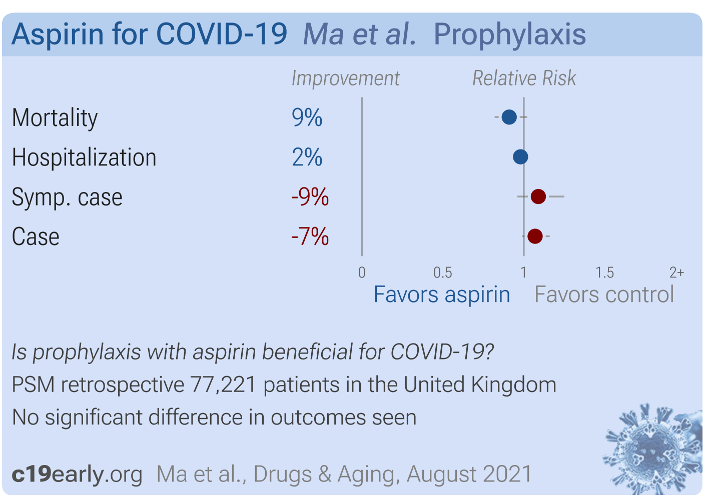
Liu: Retrospective PSM analysis of 232 hospitalized patients, 28 treated with aspirin, showing lower mortality with treatment. There was no significant difference in viral clearance.

Loucera



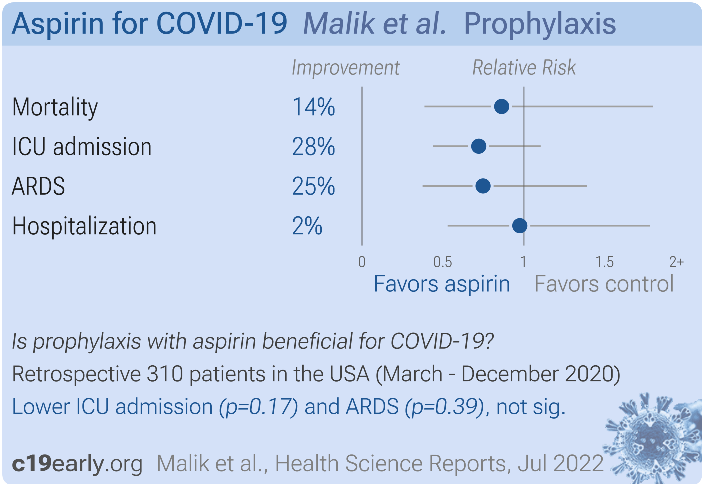
Loucera: Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

Ma



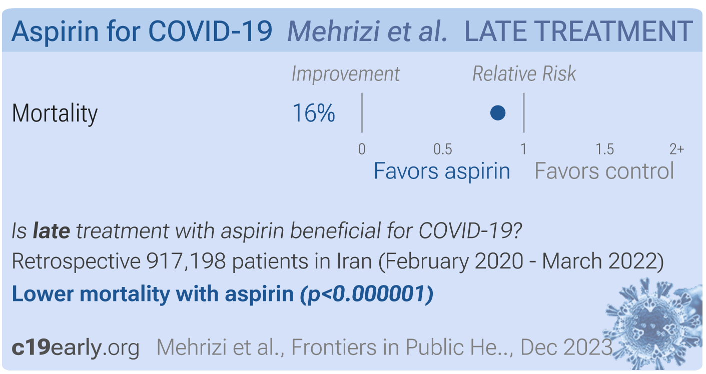
Ma: UK Biobank retrospective 77,271 patients aged 50-86, showing no significant differences with aspirin use. Matching lead to different results for the gender vs. overall analysis, for example the overall result for cases was OR 1.07, however both gender results are lower OR 0.97 and 1.02.

Malik



Malik: Retrospective 539 patients in the USA, showing lower mortality, ICU admission, and ARDS with aspirin treatment, without statistical significance.

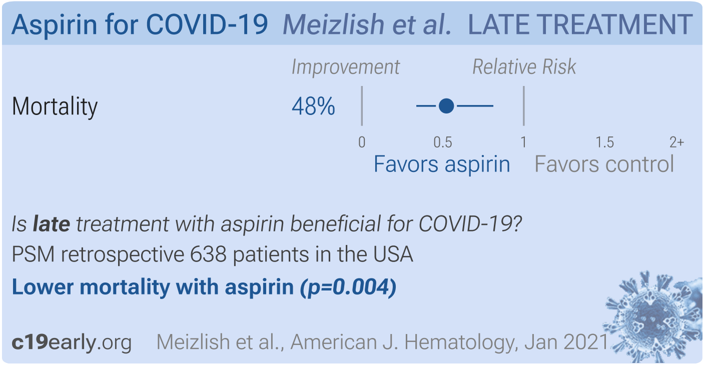
Mehrizi



Mehrizi: Retrospective study of 917,198 hospitalized COVID-19 cases covered by the Iran Health Insurance Organization over 26 months showing that antithrombotics, corticosteroids, and antivirals reduced mortality while diuretics, antibiotics, and antidiabetics increased it. Confounding makes some results very unreliable. For example, diuretics like furosemide are often used to treat fluid overload, which is more likely in ICU or advanced disease requiring aggressive fluid resuscitation. Hospitalization length has increased risk of significant confounding, for example longer hospitalization increases the chance of receiving a medication, and death may result in shorter hospitalization. Mortality results may be more reliable.

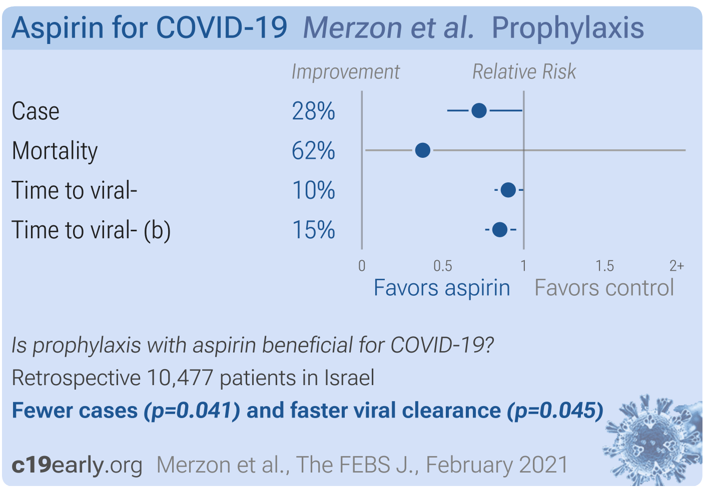
Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency, and attenuation or increase of risk for ICU vs. all patients.

Meizlish



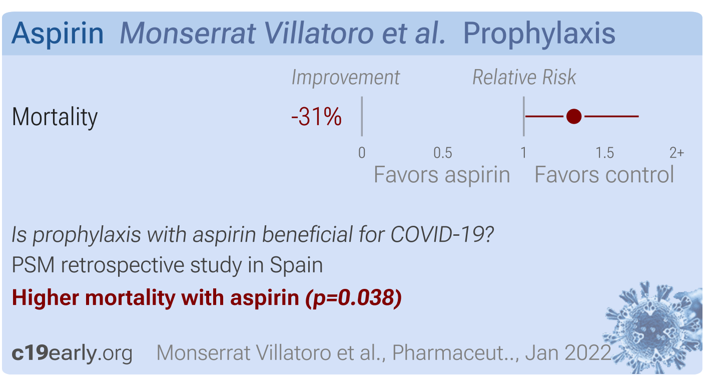
Meizlish: Retrospective 638 matched hospitalized patients in the USA, 319 treated with aspirin, showing lower mortality with treatment.

Merzon



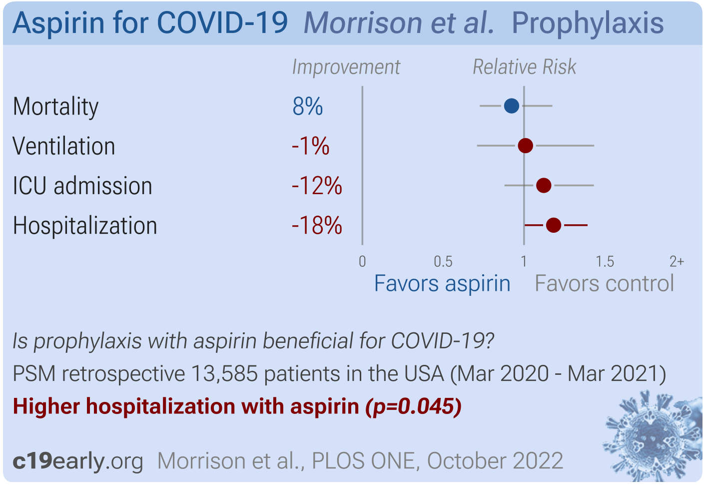
Merzon: Retrospective 10,477 patients in Israel, showing lower risk of COVID-19 cases with existing aspiring use.

Monserrat Villatoro



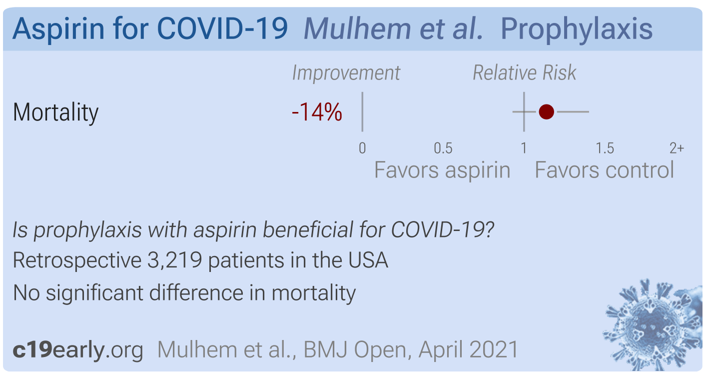
Monserrat Villatoro: PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of azithromycin, bemiparine, budesonide-formoterol fumarate, cefuroxime, colchicine, enoxaparin, ipratropium bromide, loratadine, mepyramine theophylline acetate, oral rehydration salts, and salbutamol sulphate, and higher mortality with acetylsalicylic acid, digoxin, folic acid, mirtazapine, linagliptin, enalapril, atorvastatin, and allopurinol.

Morrison



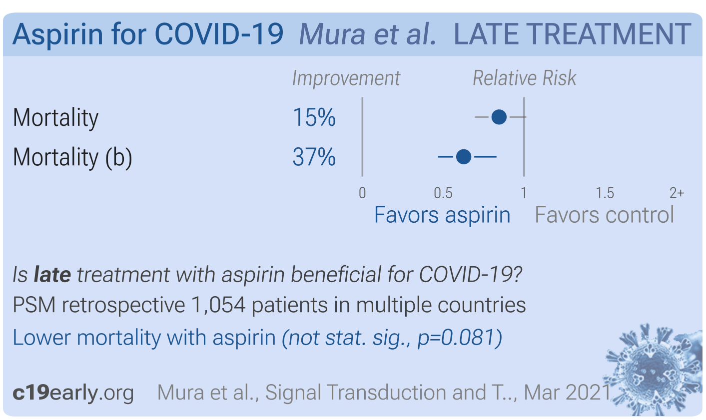
Morrison: Retrospective 13,585 COVID+ patients in the USA, showing higher hospitalization with aspirin use, and no significant difference for mortality, ventilation, and ICU admission.

Mulhem



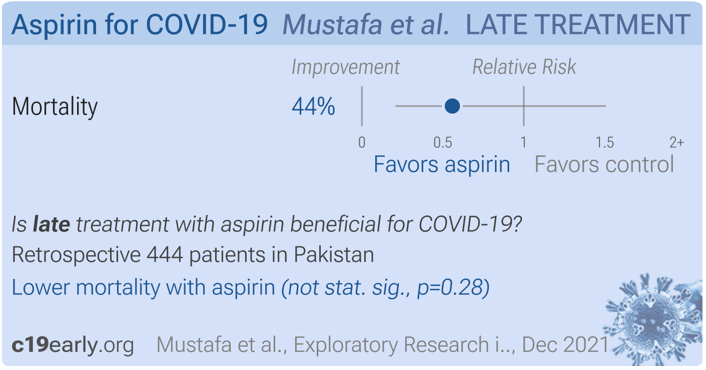
Mulhem: Retrospective database analysis of 3,219 hospitalized patients in the USA. Very different results in the time period analysis (Table S2), and results significantly different to other studies for the same medications (e.g., heparin OR 3.06 [2.44-3.83]) suggest significant confounding by indication and confounding by time.

Mura



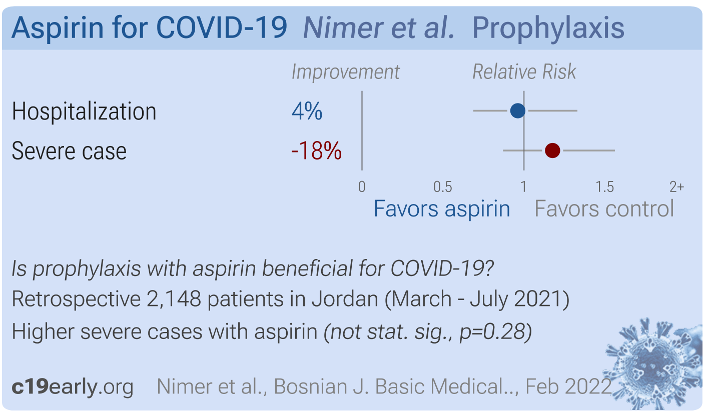
Mura: PSM retrospective TriNetX database analysis of 1,379 severe COVID-19 patients requiring respiratory support, showing lower mortality with aspirin (not reaching statistical significance) and famotidine, and improved results from the combination of both.

Mustafa



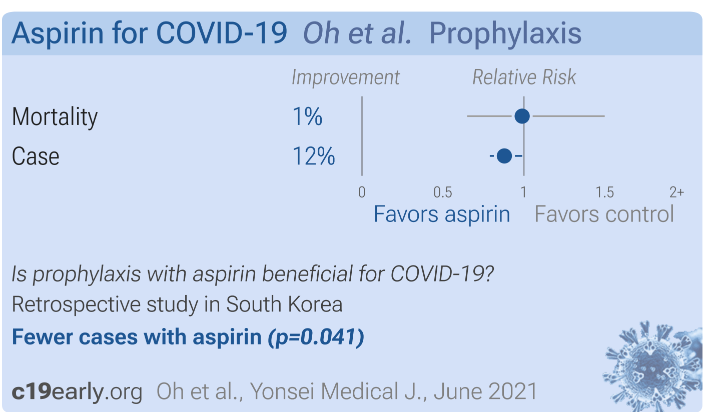
Mustafa: Retrospective 444 hospitalized patients in Pakistan, showing lower mortality with aspirin treatment in unadjusted results, not reaching statistical significance.

Nimer



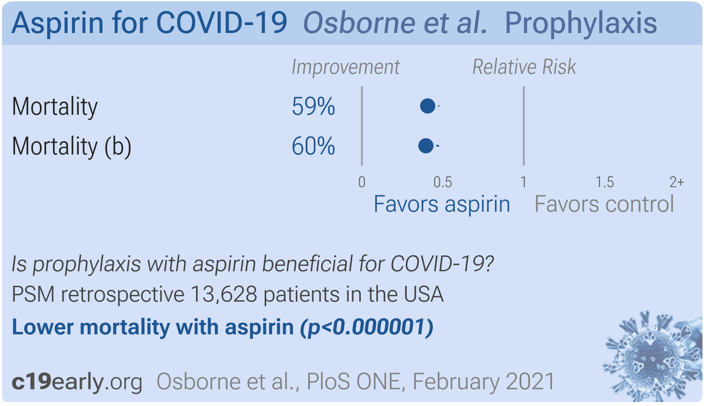
Nimer: Retrospective 2,148 COVID-19 recovered patients in Jordan, showing no significant differences in the risk of severity and hospitalization with aspirin prophylaxis.

Oh



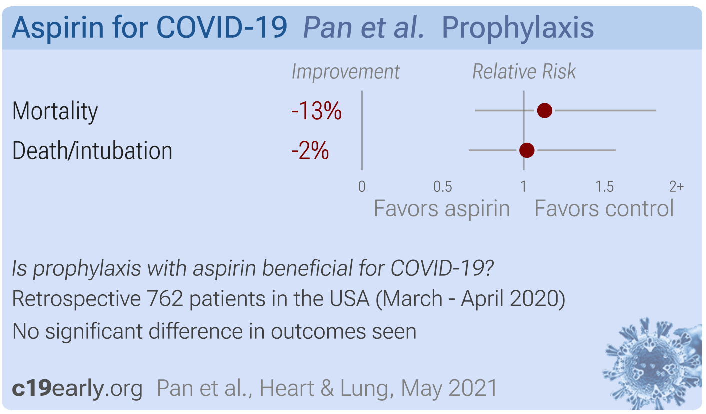
Oh: Retrospective database analysis of 328,374 adults in South Korea, showing lower risk of COVID-19 cases with aspirin use, but no difference in mortality for COVID-19 patients.

Osborne



Osborne: Retrospective PSM analysis of pre-existing aspirin use in the USA, showing lower mortality with treatment.

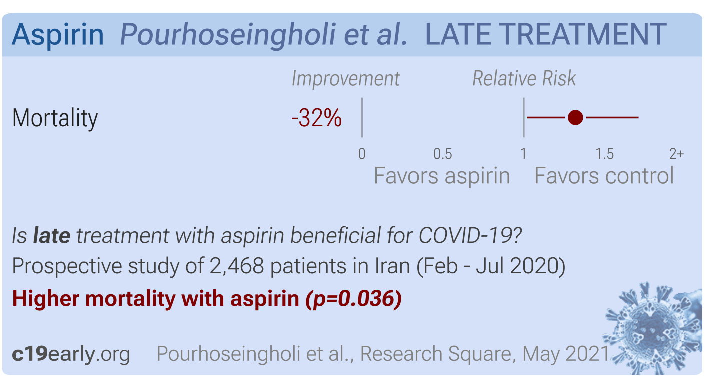
Pan



Pan: Retrospective 762 COVID+ hospitalized patients in the USA, 239 on antiplatelet medication (199 aspirin), showing no significant differences in outcomes.

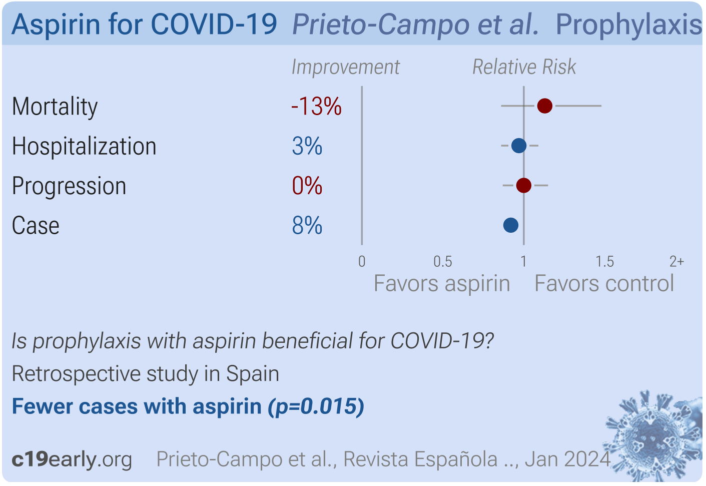
For more discussion see sciencedirect.com.

Pourhoseingholi



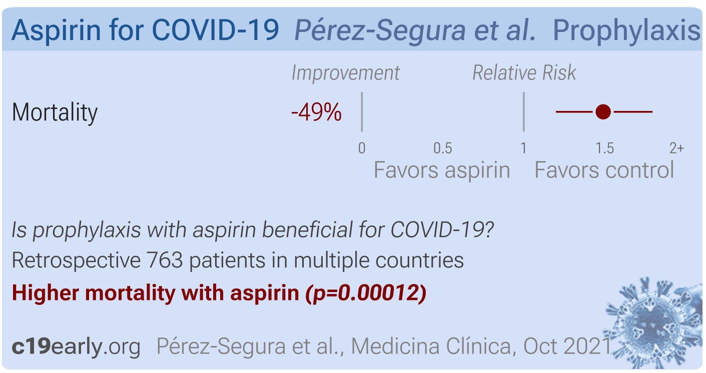
Pourhoseingholi: Prospective study of 2,468 hospitalized COVID-19 patients in Iran, showing higher mortality with aspirin treatment. IR.MUQ.REC.1399.013.

Prieto-Campo



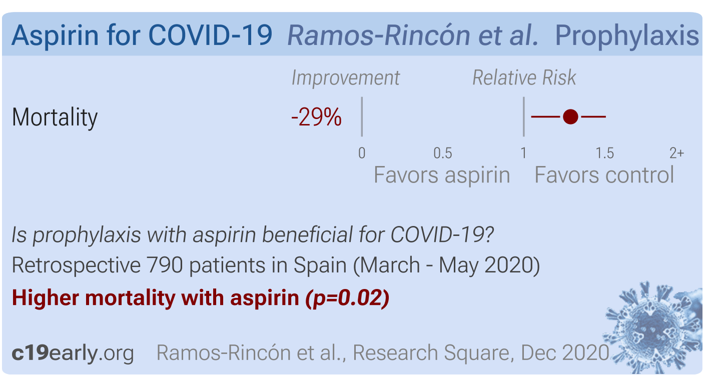
Prieto-Campo: Population-based case-control study of 86,602 people in Spain, shower lower risk of COVID-19 cases with low-dose aspirin, but no significant difference for severity, hospitalization, or mortality.

Pérez-Segura



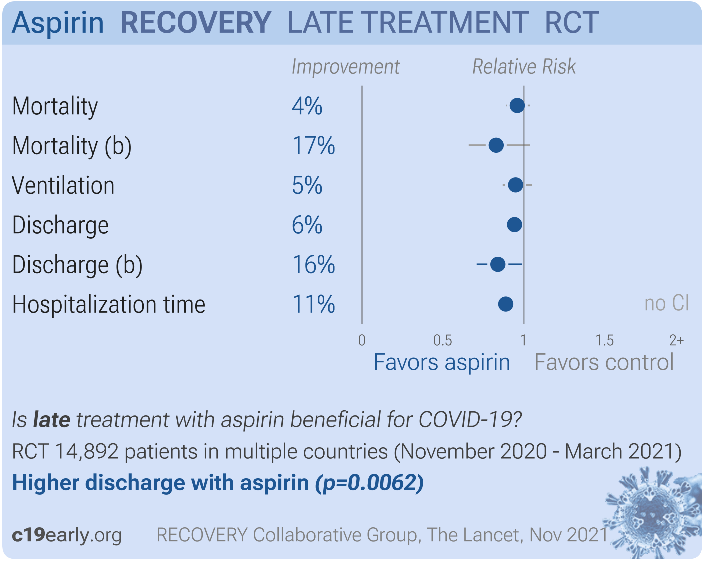
Pérez-Segura: Retrospective 770 COVID-19 patients with cancer, showing increased mortality with aspirin use in unadjusted results.

Ramos-Rincón



Ramos-Rincón: Retrospective 790 hospitalized type 2 diabetes patients ≥80 years old in Spain, showing higher mortality with existing aspirin use.

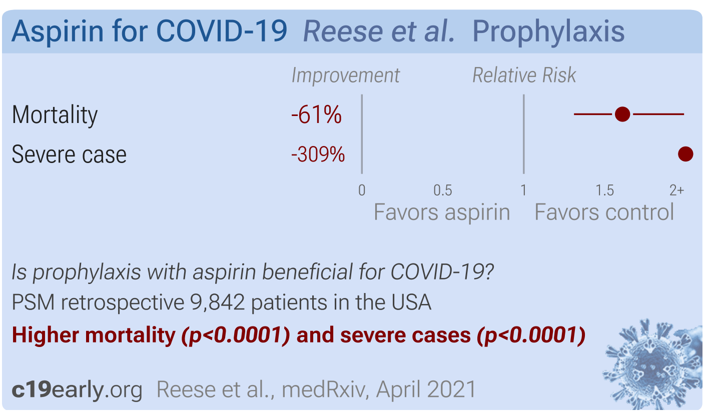
RECOVERY Collaborative Group



RECOVERY Collaborative Group: RCT 14,892 late stage patients, 7,351 treated with aspirin, showing slightly improved discharge and hospitalization time, and no significant difference for mortality.

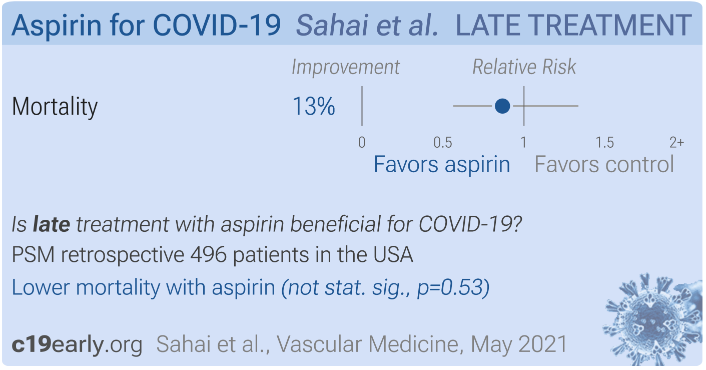
Results are limited due to low dose (150mg daily), very late treatment (9 days post symptom onset), and 96% concurrent use of low molecular weight heparin. Greater benefits were seen for non-LMWH patients, and for very late (<= 7 days from onset) vs. extremely late (>7 days) treatment. For more discussion see twitter.com *(B)*.

Reese



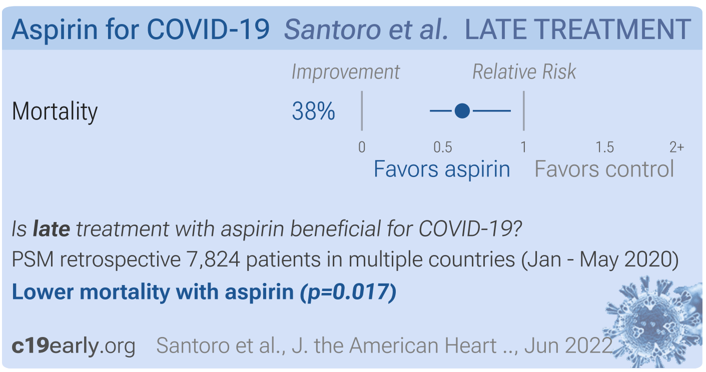
Reese: N3C retrospective 250,533 patients showing significantly higher mortality with aspirin use. Note that aspirin results were not included in the journal version or v2 of this preprint.

Sahai



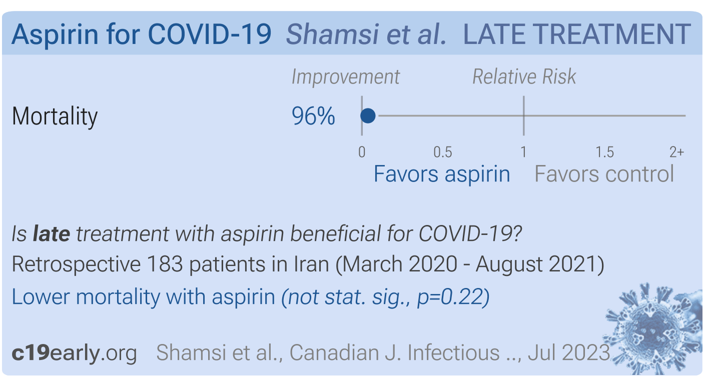
Sahai: PSM retrospective 1,994 PCR+ patients in the USA, not showing a significant difference in mortality with aspirin treatment.

Santoro



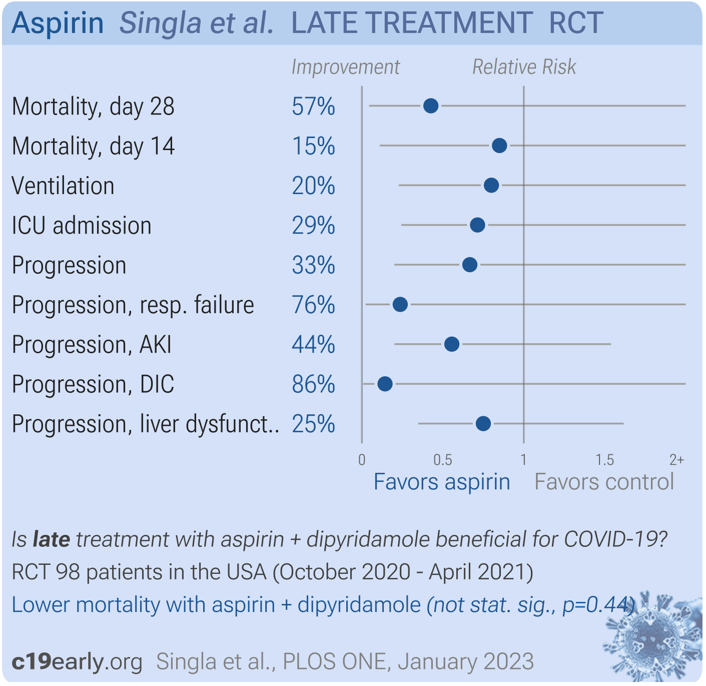
Santoro: HOPE-COVID-19 PSM retrospective 7,824 patients, comparing prophylactic anticoagulation with and without additional treatment with aspirin in hospitalized patients, showing lower mortality with aspirin treatment.

Shamsi



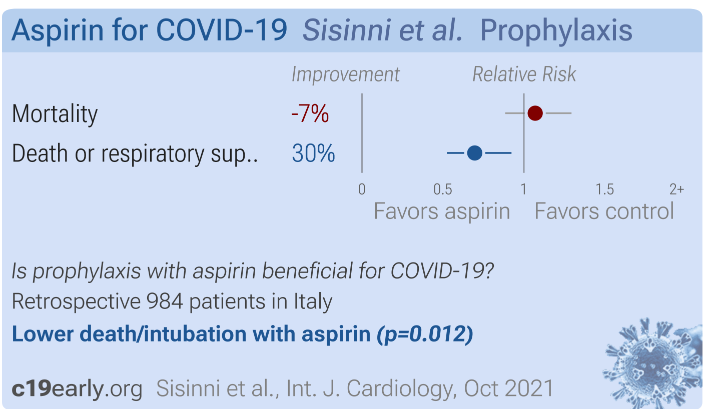
Shamsi: Retrospective 183 hospitalized pediatric COVID-19 patients in Iran, showing no significant difference in mortality with aspirin in unadjusted results.

Singla



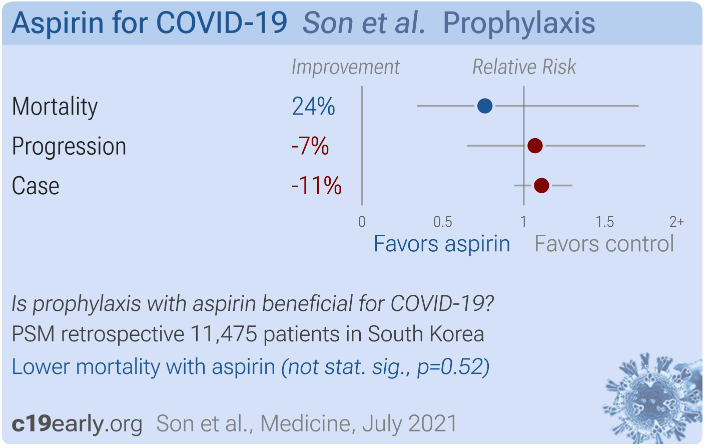
Singla: RCT 98 hospitalized patients in the USA, 49 treated with aspirin and dipyridamole, showing improved results with treatment, but without statistical significance.

Sisinni



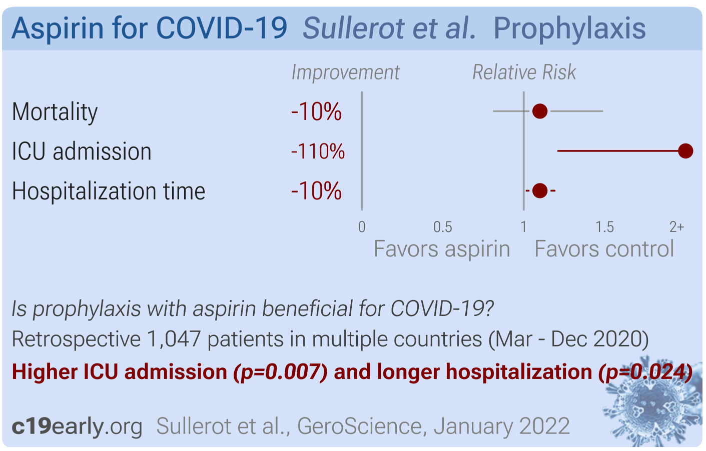
Sisinni: Retrospective 984 COVID-19 patients, 253 taking aspirin prior to admission, showing lower risk of respiratory support upgrade with treatment.

Son



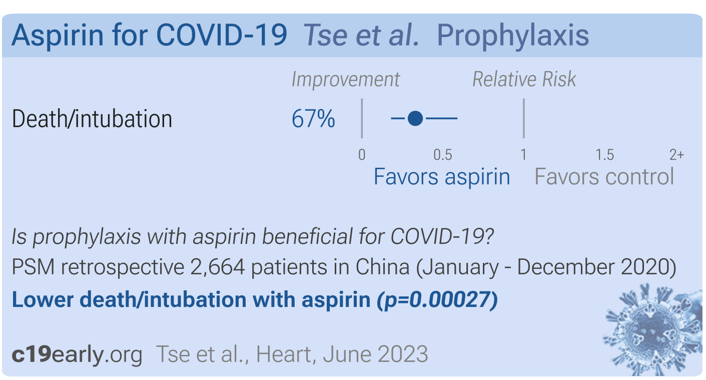
Son: PSM retrospective case control study in South Korea, showing a trend towards lower mortality, but no significant differences with aspirin use.

Sullerot



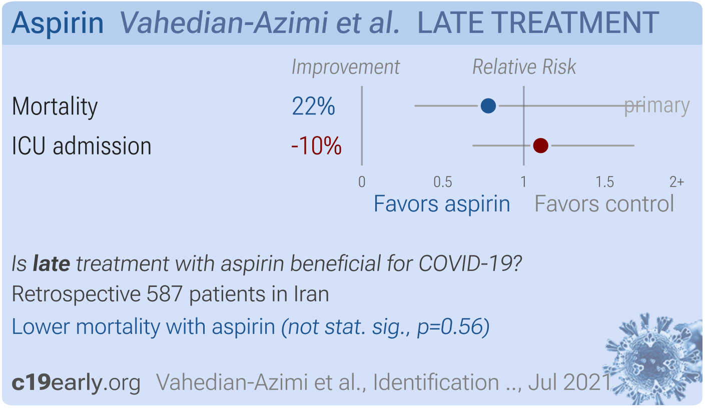
Sullerot: Retrospective 1,047 pneumonia patients in 5 COVID-19 geriatric units in France and Switzerland, significantly higher ICU admission and longer hospital stays with existing aspirin treatment. Numbers in this study appear to be inconsistent, for example the abstract says 147 of 301 aspirin patients died, shown as 34.3%, while Table 1 shows 104 of 301 (34.6%).

Tse



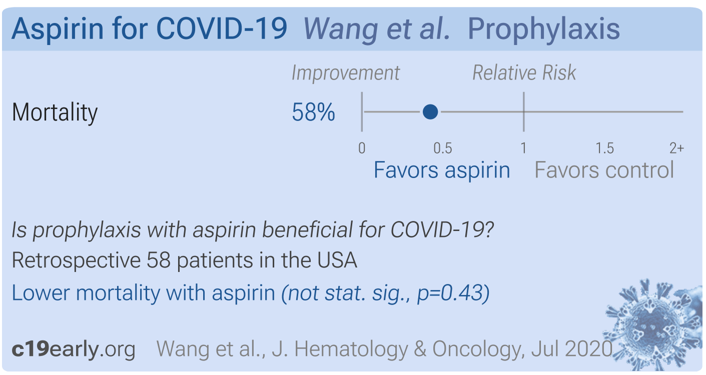
Tse: PSM retrospective 2,664 COVID-19 hospitalized patients receiving steroids/antiviral therapy in Hong Kong, showing lower risk of combined death/intubation with aspirin use.

Vahedian-Azimi



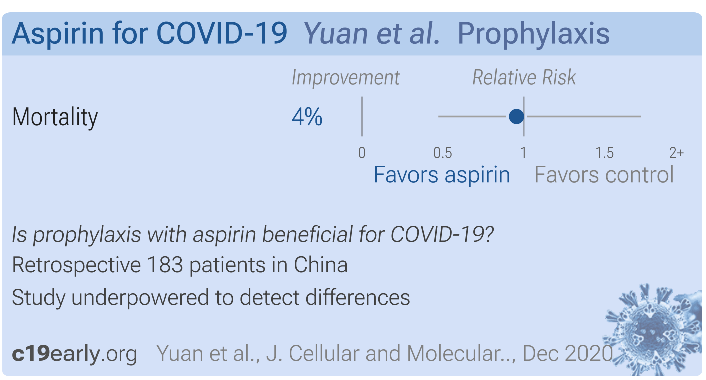
Vahedian-Azimi: Retrospective 587 COVID+ hospitalized patients in Iran, showing no significant differences in outcomes with aspirin treatment.

Wang



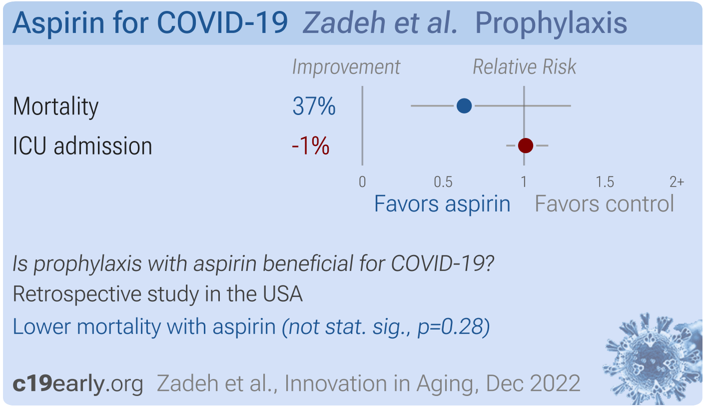
Wang: Retrospective 58 multiple myeloma COVID-19 patients in the USA, showing no significant difference with aspirin treatment.

Yuan



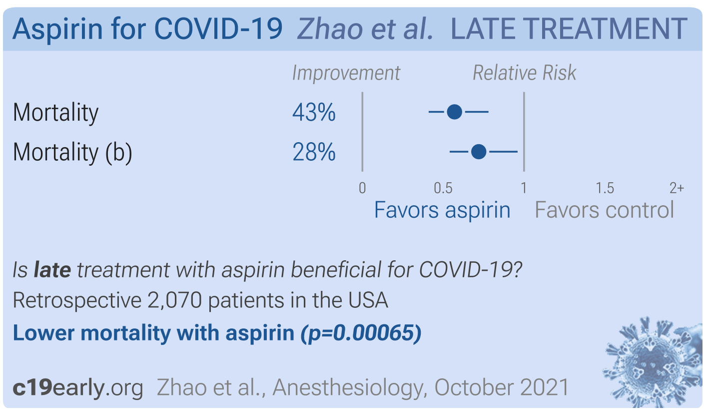
Yuan: Retrospective 183 hospitalized patients in China, 52 taking low-dose aspirin prior to hospitalization, showing no significant difference with treatment.

Zadeh



Zadeh: Retrospective 4,017 coronary artery disease patients hospitalized for COVID-19 in the USA, showing no significant difference in outcomes with low dose aspirin use.

Zhao



Zhao: Retrospective 2,070 hospitalized patients in the USA, showing lower mortality with aspirin treatment.

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 aspirin 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 aspirin 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 (5.20.0).

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/emeta.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.

Connors, 10/11/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 27 authors, study period September 2020 - June 2021, trial NCT04498273 (history) (ACTIV-4B).	risk of hospitalization, 67.3% lower, RR 0.33, *p* = 0.49, treatment 0 of 144 (0.0%), control 1 of 136 (0.7%), NNT 136, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), hospitalization for cardiovascular or pulmonary indication, suspected, started treatment.
	risk of progression, 19.0% lower, RR 0.81, *p* = 0.78, treatment 6 of 144 (4.2%), control 7 of 136 (5.1%), NNT 102, acute medical event, suspected, started treatment.

	risk of progression, 5.6% lower, RR 0.94, $p = 1.00$, treatment 1 of 144 (0.7%), control 1 of 136 (0.7%), NNT 2448, combined endpoint of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, and hospitalization for cardiovascular or pulmonary indication, suspected, started treatment, primary outcome.

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.

Abdelwahab, 7/30/2021, retrospective, Egypt, peer-reviewed, 17 authors.	risk of mechanical ventilation, 7.8% higher, RR 1.08, $p = 0.93$, treatment 11 of 31 (35.5%), control 6 of 36 (16.7%), adjusted per study, odds ratio converted to relative risk.
Aidouni, 11/30/2022, prospective, Morocco, preprint, mean age 64.0, 6 authors, study period March 2020 - March 2022.	risk of death, 30.9% lower, HR 0.69, $p = 0.003$, treatment 202 of 712 (28.4%), control 165 of 412 (40.0%), NNT 8.6, adjusted per study, multivariable, Cox proportional hazards.
	risk of mechanical ventilation, 9.6% lower, RR 0.90, $p = 0.33$, treatment 189 of 712 (26.5%), control 121 of 412 (29.4%), NNT 35.
Al Harthi, 9/3/2021, retrospective, propensity score matching, Saudi Arabia, peer-reviewed, 21 authors.	risk of death, 27.0% lower, HR 0.73, $p = 0.03$, treatment 98 of 176 (55.7%), control 107 of 173 (61.8%), adjusted per study, in-hospital mortality, multivariable Cox proportional hazards.
	risk of death, 14.0% lower, HR 0.86, $p = 0.30$, treatment 95 of 176 (54.0%), control 97 of 175 (55.4%), adjusted per study, day 30, multivariable Cox proportional hazards.
Alamdari, 9/9/2020, retrospective, Iran, peer-reviewed, 14 authors, average treatment delay 5.72 days, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death, 27.7% higher, RR 1.28, $p = 0.52$, treatment 9 of 53 (17.0%), control 54 of 406 (13.3%).
Ali, 10/31/2022, retrospective, Egypt, peer-reviewed, 3 authors.	risk of death, 39.6% lower, RR 0.60, $p < 0.001$, treatment 152 of 660 (23.0%), control 202 of 530 (38.1%), NNT 6.6.
	risk of ARDS, 37.4% lower, RR 0.63, $p = 0.001$, treatment 74 of 660 (11.2%), control 95 of 530 (17.9%), NNT 15.
Bradbury, 3/22/2022, Randomized Controlled Trial, multiple countries, peer-reviewed, 73 authors, study period 30 October, 2020 - 23 June, 2021, trial NCT02735707 (history) (REMAP-CAP).	risk of death, 16.0% lower, HR 0.84, $p = 0.05$, treatment 165 of 563 (29.3%), control 170 of 521 (32.6%), NNT 30, inverted to make HR<1 favor treatment, Kaplan–Meier, day 90.
	risk of no hospital discharge, 16.9% lower, RR 0.83, $p = 0.08$, treatment 161 of 563 (28.6%), control 167 of 521 (32.1%), NNT 29, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.

	risk of progression, 21.0% lower, RR 0.79, $p = 0.02$, treatment 204 of 563 (36.2%), control 212 of 521 (40.7%), adjusted per study, odds ratio converted to relative risk, combined death/thrombosis.
	risk of progression, 4.8% lower, OR 0.95, $p = 0.67$, treatment 563, control 521, adjusted per study, inverted to make OR<1 favor treatment, support-free days, primary outcome, RR approximated with OR.
Chow, 3/24/2022, retrospective, USA, peer-reviewed, median age 63.0, 89 authors.	risk of death, 13.5% lower, RR 0.87, $p < 0.001$, treatment 1,410 of 13,795 (10.2%), control 11,577 of 98,275 (11.8%), NNT 64, adjusted per study, odds ratio converted to relative risk, propensity score weighting.
Chow (B), 4/1/2021, retrospective, USA, peer-reviewed, 38 authors.	risk of death, 47.0% lower, HR 0.53, $p = 0.02$, treatment 26 of 98 (26.5%), control 73 of 314 (23.2%), adjusted per study, Cox proportional hazards.
	risk of mechanical ventilation, 44.0% lower, HR 0.56, $p = 0.007$, treatment 35 of 98 (35.7%), control 152 of 314 (48.4%), NNT 7.9, adjusted per study, Cox proportional hazards.
	risk of ICU admission, 43.0% lower, HR 0.57, $p = 0.007$, treatment 38 of 98 (38.8%), control 160 of 314 (51.0%), NNT 8.2, adjusted per study, Cox proportional hazards.
Eikelboom, 10/10/2022, Randomized Controlled Trial, Canada, peer-reviewed, mean age 45.0, 31 authors, study period 27 August, 2020 - 10 February, 2022, average treatment delay 5.4 days, trial NCT04324463 (history) (ACT outpatient).	risk of death, 9.0% higher, HR 1.09, $p = 0.84$, treatment 12 of 1,945 (0.6%), control 11 of 1,936 (0.6%).
	risk of progression, 20.0% lower, HR 0.80, $p = 0.21$, treatment 59 of 1,945 (3.0%), control 73 of 1,936 (3.8%), NNT 136, major thrombosis, hospitalisation, or death, primary outcome.
	risk of hospitalization, 17.0% lower, HR 0.83, $p = 0.31$, treatment 56 of 1,945 (2.9%), control 67 of 1,936 (3.5%), NNT 172.
Eikelboom (B), 10/10/2022, Randomized Controlled Trial, multiple countries, peer-reviewed, mean age 56.0, 29 authors, study period 2 October, 2020 - 10 February, 2022, average treatment delay 7.0 days, this trial uses multiple treatments in the treatment arm (combined with rivaroxaban) - results of individual treatments may vary, trial NCT04324463 (history) (ACT inpatient).	risk of death, 5.0% higher, HR 1.05, $p = 0.66$, treatment 193 of 1,063 (18.2%), control 186 of 1,056 (17.6%).
	risk of progression, 8.0% lower, HR 0.92, $p = 0.32$, treatment 281 of 1,063 (26.4%), control 300 of 1,056 (28.4%), NNT 51, major thrombosis, high-flow oxygen, ventilation, or death.
	risk of progression, 11.0% lower, HR 0.89, $p = 0.27$, treatment 191 of 1,063 (18.0%), control 210 of 1,056 (19.9%), NNT 52, high-flow oxygen or ventilation.
Elhadi, 4/30/2021, prospective, Libya, peer-reviewed, 21 authors, study period 29 May, 2020 - 30 December, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 9.7% lower, RR 0.90, $p = 0.50$, treatment 22 of 40 (55.0%), control 259 of 425 (60.9%), NNT 17.

Ghati, 7/9/2022, Randomized Controlled Trial, India, peer-reviewed, 14 authors, study period 28 July, 2020 - 27 January, 2021, average treatment delay 6.0 days, trial CTRI/2020/07/026791 (RESIST).	risk of death, 22.1% lower, RR 0.78, *p* = 0.62, treatment 11 of 442 (2.5%), control 7 of 219 (3.2%), NNT 141, aspirin and aspirin/atorvastatin vs. control, modified intention-to-treat.
	risk of death, 57.5% lower, RR 0.42, *p* = 0.22, treatment 3 of 221 (1.4%), control 7 of 219 (3.2%), NNT 54, aspirin vs. control, modified intention-to-treat.
	risk of mechanical ventilation, 9.2% lower, RR 0.91, *p* = 0.80, treatment 11 of 442 (2.5%), control 6 of 219 (2.7%), NNT 398, aspirin and aspirin/atorvastatin vs. control, modified intention-to-treat.
	risk of mechanical ventilation, 50.5% lower, RR 0.50, *p* = 0.34, treatment 3 of 221 (1.4%), control 6 of 219 (2.7%), NNT 72, aspirin vs. control, modified intention-to-treat.
	risk of progression, 30.0% lower, HR 0.70, *p* = 0.46, treatment 11 of 442 (2.5%), control 7 of 219 (3.2%), NNT 141, aspirin and aspirin/atorvastatin vs. control, Cox proportional hazards, modified intention-to-treat, primary outcome.
	risk of progression, 60.0% lower, HR 0.40, *p* = 0.18, treatment 3 of 221 (1.4%), control 7 of 219 (3.2%), NNT 54, aspirin vs. control, Cox proportional hazards, modified intention-to-treat, primary outcome.
Goshua, 11/5/2020, retrospective, USA, peer-reviewed, 15 authors.	risk of death, 35.0% lower, OR 0.65, *p* = 0.04, treatment 319, control 319, propensity score matching, RR approximated with OR.
	risk of mechanical ventilation, 49.0% higher, OR 1.49, *p* = 0.04, treatment 319, control 319, propensity score matching, RR approximated with OR.
	risk of ICU admission, 45.0% higher, OR 1.45, *p* = 0.02, treatment 319, control 319, propensity score matching, RR approximated with OR.
Haji Aghajani, 4/29/2021, retrospective, Iran, peer-reviewed, 7 authors.	risk of death, 24.7% lower, HR 0.75, *p* = 0.04, treatment 336, control 655, adjusted per study, Cox proportional hazards, RR approximated with OR.
Husain, 10/31/2020, retrospective, Bangladesh, preprint, 4 authors.	risk of death, 80.3% lower, RR 0.20, *p* = 0.55, treatment 0 of 11 (0.0%), control 3 of 31 (9.7%), NNT 10, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of no recovery, 64.8% lower, RR 0.35, *p* = 0.40, treatment 1 of 11 (9.1%), control 8 of 31 (25.8%), NNT 6.0.
	complications, 95.8% lower, RR 0.04, *p* = 0.001, treatment 0 of 11 (0.0%), control 17 of 31 (54.8%), NNT 1.8, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

Karimpour-Razkenari, 10/3/2022, retrospective, Iran, peer-reviewed, median age 58.5, 9 authors, study period 23 February, 2020 - 23 May, 2020, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of death, 123.2% higher, RR 2.23, $p = 0.008$, treatment 39 of 90 (43.3%), control 64 of 363 (17.6%), adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable.
Karruli, 9/1/2021, retrospective, Italy, peer-reviewed, 13 authors, study period March 2020 - May 2020.	risk of death, 46.3% lower, RR 0.54, $p = 0.63$, treatment 1 of 5 (20.0%), control 22 of 27 (81.5%), NNT 1.6, adjusted per study, odds ratio converted to relative risk, multivariable.
Kim, 9/4/2021, retrospective, propensity score matching, South Korea, peer-reviewed, 7 authors.	risk of death, 33.7% lower, RR 0.66, $p = 0.22$, treatment 14 of 124 (11.3%), control 23 of 135 (17.0%), NNT 17, PSM.
	risk of mechanical ventilation, 102.2% higher, RR 2.02, $p = 0.16$, treatment 13 of 124 (10.5%), control 7 of 135 (5.2%), PSM.
	risk of ICU admission, 90.5% higher, RR 1.91, $p = 0.36$, treatment 7 of 124 (5.6%), control 4 of 135 (3.0%), PSM.
Lewandowski, 3/7/2024, retrospective, Poland, peer-reviewed, 15 authors.	risk of death, 70.3% higher, OR 1.70, $p = 0.02$, RR approximated with OR.
Liu, 2/12/2021, retrospective, propensity score matching, China, peer-reviewed, 8 authors.	risk of death, 75.0% lower, HR 0.25, $p = 0.03$, treatment 2 of 28 (7.1%), control 11 of 204 (5.4%), adjusted per study, 60 days, KM, PSM.
	risk of death, 81.0% lower, HR 0.19, $p = 0.02$, treatment 1 of 28 (3.6%), control 9 of 204 (4.4%), adjusted per study, 30 days, KM, PSM.
	time to viral-, 1.9% higher, relative time 1.02, $p = 0.94$, treatment 24, control 24, PSM.
Mehrizi, 12/18/2023, retrospective, Iran, peer-reviewed, 10 authors, study period 1 February, 2020 - 20 March, 2022.	risk of death, 16.0% lower, OR 0.84, $p < 0.001$, RR approximated with OR.
Meizlish, 1/21/2021, retrospective, propensity score matching, USA, peer-reviewed, 22 authors.	risk of death, 47.8% lower, HR 0.52, $p = 0.004$, treatment 319, control 319, PSM.
Mura, 3/31/2021, retrospective, database analysis, multiple countries, peer-reviewed, 6 authors.	risk of death, 15.4% lower, RR 0.85, $p = 0.08$, treatment 527, control 527, odds ratio converted to relative risk, aspirin only, control prevalence approximated with treatment prevalence, propensity score matching.
	risk of death, 37.3% lower, RR 0.63, $p = 0.001$, treatment 305, control 305, odds ratio converted to relative risk, famotidine and aspirin, control prevalence approximated with treatment prevalence, propensity score matching.
Mustafa, 12/29/2021, retrospective, Pakistan, peer-reviewed, 7 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 44.1% lower, RR 0.56, $p = 0.28$, treatment 4 of 66 (6.1%), control 41 of 378 (10.8%), NNT 21.

Pourhoseingholi, 5/26/2021, prospective, Iran, preprint, mean age 57.9, 11 authors, study period 2 February, 2020 - 20 July, 2020, average treatment delay 7.4 days.	risk of death, 32.0% higher, HR 1.32, *p* = 0.04, treatment 71 of 290 (24.5%), control 268 of 2,178 (12.3%), adjusted per study, multivariable, Cox proportional hazards.
RECOVERY Collaborative Group, 11/18/2021, Randomized Controlled Trial, multiple countries, peer-reviewed, 1 author, study period 1 November, 2020 - 21 March, 2021, average treatment delay 9.0 days, RECOVERY trial.	risk of death, 4.0% lower, RR 0.96, *p* = 0.35, treatment 7,351, control 7,541.
	risk of death, 17.0% lower, RR 0.83, *p* = 0.35, treatment 7,351, control 7,541, non-LMWH.
	risk of mechanical ventilation, 5.0% lower, RR 0.95, *p* = 0.32, treatment 7,351, control 7,541.
	risk of no hospital discharge, 5.7% lower, RR 0.94, *p* = 0.006, treatment 7,351, control 7,541, inverted to make RR<1 favor treatment.
	risk of no hospital discharge, 16.0% lower, RR 0.84, *p* = 0.04, treatment 7,351, control 7,541, inverted to make RR<1 favor treatment, non-LMWH.
Sahai, 5/19/2021, retrospective, propensity score matching, USA, peer-reviewed, 18 authors.	risk of death, 13.2% lower, RR 0.87, *p* = 0.53, treatment 33 of 248 (13.3%), control 38 of 248 (15.3%), NNT 50.
Santoro, 6/22/2022, retrospective, propensity score matching, multivariable, multiple countries, peer-reviewed, 31 authors, study period 16 January, 2020 - 30 May, 2020.	risk of death, 38.0% lower, HR 0.62, *p* = 0.02, treatment 360, control 2,949.
Shamsi, 7/17/2023, retrospective, Iran, peer-reviewed, 4 authors, study period 1 March, 2020 - 1 August, 2021, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 96.3% lower, RR 0.04, *p* = 0.22, treatment 0 of 13 (0.0%), control 24 of 170 (14.1%), NNT 7.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Singla, 1/30/2023, Randomized Controlled Trial, USA, peer-reviewed, 26 authors, study period 1 October, 2020 - 30 April, 2021, this trial uses multiple treatments in the treatment arm (combined with dipyridamole) - results of individual treatments may vary, trial NCT04410328 (history).	risk of death, 57.4% lower, RR 0.43, *p* = 0.44, treatment 3 of 49 (6.1%), control 5 of 49 (10.2%), adjusted per study, odds ratio converted to relative risk, multivariable, day 28.
	risk of death, 15.0% lower, OR 0.85, *p* = 0.87, treatment 49, control 49, adjusted per study, multivariable, day 14, RR approximated with OR.
	risk of mechanical ventilation, 20.0% lower, RR 0.80, *p* = 1.00, treatment 4 of 49 (8.2%), control 5 of 49 (10.2%), NNT 49.
	risk of ICU admission, 28.6% lower, RR 0.71, *p* = 0.76, treatment 5 of 49 (10.2%), control 7 of 49 (14.3%), NNT 25.
	risk of progression, 33.3% lower, RR 0.67, *p* = 0.74, treatment 4 of 49 (8.2%), control 6 of 49 (12.2%), NNT 24, day 28.
	risk of progression, 76.3% lower, RR 0.24, *p* = 0.22, treatment 4 of 49 (8.2%), control 7 of 49 (14.3%), odds ratio converted to relative risk, respiratory failure, day 28.

	risk of progression, 44.4% lower, RR 0.56, *p* = 0.39, treatment 5 of 49 (10.2%), control 9 of 49 (18.4%), NNT 12, AKI.
	risk of progression, 85.7% lower, RR 0.14, *p* = 0.24, treatment 0 of 49 (0.0%), control 3 of 49 (6.1%), NNT 16, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), DIC.
	risk of progression, 25.0% lower, RR 0.75, *p* = 0.62, treatment 9 of 49 (18.4%), control 12 of 49 (24.5%), NNT 16, liver dysfunction.
Vahedian-Azimi, 7/20/2021, retrospective, Iran, peer-reviewed, 9 authors.	**risk of death, 21.9% lower, RR 0.78, *p* = 0.56**, treatment 13 of 337 (3.9%), control 28 of 250 (11.2%), adjusted per study, odds ratio converted to relative risk, multivariable, primary outcome.
	risk of ICU admission, 10.5% higher, RR 1.10, *p* = 0.67, treatment 36 of 337 (10.7%), control 44 of 250 (17.6%), adjusted per study, odds ratio converted to relative risk, multivariable.
Zhao, 10/1/2021, retrospective, USA, peer-reviewed, 6 authors.	**risk of death, 43.0% lower, HR 0.57, *p* < 0.001**, treatment 121 of 473 (25.6%), control 140 of 473 (29.6%), adjusted per study, PSM.
	risk of death, 28.0% lower, HR 0.72, *p* = 0.03, treatment 473, control 1,597, adjusted per study, multivariable.

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.

Abul, 8/4/2022, retrospective, USA, preprint, mean age 72.3, 10 authors, study period 13 December, 2020 - 18 September, 2021.	**risk of death, 33.0% lower, HR 0.67, *p* = 0.03**, treatment 46 of 511 (9.0%), control 201 of 1,176 (17.1%), Cox proportional hazards, day 56.
	risk of death, 40.0% lower, HR 0.60, *p* = 0.01, treatment 33 of 511 (6.5%), control 154 of 1,176 (13.1%), Cox proportional hazards, day 30.
	risk of hospitalization, 20.0% lower, HR 0.80, *p* = 0.13, treatment 103 of 511 (20.2%), control 352 of 1,176 (29.9%), Cox proportional hazards.
Ali (B), 11/19/2022, retrospective, USA, peer-reviewed, 8 authors.	**risk of death, 28.0% lower, HR 0.72, *p* = 0.07**, treatment 481, control 1,164, Cox proportional hazards.
Aweimer, 3/29/2023, retrospective, Germany, peer-reviewed, median age 67.0, 19 authors, study period 1 March, 2020 - 31 August, 2021, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 9.6% higher, RR 1.10, *p* = 0.43**, treatment 34 of 44 (77.3%), control 74 of 105 (70.5%).

Azizi, 2/17/2023, retrospective, Iran, peer-reviewed, 6 authors, excluded in exclusion analyses: age matching based on only two categories, matching may be very poor given the relationship between age and COVID-19 risk; inconsistent data.	risk of death, no change, RR 1.00, *p* = 1.00, treatment 17 of 131 (13.0%), control 17 of 131 (13.0%).
Basheer, 10/2/2021, retrospective, Israel, peer-reviewed, 4 authors.	risk of death, 13.0% higher, RR 1.13, *p* < 0.001, treatment 45 of 140 (32.1%), control 29 of 250 (11.6%), adjusted per study, odds ratio converted to relative risk, group sizes approximated (only percentages provided).
Bejan, 2/28/2021, retrospective, USA, peer-reviewed, mean age 42.0, 6 authors.	risk of mechanical ventilation, 1.0% lower, OR 0.99, *p* = 0.97, treatment 1,899, control 7,330, adjusted per study, RR approximated with OR.
Botton, 6/17/2022, retrospective, France, peer-reviewed, 7 authors.	risk of death/intubation, 4.0% higher, HR 1.04, *p* = 0.18, Cox proportional hazards.
	risk of hospitalization, 3.0% higher, HR 1.03, *p* = 0.046, Cox proportional hazards.
Campbell, 5/5/2022, retrospective, USA, peer-reviewed, 4 authors, study period 2 March, 2020 - 14 December, 2020.	risk of death, 3.0% lower, OR 0.97, *p* = 0.06, treatment 419, control 20,311, adjusted per study, propensity score weighting, multivariable, day 60, RR approximated with OR.
	risk of death, 2.0% lower, OR 0.98, *p* = 0.10, treatment 419, control 20,311, adjusted per study, propensity score weighting, multivariable, day 30, RR approximated with OR.
Chow (C), 8/29/2021, retrospective, propensity score matching, USA, peer-reviewed, 12 authors.	risk of death, 19.0% lower, HR 0.81, *p* < 0.005, treatment 1,280 of 6,781 (18.9%), control 2,271 of 10,566 (21.5%), NNT 38, adjusted per study, Kaplan Meier.
	risk of mechanical ventilation, 2.8% lower, HR 0.97, *p* = 0.21, treatment 2,122 of 6,781 (31.3%), control 3,403 of 10,566 (32.2%), NNT 109.
Drew, 5/2/2021, retrospective, multiple countries, preprint, 25 authors, study period 24 March, 2020 - 8 May, 2020.	risk of progression, 22.0% lower, HR 0.78, *p* = 0.30, adjusted per study, seen in hospital/clinic, comorbidity and symptom adjusted, multivariable.
	risk of case, 3.0% higher, HR 1.03, *p* = 0.80, adjusted per study, comorbidity and symptom adjusted, multivariable.
Formiga, 11/29/2021, retrospective, USA, peer-reviewed, 24 authors, study period 1 March, 2020 - 1 May, 2021.	risk of death, 3.4% higher, RR 1.03, *p* = 0.48, treatment 1,000 of 3,291 (30.4%), control 874 of 2,885 (30.3%), odds ratio converted to relative risk, propensity score matching.
	risk of mechanical ventilation, 3.2% higher, RR 1.03, *p* = 0.75, treatment 213 of 3,291 (6.5%), control 181 of 2,885 (6.3%), propensity score matching.
	risk of ICU admission, 4.2% higher, RR 1.04, *p* = 0.65, treatment 283 of 3,291 (8.6%), control 238 of 2,885 (8.2%), propensity score matching.

Gogtay, 3/9/2022, retrospective, USA, peer-reviewed, 4 authors, study period March 2020 - April 2020.	**risk of death, 5.9% higher, RR 1.06, *p* = 0.87**, treatment 12 of 38 (31.6%), control 21 of 87 (24.1%), adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable.
	risk of mechanical ventilation, 49.8% lower, RR 0.50, *p* = 0.16, treatment 5 of 38 (13.2%), control 21 of 87 (24.1%), NNT 9.1, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of ICU admission, 49.2% lower, RR 0.51, *p* = 0.41, treatment 9 of 38 (23.7%), control 38 of 87 (43.7%), NNT 5.0, adjusted per study, odds ratio converted to relative risk, multivariable.
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, 34.0% higher, RR 1.34, *p* = 0.09**, treatment 35 of 116 (30.2%), control 129 of 573 (22.5%).
Huh, 5/4/2020, retrospective, database analysis, South Korea, preprint, 10 authors.	**risk of case, 71.0% lower, RR 0.29, *p* = 0.001**, treatment 8 of 543 (1.5%), control 5,164 of 64,606 (8.0%), adjusted per study, multivariable.
Kim (B), 9/4/2021, retrospective, propensity score matching, South Korea, peer-reviewed, 7 authors.	**risk of death, 700.0% higher, RR 8.00, *p* = 0.03**, treatment 6 of 15 (40.0%), control 1 of 20 (5.0%), PSM, prior aspirin use.
	risk of mechanical ventilation, 433.3% higher, RR 5.33, *p* = 0.14, treatment 4 of 15 (26.7%), control 1 of 20 (5.0%), PSM, prior aspirin use.
	risk of ICU admission, 433.3% higher, RR 5.33, *p* = 0.14, treatment 4 of 15 (26.7%), control 1 of 20 (5.0%), PSM, prior aspirin use.
	risk of case, 33.4% lower, RR 0.67, *p* = 0.29, treatment 15 of 136 (11.0%), control 20 of 136 (14.7%), NNT 27, adjusted per study, odds ratio converted to relative risk, PSM, logistic regression, prior aspirin use.
	risk of death, 33.7% lower, RR 0.66, *p* = 0.22, treatment 14 of 124 (11.3%), control 23 of 135 (17.0%), NNT 17, PSM, aspirin treatment after diagnosis.
	risk of mechanical ventilation, 102.2% higher, RR 2.02, *p* = 0.16, treatment 13 of 124 (10.5%), control 7 of 135 (5.2%), PSM, aspirin treatment after diagnosis.
	risk of ICU admission, 90.5% higher, RR 1.91, *p* = 0.36, treatment 7 of 124 (5.6%), control 4 of 135 (3.0%), PSM, aspirin treatment after diagnosis.
Lal, 5/5/2022, retrospective, USA, peer-reviewed, 20 authors, study period 15 February, 2020 - 30 September, 2021, trial NCT04323787 (history).	**risk of death, 11.0% lower, HR 0.89, *p* = 0.01**, treatment 4,691, control 16,888, adjusted per study, multivariable.
	risk of ICU admission, 22.0% lower, HR 0.78, *p* < 0.001, treatment 4,691, control 16,888, adjusted per study,

	multivariable.
	risk of progression, 9.0% lower, HR 0.91, $p = 0.02$, treatment 4,691, control 16,888, adjusted per study, multivariable.
Levy, 1/31/2022, retrospective, Israel, peer-reviewed, 10 authors.	**risk of death/hospitalization, 26.0% lower, HR 0.74, $p = 0.13$**, treatment 29 of 159 (18.2%), control 178 of 690 (25.8%), NNT 13, adjusted per study, multivariable, Cox proportional hazards, day 40.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	**risk of death, 17.7% lower, HR 0.82, $p < 0.001$**, treatment 2,127, control 13,841, Cox proportional hazards, day 30.
Ma, 8/18/2021, retrospective, propensity score matching, United Kingdom, peer-reviewed, 9 authors.	**risk of death, 9.0% lower, OR 0.91, $p = 0.12$**, treatment 12,471, control 64,750, RR approximated with OR.
	risk of hospitalization, 2.0% lower, OR 0.98, $p = 0.47$, treatment 12,471, control 64,750, RR approximated with OR.
	risk of symptomatic case, 9.0% higher, OR 1.09, $p = 0.18$, treatment 12,471, control 64,750, RR approximated with OR.
	risk of case, 7.0% higher, OR 1.07, $p = 0.09$, treatment 12,471, control 64,750, RR approximated with OR.
Malik, 7/11/2022, retrospective, USA, peer-reviewed, 16 authors, study period 1 March, 2020 - 1 December, 2020.	**risk of death, 13.6% lower, RR 0.86, $p = 0.72$**, treatment 15 of 87 (17.2%), control 24 of 223 (10.8%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of ICU admission, 27.8% lower, RR 0.72, $p = 0.17$, treatment 28 of 87 (32.2%), control 77 of 223 (34.5%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of ARDS, 25.1% lower, RR 0.75, $p = 0.39$, treatment 13 of 87 (14.9%), control 40 of 223 (17.9%), NNT 33, adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of hospitalization, 2.4% lower, OR 0.98, $p = 0.94$, treatment 25, control 176, adjusted per study, multivariable, RR approximated with OR.
Merzon, 2/23/2021, retrospective, Israel, peer-reviewed, 8 authors.	**risk of case, 27.6% lower, RR 0.72, $p = 0.04$**, treatment 73 of 1,621 (4.5%), control 589 of 8,856 (6.7%), NNT 47, adjusted per study, odds ratio converted to relative risk.
	risk of death, 62.4% lower, RR 0.38, $p = 0.51$, treatment 1 of 21 (4.8%), control 6 of 91 (6.6%), adjusted per study, odds ratio converted to relative risk.
	time to viral-, 9.6% lower, relative time 0.90, $p = 0.045$, treatment 73, control 589, time to 2nd negative test.
	time to viral-, 14.8% lower, relative time 0.85, $p = 0.005$, treatment 73, control 589, time to 1st negative test.

Monserrat Villatoro, 1/8/2022, retrospective, propensity score matching, Spain, peer-reviewed, 18 authors.	**risk of death, 31.0% higher, OR 1.31, *p* = 0.04**, RR approximated with OR.
Morrison, 10/10/2022, retrospective, USA, peer-reviewed, mean age 62.5, 3 authors, study period March 2020 - March 2021.	**risk of death, 7.7% lower, OR 0.92, *p* = 0.52**, treatment 1,667, control 1,667, propensity score matching, RR approximated with OR.
	risk of mechanical ventilation, 0.9% higher, OR 1.01, *p* = 0.96, treatment 1,667, control 1,667, propensity score matching, RR approximated with OR.
	risk of ICU admission, 12.2% higher, OR 1.12, *p* = 0.36, treatment 1,667, control 1,667, propensity score matching, RR approximated with OR.
	risk of hospitalization, 18.3% higher, OR 1.18, *p* = 0.04, treatment 1,667, control 1,667, propensity score matching, RR approximated with OR.
Mulhem, 4/7/2021, retrospective, database analysis, USA, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; substantial confounding by time likely due to declining usage over the early stages of the pandemic when overall treatment protocols improved dramatically.	**risk of death, 13.9% higher, RR 1.14, *p* = 0.21**, treatment 300 of 1,354 (22.2%), control 216 of 1,865 (11.6%), adjusted per study, odds ratio converted to relative risk, Table S1, logistic regression.
Nimer, 2/28/2022, retrospective, Jordan, peer-reviewed, survey, 4 authors, study period March 2021 - July 2021.	**risk of hospitalization, 3.7% lower, RR 0.96, *p* = 0.08**, treatment 83 of 427 (19.4%), control 136 of 1,721 (7.9%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of severe case, 17.8% higher, RR 1.18, *p* = 0.28, treatment 98 of 427 (23.0%), control 162 of 1,721 (9.4%), adjusted per study, odds ratio converted to relative risk, multivariable.
Oh, 6/17/2021, retrospective, database analysis, South Korea, peer-reviewed, 4 authors.	**risk of death, 1.0% lower, OR 0.99, *p* = 0.95**, adjusted per study, multivariable, RR approximated with OR.
	risk of case, 12.0% lower, RR 0.88, *p* = 0.04, adjusted per study, odds ratio converted to relative risk, multivariable, control prevalance approximated with overall prevalence.
Osborne, 2/11/2021, retrospective, propensity score matching, USA, peer-reviewed, 6 authors.	**risk of death, 59.4% lower, RR 0.41, *p* < 0.001**, treatment 272 of 6,300 (4.3%), control 661 of 6,300 (10.5%), NNT 16, odds ratio converted to relative risk, 30 days, PSM.
	risk of death, 60.5% lower, RR 0.40, *p* < 0.001, treatment 170 of 6,814 (2.5%), control 427 of 6,814 (6.3%), NNT 27, odds ratio converted to relative risk, 14 days, PSM.
Pan, 5/26/2021, retrospective, USA, peer-reviewed, 11 authors, study period 1 March, 2020 - 9 April, 2020.	**risk of death, 13.0% higher, OR 1.13, *p* = 0.63**, treatment 239, control 523, adjusted per study, MOS 6 vs. <6, multivariable, RR approximated with OR.

	risk of death/intubation, 2.0% higher, OR 1.02, $p = 0.93$, treatment 239, control 523, adjusted per study, MOS 5+ vs. <5, multivariable, RR approximated with OR.
Prieto-Campo, 1/6/2024, retrospective, Spain, peer-reviewed, 6 authors.	risk of death, 13.0% higher, OR 1.13, $p = 0.38$, adjusted per study, case control OR.
	risk of hospitalization, 3.0% lower, OR 0.97, $p = 0.64$, adjusted per study, case control OR.
	risk of progression, no change, OR 1.00, $p = 0.98$, adjusted per study, case control OR.
	risk of case, 8.0% lower, OR 0.92, $p = 0.02$, adjusted per study, case control OR.
Pérez-Segura, 10/4/2021, retrospective, multiple countries, peer-reviewed, 23 authors.	risk of death, 49.1% higher, RR 1.49, $p < 0.001$, treatment 66 of 155 (42.6%), control 183 of 608 (30.1%), odds ratio converted to relative risk.
Ramos-Rincón, 12/28/2020, retrospective, Spain, preprint, 25 authors, study period 1 March, 2020 - 29 May, 2020.	risk of death, 28.9% higher, RR 1.29, $p = 0.02$, treatment 132 of 264 (50.0%), control 253 of 526 (48.1%), adjusted per study, odds ratio converted to relative risk, multivariable.
Reese, 4/20/2021, retrospective, USA, preprint, 23 authors.	risk of death, 61.0% higher, HR 1.61, $p < 0.001$, treatment 4,921, control 4,921, propensity score matching, Cox proportional hazards, Table S55.
	risk of severe case, 309.0% higher, OR 4.09, $p < 0.001$, treatment 4,921, control 4,921, propensity score matching, Table S47, RR approximated with OR.
Sisinni, 10/4/2021, retrospective, Italy, peer-reviewed, 18 authors.	risk of death, 7.1% higher, RR 1.07, $p = 0.65$, treatment 93 of 253 (36.8%), control 251 of 731 (34.3%).
	risk of death or respiratory support upgrade, 30.3% lower, RR 0.70, $p = 0.01$, treatment 253, control 731, multivariate.
Son, 7/30/2021, retrospective, propensity score matching, South Korea, peer-reviewed, 6 authors.	risk of death, 24.0% lower, OR 0.76, $p = 0.52$, treatment 37 of 128 (28.9%) cases, 31 of 128 (24.2%) controls, adjusted per study, case control OR, group 1, model 2 (most data in group and adjustments), multivariable.
	risk of progression, 7.0% higher, OR 1.07, $p = 0.80$, treatment 77 of 339 (22.7%) cases, 58 of 339 (17.1%) controls, adjusted per study, case control OR, complications, group 1, model 2 (most data in group and adjustments), multivariable.
	risk of case, 11.0% higher, OR 1.11, $p = 0.21$, treatment 313 of 3,825 (8.2%) cases, 617 of 7,650 (8.1%) controls, adjusted per study, case control OR, group 1, PSM 1, model 2 (most data in group and adjustments), multivariable.

Sullerot, 1/7/2022, retrospective, propensity score weighting, multiple countries, peer-reviewed, 15 authors, study period 1 March, 2020 - 31 December, 2020.	risk of death, 10.0% higher, RR 1.10, *p* = 0.52, treatment 101 of 301 (33.6%), control 224 of 746 (30.0%).
	risk of ICU admission, 109.7% higher, RR 2.10, *p* = 0.007, treatment 22 of 301 (7.3%), control 26 of 746 (3.5%).
	hospitalization time, 10.0% higher, relative time 1.10, *p* = 0.02, treatment 301, control 746.
Tse, 6/2/2023, retrospective, China, peer-reviewed, 12 authors, study period 1 January, 2020 - 8 December, 2020.	risk of death/intubation, 67.0% lower, OR 0.33, *p* < 0.001, adjusted per study, propensity score matching, multivariable, day 30, RR approximated with OR.
Wang, 7/14/2020, retrospective, USA, peer-reviewed, 13 authors.	risk of death, 57.7% lower, RR 0.42, *p* = 0.43, treatment 1 of 9 (11.1%), control 13 of 49 (26.5%), NNT 6.5, odds ratio converted to relative risk.
Yuan, 12/18/2020, retrospective, China, peer-reviewed, 6 authors.	risk of death, 4.4% lower, RR 0.96, *p* = 0.89, treatment 11 of 52 (21.2%), control 29 of 131 (22.1%), NNT 102, odds ratio converted to relative risk, mutivariate.
Zadeh, 12/20/2022, retrospective, USA, peer-reviewed, mean age 62.2, 8 authors.	risk of death, 37.0% lower, RR 0.63, *p* = 0.28.
	risk of ICU admission, 1.0% higher, RR 1.01, *p* = 0.79.

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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