Metformin for COVID-19: real-time meta analysis of 84 studies

@CovidAnalysis, March 2024, Version 71
https://c19early.org/mfmeta.html

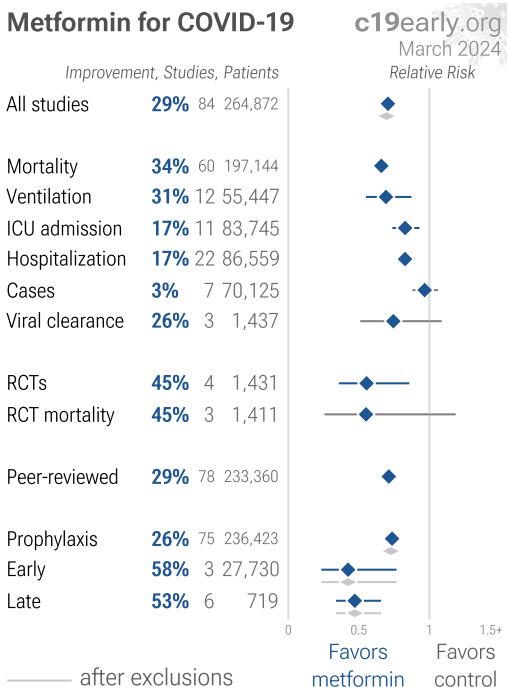
Abstract

Statistically significant lower risk is seen for mortality, ventilation, ICU admission, hospitalization, progression, and recovery. 53 studies from 50 independent teams in 17 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 29% [25-33%] lower risk. Results are similar for higher quality and peer-reviewed studies and better for Randomized Controlled Trials.

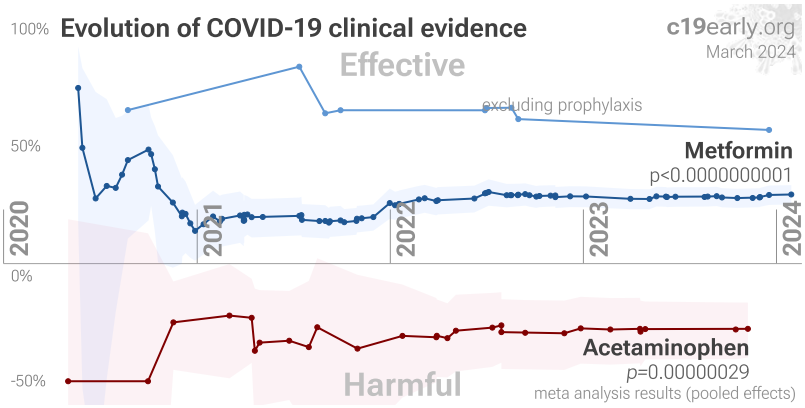
Results are robust — in exclusion sensitivity analysis 64 of 84 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Most studies analyze existing use with diabetic patients, and many results may be subject to confounding by indication — metformin is typically used early in the progression of type 2 diabetes. Prophylaxis results typically include continuing use after infection and hospitalization, and greater benefit is seen for more serious outcomes. The TOGETHER RCT shows 27% lower mortality. While not statistically significant, p = 0.53, this is consistent with the mortality results from all studies, 34% [29-39%].



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 more effective.

All data to reproduce this paper and sources are in the appendix. Other meta analyses show significant improvements with metformin for mortality *Hariyanto, Kan, Kow, Li, Lukito, Ma, Oscanoa, Parveen, Petrelli, Poly, Schlesinger, Yang*, hospitalization *Li*, progression *Yang*, and severity *Petrelli, Schlesinger*.



HIGHLIGHTS

Metformin reduces risk for COVID-19 with very high confidence for mortality, ventilation, ICU admission, hospitalization, progression, recovery, and in pooled analysis, and very low confidence for viral clearance.

Metformin was the 3rd treatment shown effective with ≥3 clinical studies in July 2020, now known with $p < 0.00000000001$ from 84 studies.

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

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

84 metformin COVID-19 studies

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	Improvement, RR [CI]			Treatment	Control
Reis (DB RCT)	27%	0.73 [0.28-1.94]	death	7/215	9/203
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	death	1/408	1/396
Early treatment	**58%**	0.42 [0.23-0.77]		81/4,579	1,549/23,151

$Tau^2 = 0.12$, $I^2 = 33.5\%$, $p = 0.0046$

	Improvement, RR [CI]			Treatment	Control
Abu-Jamous	65%	0.35 [0.11-0.84]	death	4/23	94/168
Tamura	97%	0.03 [0.00-0.58]	death	115 (n)	73 (n)
Li	76%	0.24 [0.06-0.98]	death	2/37	21/94
Shaseb (RCT)	74%	0.26 [0.06-1.06]	death	85 (n)	104 (n)
Ventura-.. (DB RCT)	44%	0.56 [0.33-0.95]	oxygen time	10 (n)	10 (n)
Mehrizi	44%	0.56 [0.53-0.60]	death	population-based cohort	
Late treatment	**53%**	0.47 [0.34-0.66]		6/270	115/449

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Choi (PSM)	-120%	2.20 [0.51-9.58]	progression	case control	
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49
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Pérez-Bel.. (PSM)	-10%	1.10 [0.84-1.40]	death	79/249	79/249
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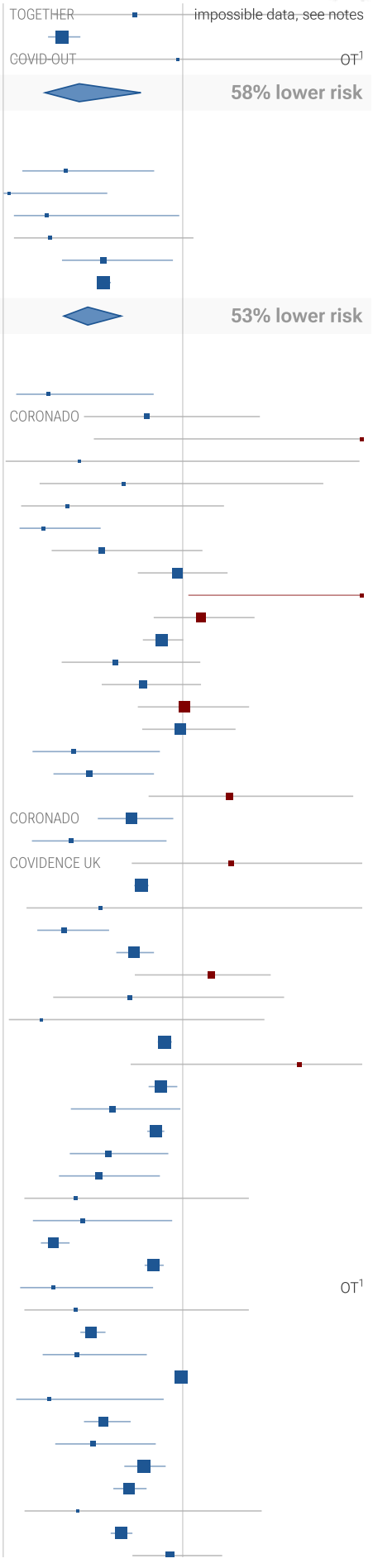
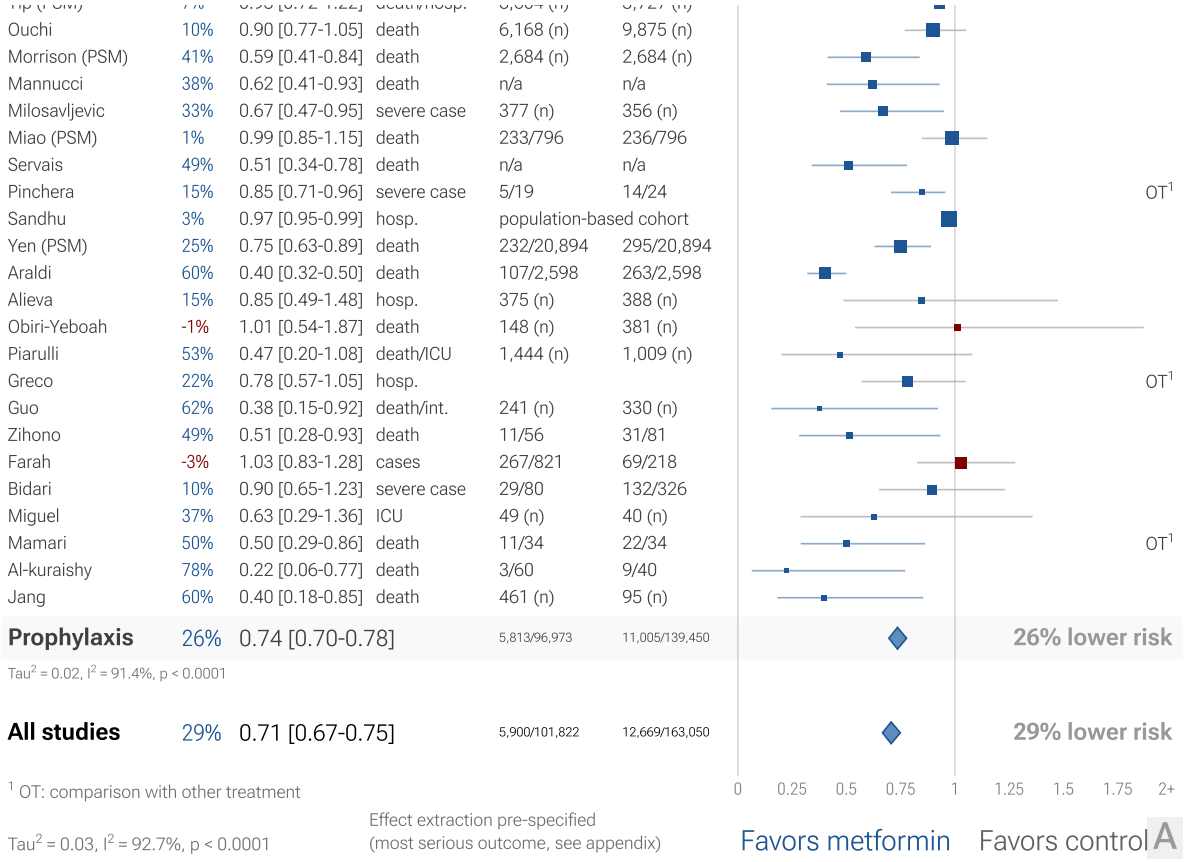
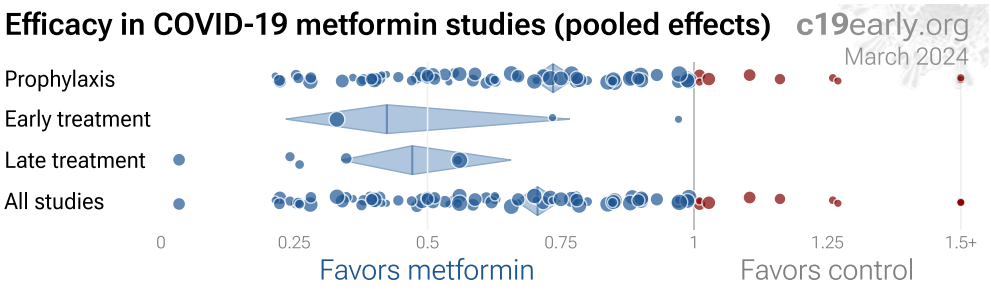
Khunti	23%	0.77 [0.73-0.81]	death	population-based cohort	
Jiang (PSM)	46%	0.54 [0.13-2.26]	death	3/74	10/74
Ghany	66%	0.34 [0.19-0.59]	death	392 (n)	747 (n)
Alamgir	27%	0.73 [0.63-0.84]	death	11,062 (n)	11,062 (n)
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	death	20 (n)	83 (n)
Ravindra	30%	0.70 [0.28-1.56]	death	5/53	57/313
Blanc	79%	0.21 [0.03-1.46]	death	1/14	25/75
Boye	10%	0.90 [0.86-0.94]	hosp.	2,067/4,250	3,196/5,281
Cheng (PSM)	-65%	1.65 [0.71-3.86]	death	678 (n)	535 (n)
Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)
Ando	39%	0.61 [0.38-0.99]	hosp.		
Wander	15%	0.85 [0.80-0.90]	death		
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169
Bliden	60%	0.40 [0.12-1.37]	death	3/34	9/41
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41
Wong	51%	0.49 [0.43-0.57]	death		
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort	
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)
Chan	59%	0.41 [0.12-1.44]	death	400 (n)	2,736 (n)
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort	
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)




Ouchi 10% 0.90 [0.77-1.05] death 6,168 (n) 9,875 (n)
Morrison (PSM) 41% 0.59 [0.41-0.84] death 2,684 (n) 2,684 (n)
Mannucci 38% 0.62 [0.41-0.93] death n/a n/a
Milosavljevic 33% 0.67 [0.47-0.95] severe case 377 (n) 356 (n)
Miao (PSM) 1% 0.99 [0.85-1.15] death 233/796 236/796
Servais 49% 0.51 [0.34-0.78] death n/a n/a
Pinchera 15% 0.85 [0.71-0.96] severe case 5/19 14/24 OT1
Sandhu 3% 0.97 [0.95-0.99] hosp. population-based cohort
Yen (PSM) 25% 0.75 [0.63-0.89] death 232/20,894 295/20,894
Araldi 60% 0.40 [0.32-0.50] death 107/2,598 263/2,598
Alieva 15% 0.85 [0.49-1.48] hosp. 375 (n) 388 (n)
Obiri-Yeboah -1% 1.01 [0.54-1.87] death 148 (n) 381 (n)
Piarulli 53% 0.47 [0.20-1.08] death/ICU 1,444 (n) 1,009 (n)
Greco 22% 0.78 [0.57-1.05] hosp. OT1
Guo 62% 0.38 [0.15-0.92] death/int. 241 (n) 330 (n)
Zihono 49% 0.51 [0.28-0.93] death 11/56 31/81
Farah -3% 1.03 [0.83-1.28] cases 267/821 69/218
Bidari 10% 0.90 [0.65-1.23] severe case 29/80 132/326
Miguel 37% 0.63 [0.29-1.36] ICU 49 (n) 40 (n)
Mamari 50% 0.50 [0.29-0.86] death 11/34 22/34 OT1
Al-kuraishy 78% 0.22 [0.06-0.77] death 3/60 9/40
Jang 60% 0.40 [0.18-0.85] death 461 (n) 95 (n)
Prophylaxis 26% 0.74 [0.70-0.78] 5,813/96,973 11,005/139,450 26% lower risk
Tau2 = 0.02, I2 = 91.4%, p < 0.0001
All studies 29% 0.71 [0.67-0.75] 5,900/101,822 12,669/163,050 29% lower risk
1 OT: comparison with other treatment
Tau2 = 0.03, I2 = 92.7%, p < 0.0001
Effect extraction pre-specified
(most serious outcome, see appendix)
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Favors metformin
Favors control
A


Efficacy in COVID-19 metformin studies (pooled effects)
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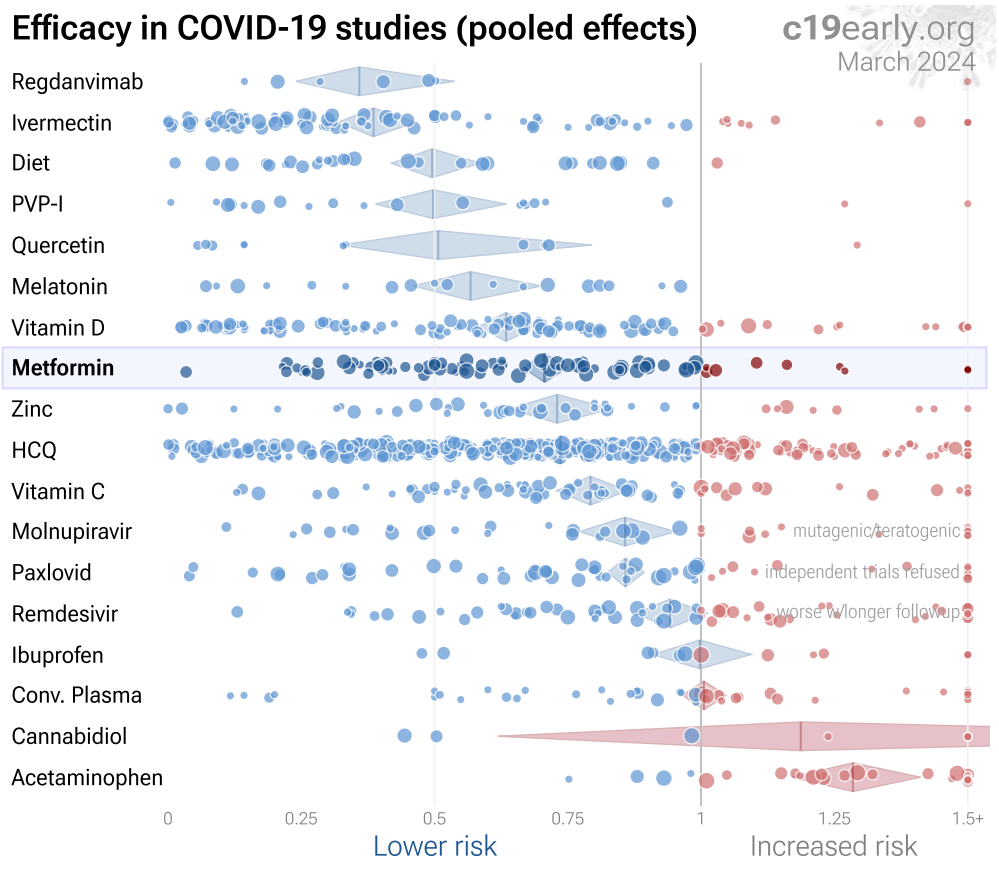
Prophylaxis
Early treatment
Late treatment
All studies
0 0.25 0.5 0.75 1 1.25 1.5+
Favors metformin
Favors control
B



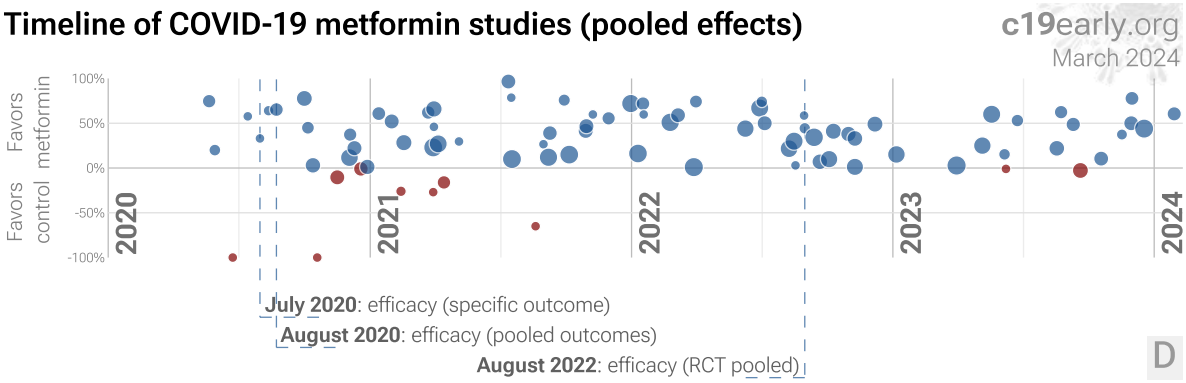


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in metformin studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, and pooled outcomes in RCTs. Efficacy based on RCTs only was delayed by 25.0 months, compared to using all studies.

Introduction

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

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors [Note A, Malone, Murigneux, Lv, Lui], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk [c19early.org (B)], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research. A systematic review and meta-analysis of 15 non-COVID-19 preclinical studies showed that metformin inhibits pulmonary inflammation and oxidative stress, minimizes lung injury, and improves survival in animal models of acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) [Wang]. Metformin inhibits SARS-CoV-2 *in vitro* [Parthasarathy, Ventura-López], minimizes LPS-induced cytokine storm in a mouse model [Taher], minimizes lung damage and fibrosis in a mouse model of LPS-induced ARDS [Miguel], may protect against SARS-CoV-2-induced neurological disorders [Yang (B)], may be beneficial via inhibitory effects on ORF3a-mediated inflammasome activation [Zhang], reduces UUO and FAN-induced kidney fibrosis [Miguel], increases mitochondrial function and decreases TGF-β-induced fibrosis, apoptosis, and inflammation markers in lung epithelial cells [Miguel], and may improve outcomes via modulation of immune responses with increased anti-inflammatory T lymphocyte gene expression and via enhanced gut microbiota diversity [Petakh].

Other infections. Efficacy with metformin has been shown for influenza A [Lee].

Analysis. We analyze all significant controlled studies of metformin 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.

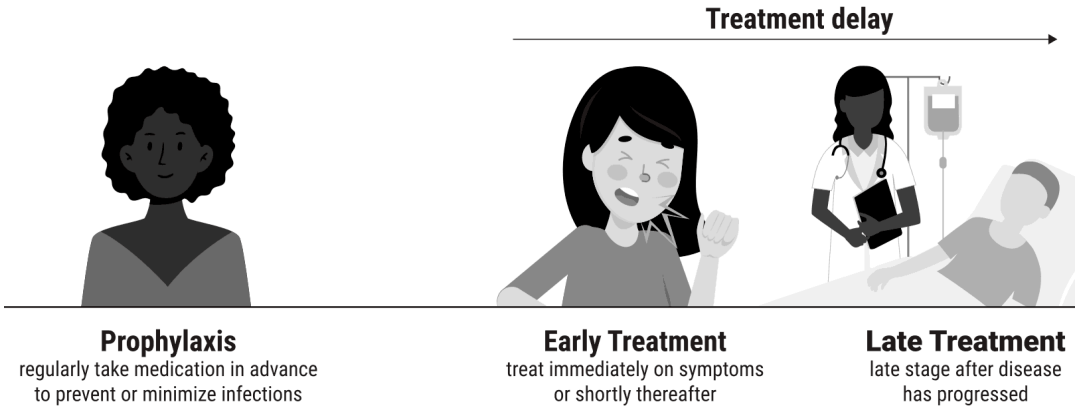


Figure 2. Treatment stages.

Preclinical Research

A systematic review and meta-analysis of 15 non-COVID-19 preclinical studies showed that metformin inhibits pulmonary inflammation and oxidative stress, minimizes lung injury, and improves survival in animal models of acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) [Wang]. Metformin inhibits SARS-CoV-2 *in vitro* [Parthasarathy, Ventura-López], minimizes LPS-induced cytokine storm in a mouse model [Taher], minimizes lung damage and fibrosis in a mouse model of LPS-induced ARDS [Miguel], may protect against SARS-CoV-2-induced neurological disorders [Yang (B)], may be beneficial via inhibitory effects on ORF3a-mediated inflammasome activation [Zhang], reduces UUO and FAN-induced kidney fibrosis [Miguel], and increases mitochondrial function and decreases TGF-β-induced fibrosis, apoptosis, and inflammation markers in lung epithelial cells [Miguel].

4 *In Vitro* studies support the efficacy of metformin *Miguel, Parthasarathy, Ventura-López, Yang (B)*.

2 *In Vivo* animal studies support the efficacy of metformin *Miguel, Taher*.

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

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	29% [25-33%] ****	84	264,872	1,014
After exclusions	30% [26-34%] ****	77	246,896	920
Peer-reviewed studies	29% [24-33%] ****	78	233,360	944
Randomized Controlled Trials	45% [14-64%] **	4	1,431	66
Mortality	34% [29-39%] ****	60	197,144	771
Ventilation	31% [13-45%] **	12	55,447	144
ICU admission	**17%** [7-26%] **	11	83,745	117
Hospitalization	**17%** [11-23%] ****	22	86,559	233
Recovery	41% [13-60%] **	4	4,176	78
Cases	**3%** [-6-12%]	7	70,125	89
Viral	26% [-9-49%]	3	1,437	40
RCT mortality	45% [-19-74%]	3	1,411	52
RCT hospitalization	**7%** [-6-17%]	3	627	63

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	*Late treatment*	*Prophylaxis*
All studies	**58%** [23-77%] **	**53%** [34-66%] ****	**26%** [22-30%] ****
After exclusions	**58%** [23-77%] **	**53%** [34-66%] ****	**27%** [23-31%] ****
Peer-reviewed studies	**58%** [23-77%] **	**52%** [30-67%] ***	**26%** [21-30%] ****
Randomized Controlled Trials	**24%** [-89-70%]	**49%** [17-69%] **	
Mortality	**58%** [23-77%] **	**63%** [34-79%] ***	**31%** [26-35%] ****
Ventilation		**79%** [1-96%] *	**29%** [11-44%] **
ICU admission		**63%** [-9-87%]	**16%** [6-25%] **
Hospitalization	**6%** [-61-45%]	**7%** [-6-18%]	**19%** [11-25%] ****
Recovery			**41%** [13-60%] **
Cases			**3%** [-6-12%]
Viral	**19%** [-25-48%]	**41%** [5-63%] *	
RCT mortality	**24%** [-89-70%]	**74%** [-6-94%]	
RCT hospitalization	**6%** [-61-45%]	**7%** [-6-18%]	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

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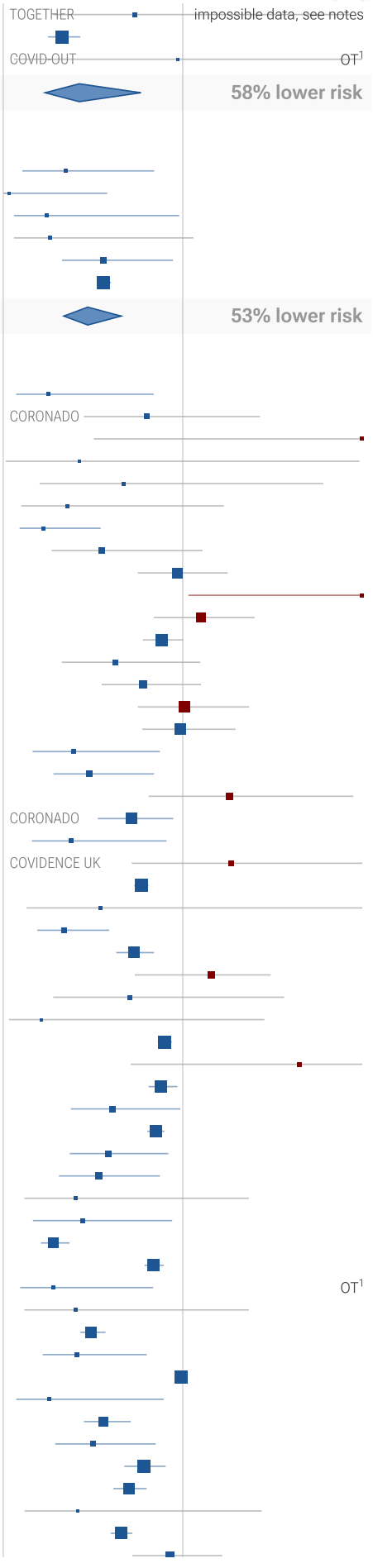
Jiang (PSM)	46%	0.54 [0.13-2.26]	death	3/74	10/74
Ghany	66%	0.34 [0.19-0.59]	death	392 (n)	747 (n)
Alamgir	27%	0.73 [0.63-0.84]	death	11,062 (n)	11,062 (n)
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	death	20 (n)	83 (n)
Ravindra	30%	0.70 [0.28-1.56]	death	5/53	57/313
Blanc	79%	0.21 [0.03-1.46]	death	1/14	25/75
Boye	10%	0.90 [0.86-0.94]	hosp.	2,067/4,250	3,196/5,281
Cheng (PSM)	-65%	1.65 [0.71-3.86]	death	678 (n)	535 (n)
Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)
Ando	39%	0.61 [0.38-0.99]	hosp.		
Wander	15%	0.85 [0.80-0.90]	death		
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169
Bliden	60%	0.40 [0.12-1.37]	death	3/34	9/41
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41
Wong	51%	0.49 [0.43-0.57]	death		
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort	
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)
Chan	59%	0.41 [0.12-1.44]	death	400 (n)	2,736 (n)
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort	
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)



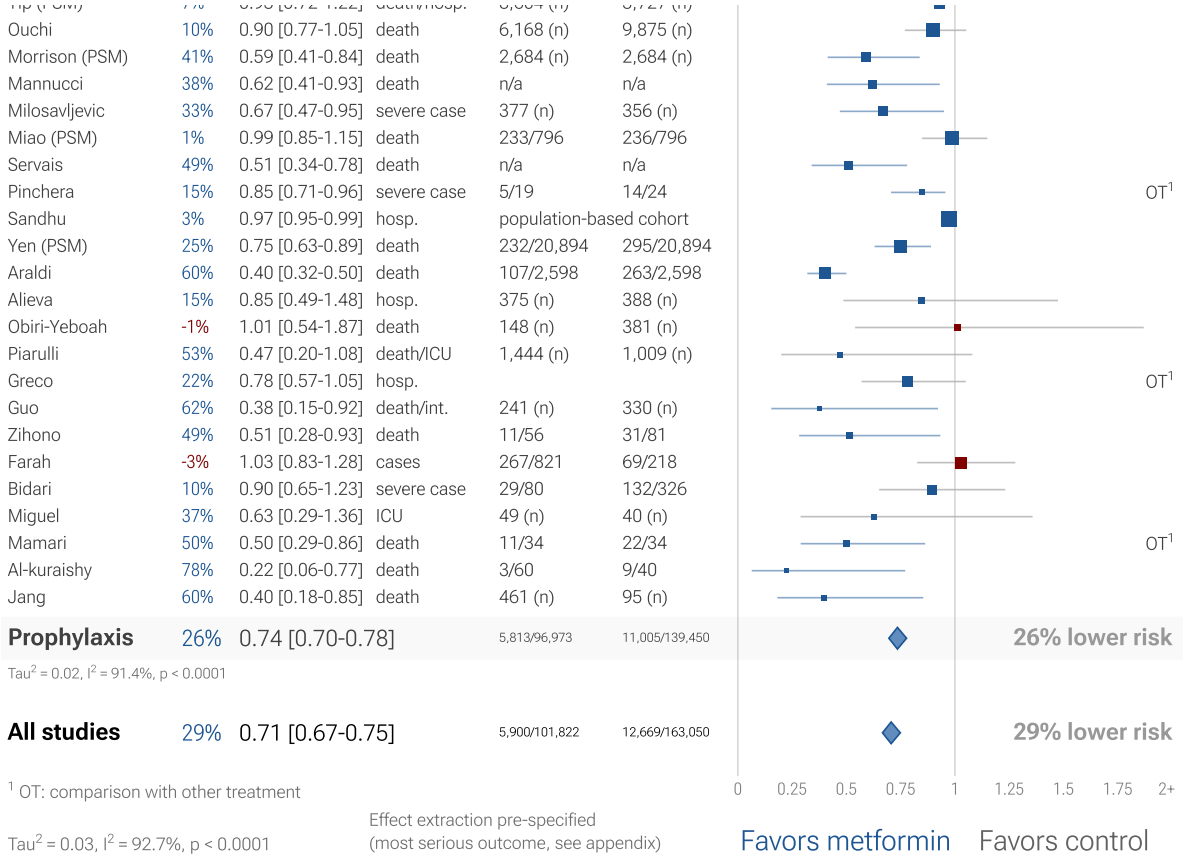


Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

60 metformin COVID-19 mortality results

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	Improvement	RR [CI]	Treatment	Control
Reis (DB RCT)	27%	0.73 [0.28-1.94]	7/215	9/203
Hunt	67%	0.33 [0.25-0.43]	73/3,956	1,539/22,552
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	1/408	1/396
Early treatment	58%	0.42 [0.23-0.77]	81/4,579	1,549/23,151
$Tau^2 = 0.12$, $I^2 = 33.5\%$, p = 0.0046				
	Improvement	*RR [CI]*	*Treatment*	*Control*
Abu-Jamous	65%	0.35 [0.11-0.84]	4/23	94/168
Tamura	97%	0.03 [0.00-0.58]	115 (n)	73 (n)
Li	76%	0.24 [0.06-0.98]	2/37	21/94
Shaseb (RCT)	74%	0.26 [0.06-1.06]	85 (n)	104 (n)
Mehrizi	44%	0.56 [0.53-0.60]	population-based cohort	
Late treatment	63%	0.37 [0.21-0.66]	6/260	115/439
$Tau^2 = 0.18$, $I^2 = 45.3\%$, p = 0.00081				
	Improvement	*RR [CI]*	*Treatment*	*Control*
Luo	75%	0.25 [0.07-0.84]	3/104	22/179
Cariou	20%	0.80 [0.45-1.43]	746 (n)	571 (n)
Wang	58%	0.42 [0.01-1.98]	1/9	13/49
Chen	33%	0.67 [0.20-1.78]	4/43	15/77
Kim	64%	0.36 [0.10-1.23]	113 (n)	122 (n)
Li	78%	0.22 [0.09-0.54]	2/37	21/94
Mirani	45%	0.55 [0.27-1.11]	25/69	13/21
Goodall	3%	0.97 [0.75-1.25]	74/210	280/771
Pérez-Bel.. (PSM)	-10%	1.10 [0.84-1.40]	79/249	79/249
Bramante	12%	0.88 [0.78-1.00]	394/2,333	791/3,923
Sourij	37%	0.63 [0.33-1.10]	14/77	44/161
Lalau (PSM)	22%	0.78 [0.55-1.10]	671 (n)	419 (n)
Ramos-Rincón	1%	0.99 [0.77-1.29]	206/420	179/370
Crouse	61%	0.39 [0.16-0.87]	8/76	34/144
Lally	52%	0.48 [0.28-0.84]	16/127	144/648
Oh	-26%	1.26 [0.81-1.95]	5,946 (n)	5,946 (n)
Wargny	28%	0.72 [0.53-0.95]	247/1,553	330/1,241
Bramante (PSM)	62%	0.38 [0.16-0.91]	342 (n)	342 (n)
Khunti	23%	0.77 [0.73-0.81]	population-based cohort	
Jiang (PSM)	46%	0.54 [0.13-2.26]	3/74	10/74
Ghany	66%	0.34 [0.19-0.59]	392 (n)	747 (n)
Alamgir	27%	0.73 [0.63-0.84]	11,062 (n)	11,062 (n)
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	20 (n)	83 (n)
Ravindra	30%	0.70 [0.28-1.56]	5/53	57/313
Blanc	79%	0.21 [0.03-1.46]	1/14	25/75
Cheng (PSM)	-65%	1.65 [0.71-3.86]	678 (n)	535 (n)
Wander	15%	0.85 [0.80-0.90]		
Saygili (PSM)	42%	0.58 [0.37-0.92]	120 (n)	120 (n)
Ong	47%	0.53 [0.31-0.87]	33/186	57/169
Bliden	60%	0.40 [0.12-1.37]	3/34	9/41
Wallace (PSW)	72%	0.28 [0.21-0.37]	103/1,203	1,536/6,970
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	1,476/6,556	1,787/6,556
Usman	60%	0.40 [0.12-1.37]	3/34	9/41
Wong	51%	0.49 [0.43-0.57]		
Wong (PSW)	59%	0.41 [0.22-0.80]	786 (n)	428 (n)
Ma (PSW)	74%	0.26 [0.07-0.89]	3/361	40/995
Shestakova	22%	0.78 [0.67-0.91]	population-based cohort	
Loucera	30%	0.70 [0.61-0.80]	1,896 (n)	14,072 (n)
Chan	59%	0.41 [0.12-1.44]	400 (n)	2,736 (n)
Zaccardi	34%	0.66 [0.60-0.72]	population-based cohort	
Ouchi	10%	0.90 [0.77-1.05]	6,168 (n)	9,875 (n)
Morrison (PSM)	41%	0.59 [0.41-0.84]	2,684 (n)	2,684 (n)
Mannucci	38%	0.62 [0.41-0.93]	n/a	n/a
Miao (PSM)	1%	0.99 [0.85-1.15]	233/796	236/796
Servais	49%	0.51 [0.34-0.78]	n/a	n/a
Yen (PSM)	25%	0.75 [0.63-0.89]	232/20,894	295/20,894
Araldi	60%	0.40 [0.32-0.50]	107/2,598	263/2,598
Obiri-Yeboah	-1%	1.01 [0.54-1.87]	148 (n)	381 (n)
Zihono	49%	0.51 [0.28-0.93]	11/56	31/81
Mamari	50%	0.50 [0.29-0.86]	11/34	22/34
Al-kuraishy	78%	0.22 [0.06-0.77]	3/60	9/40
Jang	60%	0.40 [0.18-0.85]	461 (n)	95 (n)
Prophylaxis	31%	0.69 [0.65-0.74]	3,300/70,893	6,351/97,822

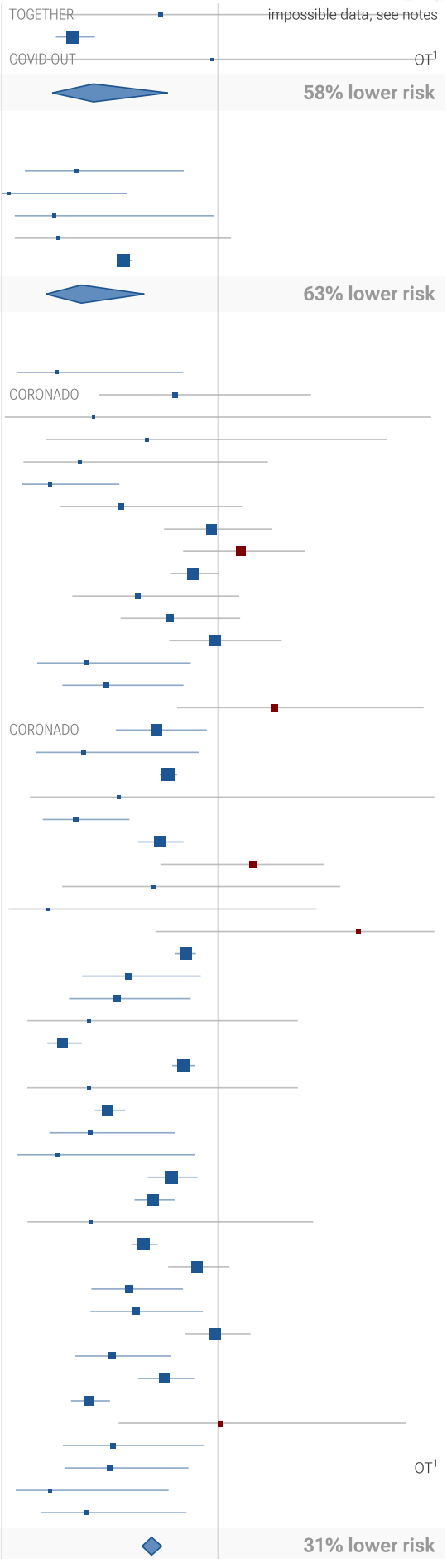

Figure 4. Random effects meta-analysis for mortality results.

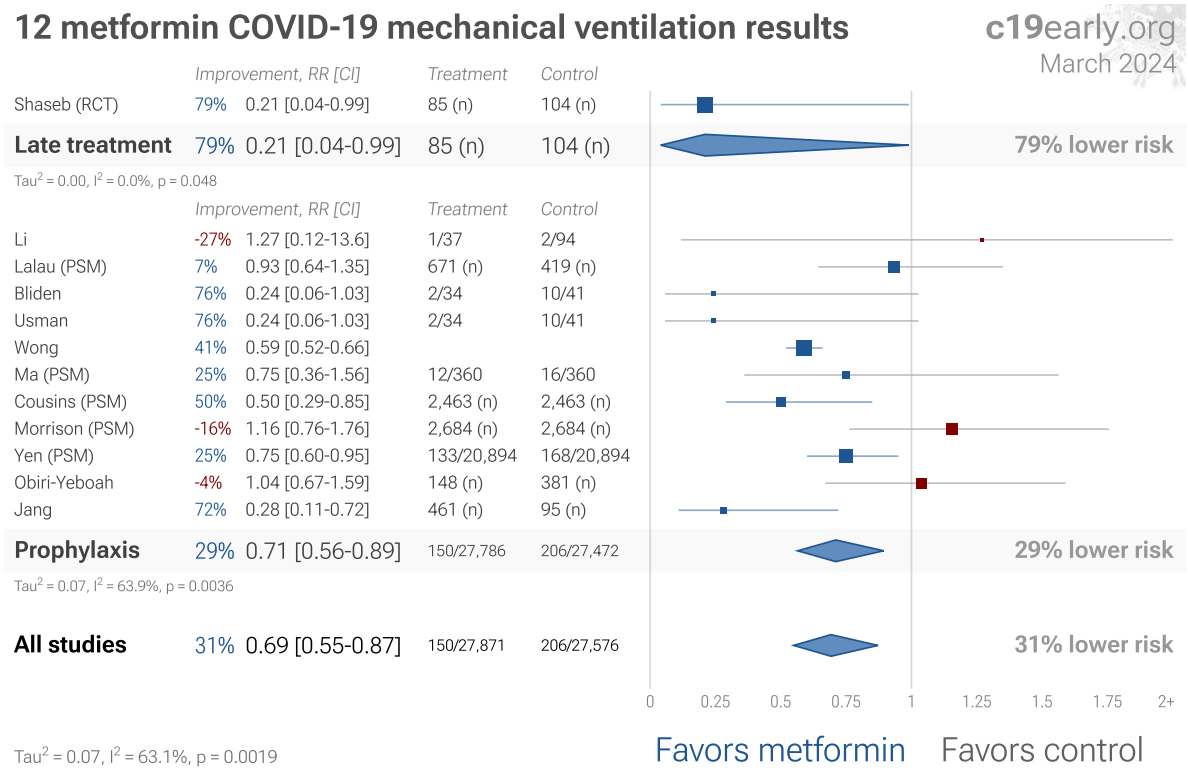

Figure 5. Random effects meta-analysis for ventilation.

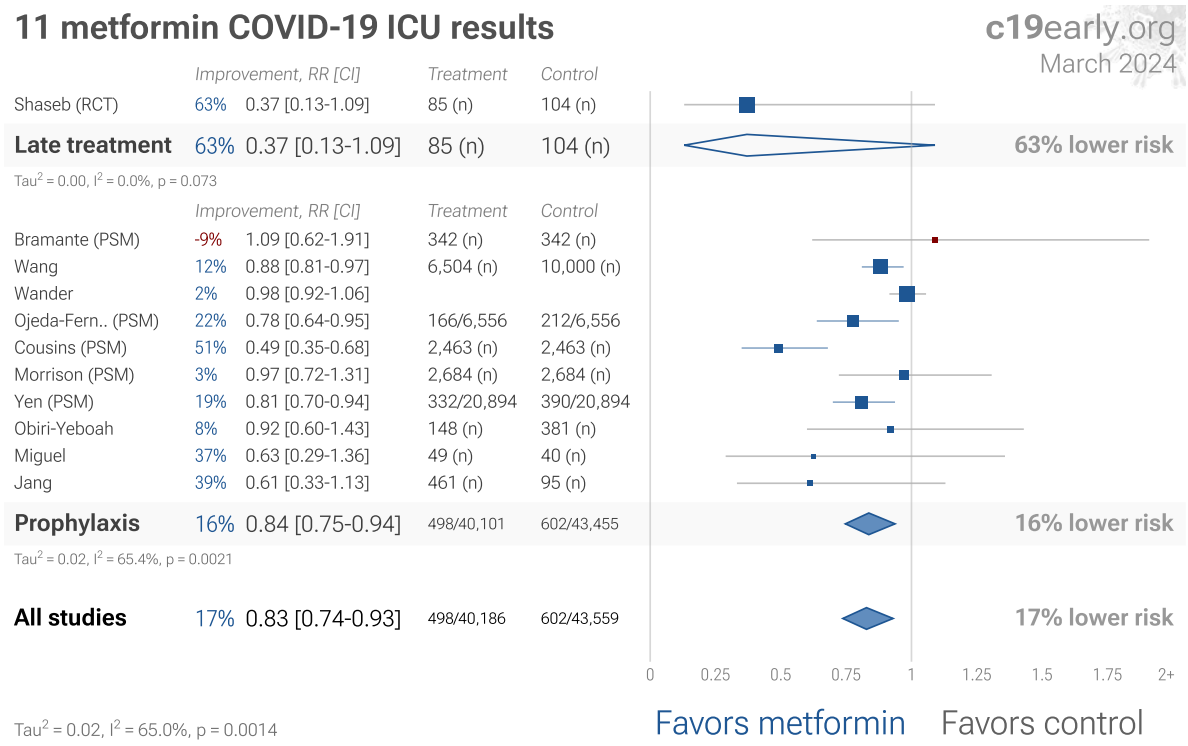

Figure 6. Random effects meta-analysis for ICU admission.

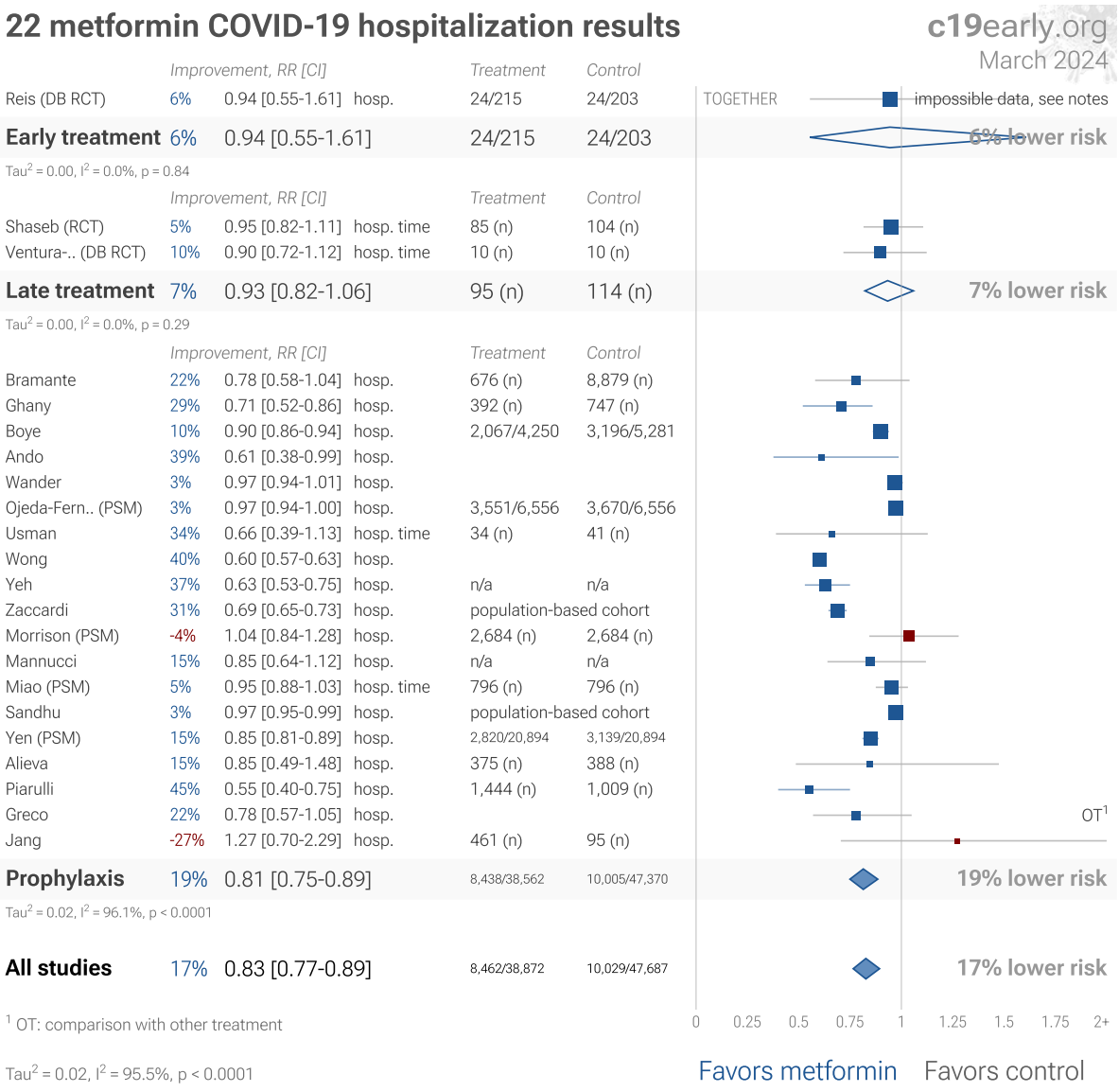

Figure 7. Random effects meta-analysis for hospitalization.

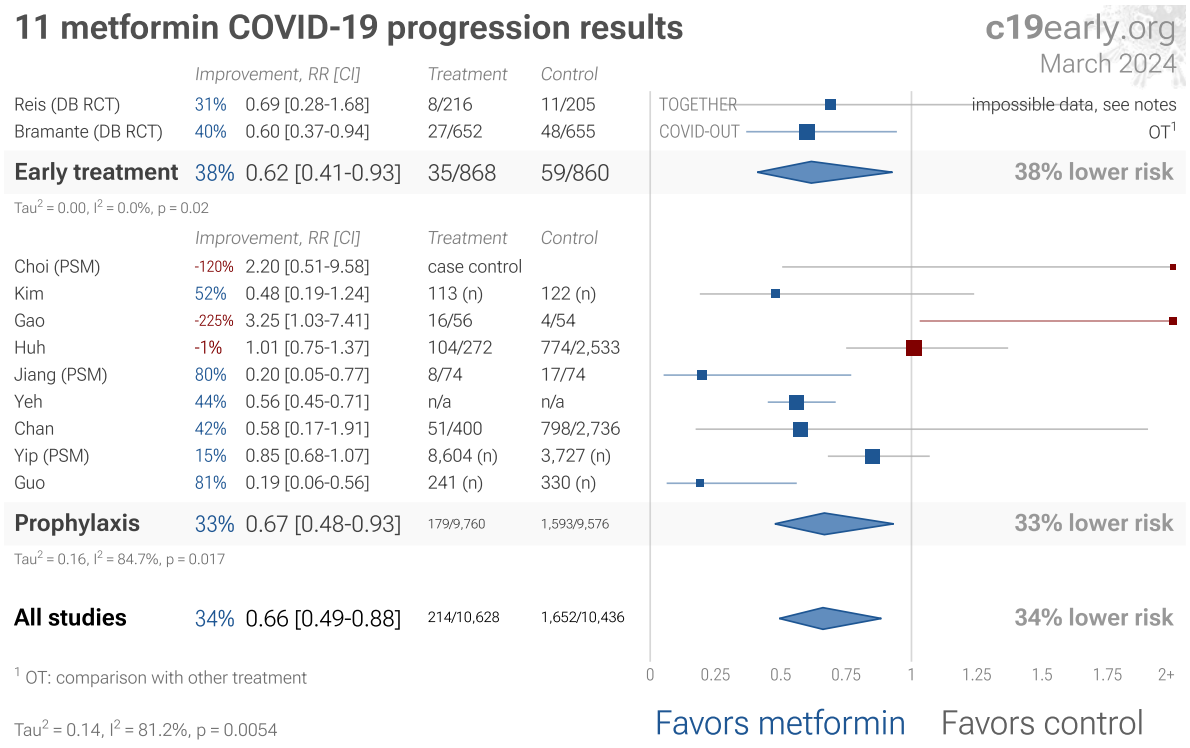

Figure 8. Random effects meta-analysis for progression.

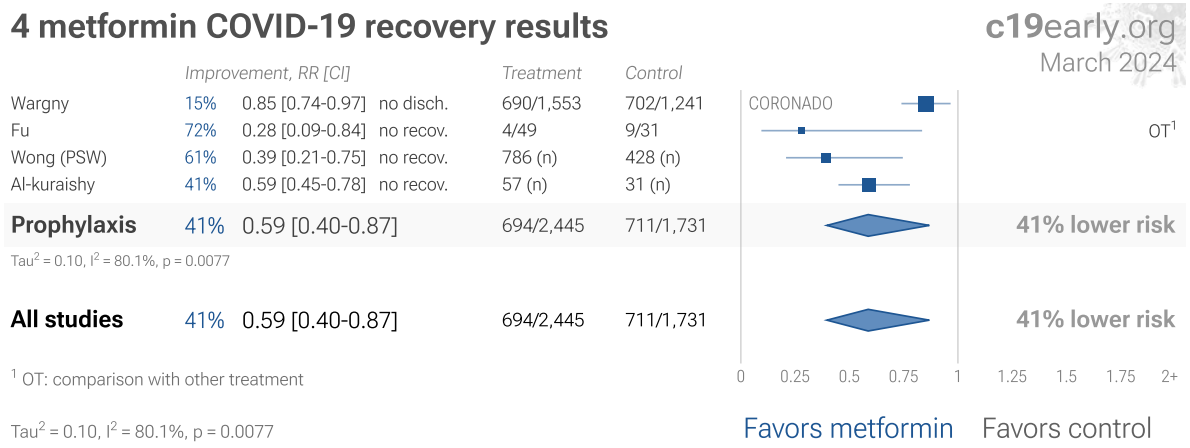

Figure 9. Random effects meta-analysis for recovery.

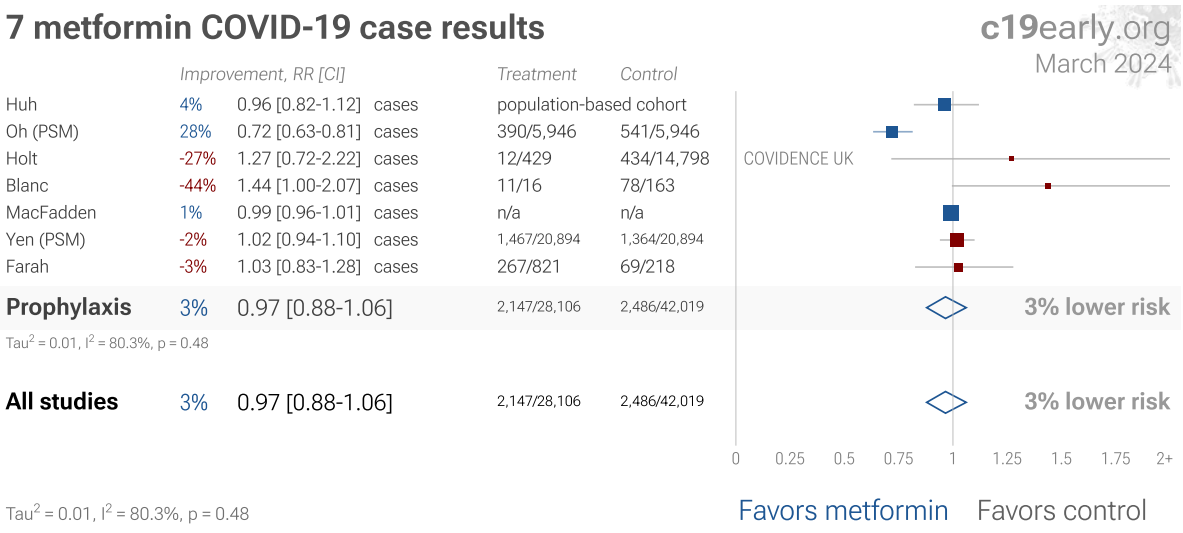

Figure 10. Random effects meta-analysis for cases.

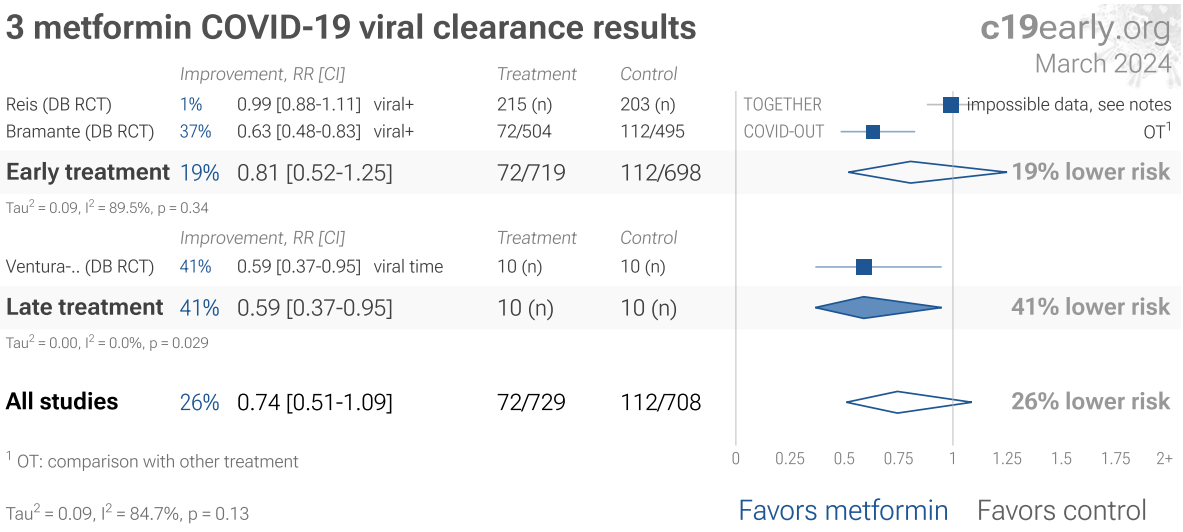

Figure 11. Random effects meta-analysis for viral clearance.

78 metformin COVID-19 peer reviewed studies

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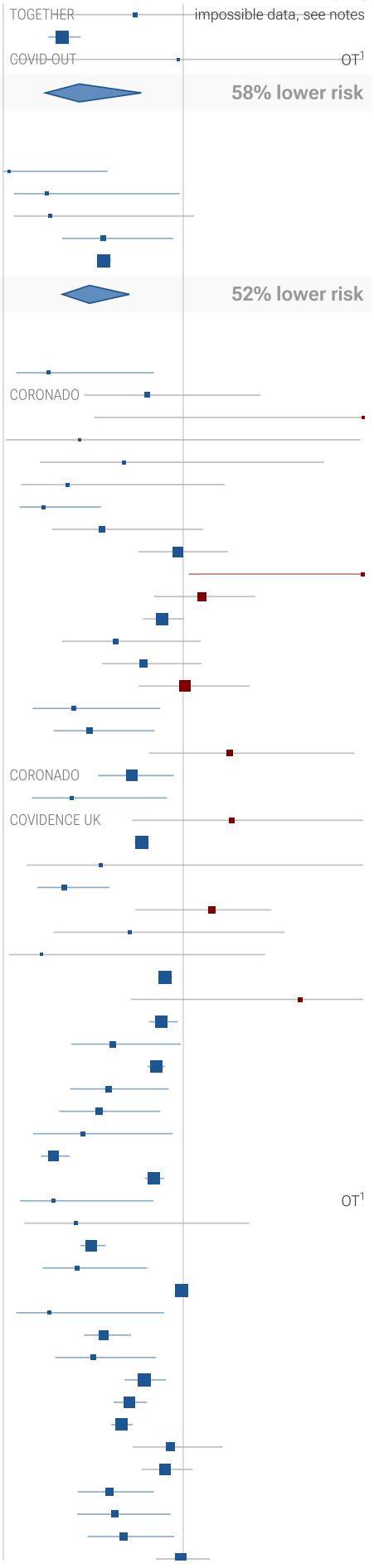
March 2024

	Improvement, RR [CI]			Treatment	Control
Reis (DB RCT)	27%	0.73 [0.28-1.94]	death	7/215	9/203
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	death	1/408	1/396
Early treatment	58%	0.42 [0.23-0.77]		81/4,579	1,549/23,151
Tau² = 0.12, I² = 33.5%, p = 0.0046					
	Improvement, RR [CI]			Treatment	Control
Tamura	97%	0.03 [0.00-0.58]	death	115 (n)	73 (n)
Li	76%	0.24 [0.06-0.98]	death	2/37	21/94
Shaseb (RCT)	74%	0.26 [0.06-1.06]	death	85 (n)	104 (n)
Ventura-.. (DB RCT)	44%	0.56 [0.33-0.95]	oxygen time	10 (n)	10 (n)
Mehrizi	44%	0.56 [0.53-0.60]	death	population-based cohort	
Late treatment	52%	0.48 [0.33-0.70]		2/247	21/281
Tau² = 0.06, I² = 36.1%, p = 0.00016					
	Improvement, RR [CI]			Treatment	Control
Luo	75%	0.25 [0.07-0.84]	death	3/104	22/179
Cariou	20%	0.80 [0.45-1.43]	death	746 (n)	571 (n)
Choi (PSM)	-120%	2.20 [0.51-9.58]	progression	case control	
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49
Chen	33%	0.67 [0.20-1.78]	death	4/43	15/77
Kim	64%	0.36 [0.10-1.23]	death	113 (n)	122 (n)
Li	78%	0.22 [0.09-0.54]	death	2/37	21/94
Mirani	45%	0.55 [0.27-1.11]	death	25/69	13/21
Goodall	3%	0.97 [0.75-1.25]	death	74/210	280/771
Gao	-225%	3.25 [1.03-7.41]	progression	16/56	4/54
Pérez-Bel.. (PSM)	-10%	1.10 [0.84-1.40]	death	79/249	79/249
Bramante	12%	0.88 [0.78-1.00]	death	394/2,333	791/3,923
Sourij	37%	0.63 [0.33-1.10]	death	14/77	44/161
Lalau (PSM)	22%	0.78 [0.55-1.10]	death	671 (n)	419 (n)
Huh	-1%	1.01 [0.75-1.37]	progression	104/272	774/2,533
Crouse	61%	0.39 [0.16-0.87]	death	8/76	34/144
Lally	52%	0.48 [0.28-0.84]	death	16/127	144/648
Oh	-26%	1.26 [0.81-1.95]	death	5,946 (n)	5,946 (n)
Wargny	28%	0.72 [0.53-0.95]	death	247/1,553	330/1,241
Bramante (PSM)	62%	0.38 [0.16-0.91]	death	342 (n)	342 (n)
Holt	-27%	1.27 [0.72-2.22]	cases	12/429	434/14,798
Khunti	23%	0.77 [0.73-0.81]	death	population-based cohort	
Jiang (PSM)	46%	0.54 [0.13-2.26]	death	3/74	10/74
Ghany	66%	0.34 [0.19-0.59]	death	392 (n)	747 (n)
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	death	20 (n)	83 (n)
Ravindra	30%	0.70 [0.28-1.56]	death	5/53	57/313
Blanc	79%	0.21 [0.03-1.46]	death	1/14	25/75
Boye	10%	0.90 [0.86-0.94]	hosp.	2,067/4,250	3,196/5,281
Cheng (PSM)	-65%	1.65 [0.71-3.86]	death	678 (n)	535 (n)
Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)
Ando	39%	0.61 [0.38-0.99]	hosp.		
Wander	15%	0.85 [0.80-0.90]	death		
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41
Wong	51%	0.49 [0.43-0.57]	death		
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort	
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort	
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)
Ouchi	10%	0.90 [0.77-1.05]	death	6,168 (n)	9,875 (n)
Morrison (PSM)	41%	0.59 [0.41-0.84]	death	2,684 (n)	2,684 (n)
Mannucci	38%	0.62 [0.41-0.93]	death	n/a	n/a
Milosavljevic	33%	0.67 [0.47-0.95]	severe case	377 (n)	356 (n)
Miao (PSM)	1%	0.99 [0.85-1.15]	death	233/796	236/796



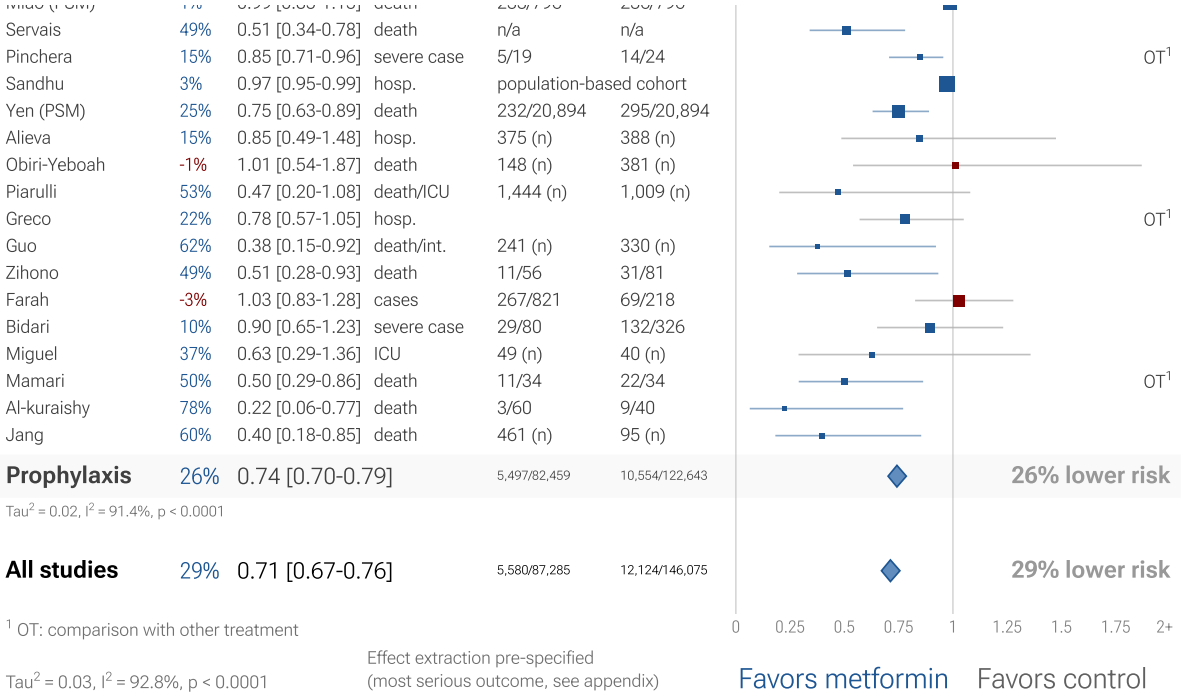


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with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

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and non-RCT studies. Figure 14, 15, and 16 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

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

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

experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

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

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

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

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

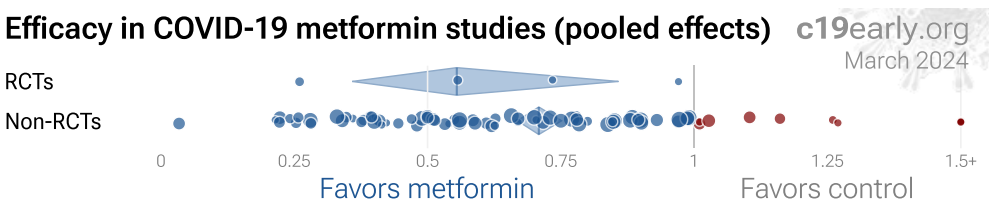


Figure 13. **Results for RCTs and non-RCT studies.**

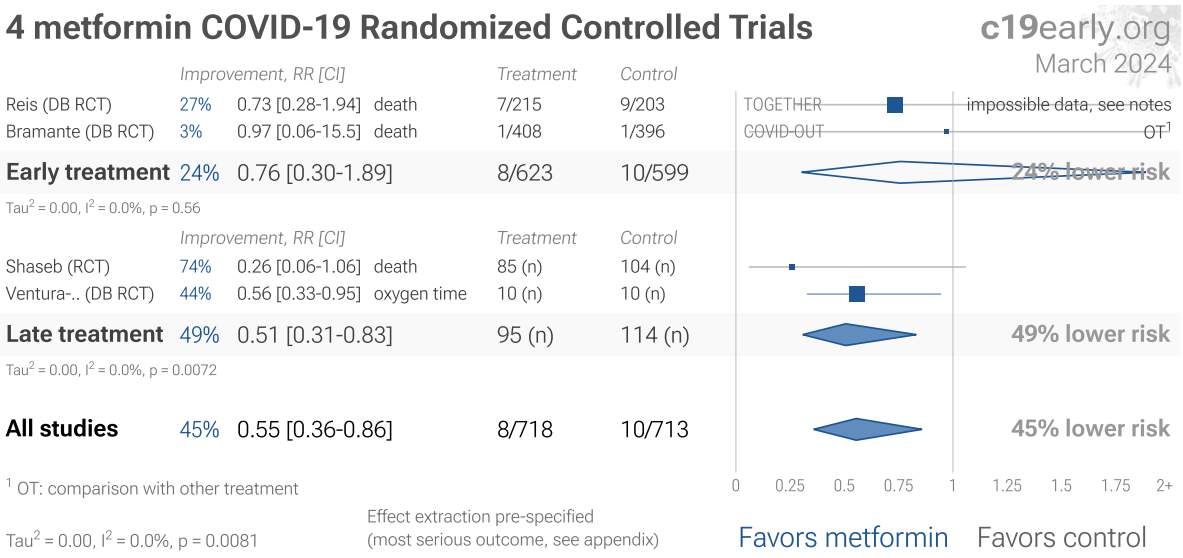


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details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

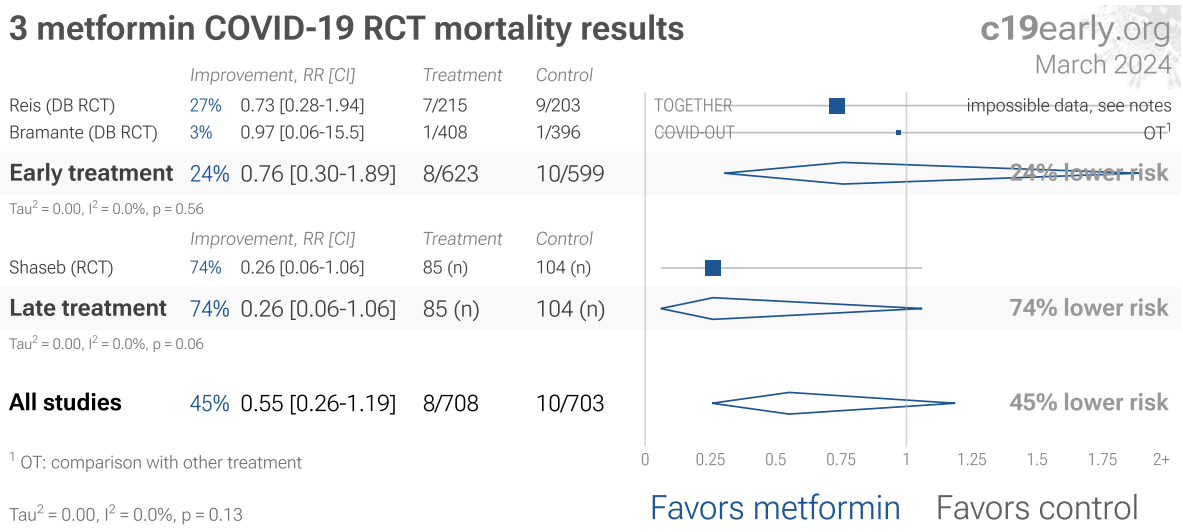


Figure 15. **Random effects meta-analysis for RCT mortality results.**

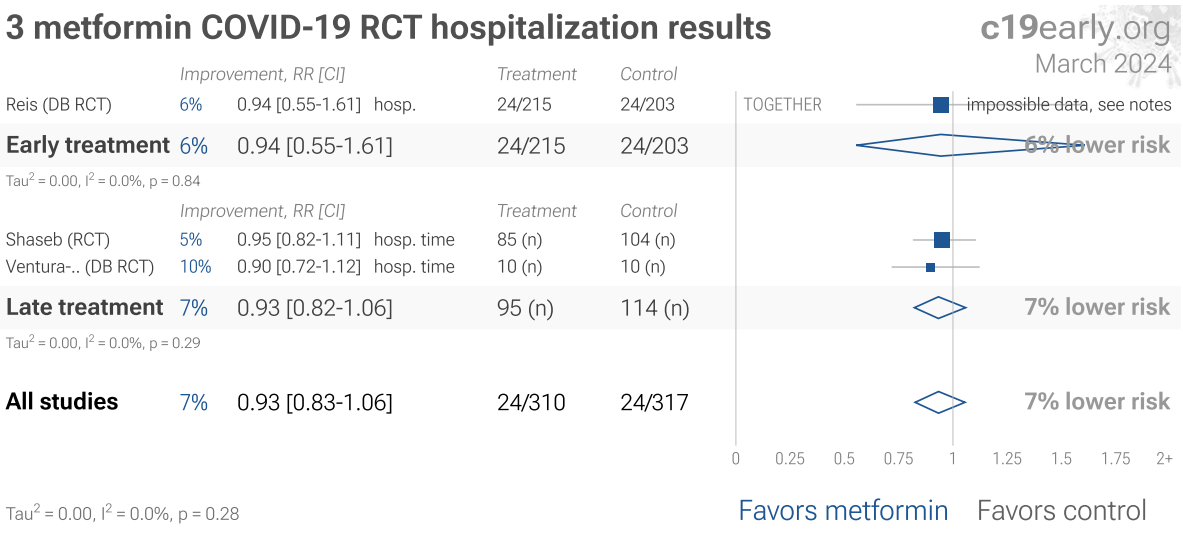


Figure 16. Random effects meta-analysis for RCT hospitalization results.

Exclusions

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

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

Al-kuraishy, unadjusted results with significant baseline differences.

Alieva, unadjusted results with no group details.

Bidari, unadjusted results with no group details.

Bliden, unadjusted results with minimal group details.

Farah, unadjusted results with no group details.

Holt, significant unadjusted confounding possible.

Ravindra, minimal details provided.

77 metformin COVID-19 studies after exclusions

c19early.org
March 2024

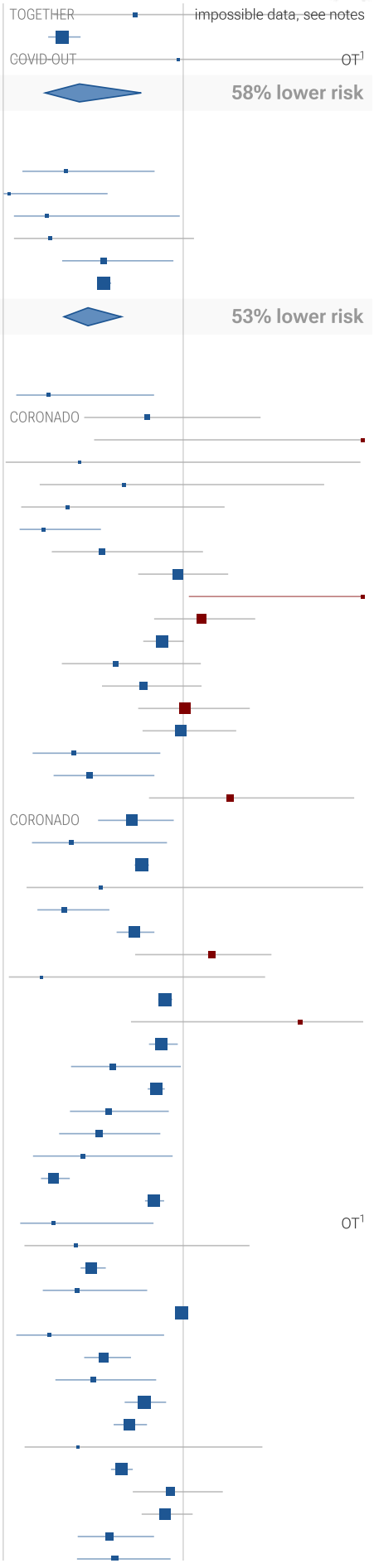
	Improvement	RR [CI]		Treatment	Control
Reis (DB RCT)	27%	0.73 [0.28-1.94]	death	7/215	9/203
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	death	1/408	1/396
Early treatment	**58%**	0.42 [0.23-0.77]		81/4,579	1,549/23,151

$Tau^2 = 0.12$, $I^2 = 33.5\%$, $p = 0.0046$

	Improvement	RR [CI]		Treatment	Control
Abu-Jamous	65%	0.35 [0.11-0.84]	death	4/23	94/168
Tamura	97%	0.03 [0.00-0.58]	death	115 (n)	73 (n)
Li	76%	0.24 [0.06-0.98]	death	2/37	21/94
Shaseb (RCT)	74%	0.26 [0.06-1.06]	death	85 (n)	104 (n)
Ventura-.. (DB RCT)	44%	0.56 [0.33-0.95]	oxygen time	10 (n)	10 (n)
Mehrizi	44%	0.56 [0.53-0.60]	death	population-based cohort	
Late treatment	**53%**	0.47 [0.34-0.66]		6/270	115/449

$Tau^2 = 0.05$, $I^2 = 31.6\%$, $p < 0.0001$

	Improvement	RR [CI]		Treatment	Control
Luo	75%	0.25 [0.07-0.84]	death	3/104	22/179
Cariou	20%	0.80 [0.45-1.43]	death	746 (n)	571 (n)
Choi (PSM)	-120%	2.20 [0.51-9.58]	progression	case control	
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49
Chen	33%	0.67 [0.20-1.78]	death	4/43	15/77
Kim	64%	0.36 [0.10-1.23]	death	113 (n)	122 (n)
Li	78%	0.22 [0.09-0.54]	death	2/37	21/94
Mirani	45%	0.55 [0.27-1.11]	death	25/69	13/21
Goodall	3%	0.97 [0.75-1.25]	death	74/210	280/771
Gao	-225%	3.25 [1.03-7.41]	progression	16/56	4/54
Pérez-Bel.. (PSM)	-10%	1.10 [0.84-1.40]	death	79/249	79/249
Bramante	12%	0.88 [0.78-1.00]	death	394/2,333	791/3,923
Sourij	37%	0.63 [0.33-1.10]	death	14/77	44/161
Lalau (PSM)	22%	0.78 [0.55-1.10]	death	671 (n)	419 (n)
Huh	-1%	1.01 [0.75-1.37]	progression	104/272	774/2,533
Ramos-Rincón	1%	0.99 [0.77-1.29]	death	206/420	179/370
Crouse	61%	0.39 [0.16-0.87]	death	8/76	34/144
Lally	52%	0.48 [0.28-0.84]	death	16/127	144/648
Oh	-26%	1.26 [0.81-1.95]	death	5,946 (n)	5,946 (n)
Wargny	28%	0.72 [0.53-0.95]	death	247/1,553	330/1,241
Bramante (PSM)	62%	0.38 [0.16-0.91]	death	342 (n)	342 (n)
Khunti	23%	0.77 [0.73-0.81]	death	population-based cohort	
Jiang (PSM)	46%	0.54 [0.13-2.26]	death	3/74	10/74
Ghany	66%	0.34 [0.19-0.59]	death	392 (n)	747 (n)
Alamgir	27%	0.73 [0.63-0.84]	death	11,062 (n)	11,062 (n)
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	death	20 (n)	83 (n)
Blanc	79%	0.21 [0.03-1.46]	death	1/14	25/75
Boye	10%	0.90 [0.86-0.94]	hosp.	2,067/4,250	3,196/5,281
Cheng (PSM)	-65%	1.65 [0.71-3.86]	death	678 (n)	535 (n)
Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)
Ando	39%	0.61 [0.38-0.99]	hosp.		
Wander	15%	0.85 [0.80-0.90]	death		
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41
Wong	51%	0.49 [0.43-0.57]	death		
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort	
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)
Chan	59%	0.41 [0.12-1.44]	death	400 (n)	2,736 (n)
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort	
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)
Ouchi	10%	0.90 [0.77-1.05]	death	6,168 (n)	9,875 (n)
Morrison (PSM)	41%	0.59 [0.41-0.84]	death	2,684 (n)	2,684 (n)
Manpucci	38%	0.62 [0.41-0.93]	death	n/a	n/a



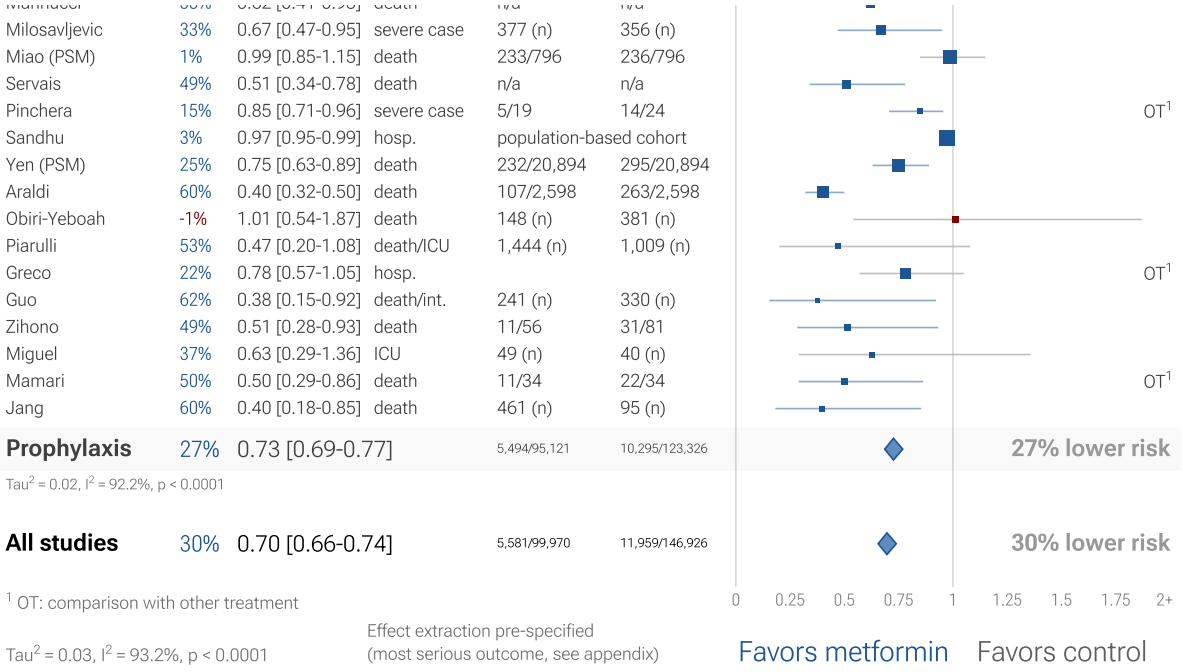


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

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

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

Table 3. **Studies of baloxavir for influenza show that early treatment is more effective.**

Figure 18 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

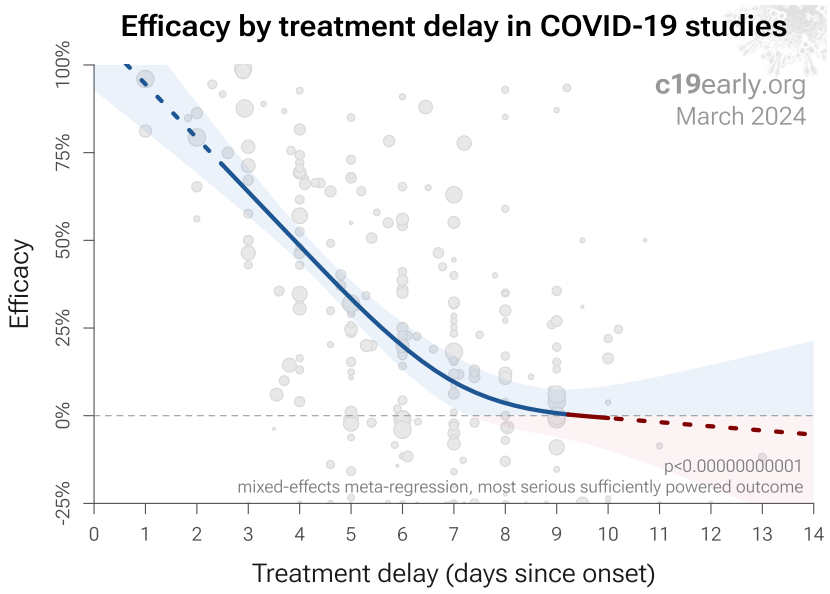


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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

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

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

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

Other treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

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

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

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

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

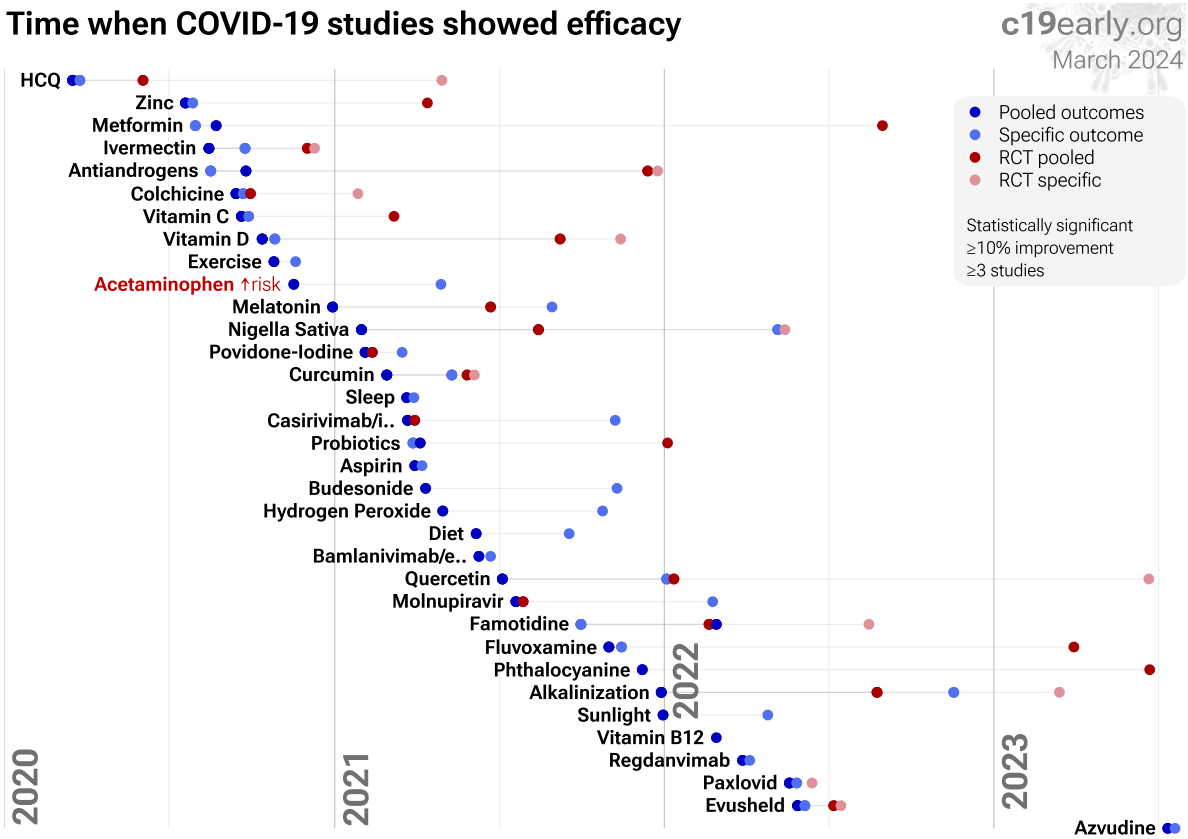


Figure 19. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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

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

Discussion

Results for other viruses. Efficacy with metformin has also been shown for influenza A [Lee].

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]. For metformin, there is currently not enough data to evaluate publication bias with high confidence.

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

Figure 20 shows a scatter plot of results for prospective and retrospective studies. 63% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 67% of prospective studies, showing similar results. The median effect size for retrospective studies is 38% improvement, compared to 35% for prospective studies, showing similar results.

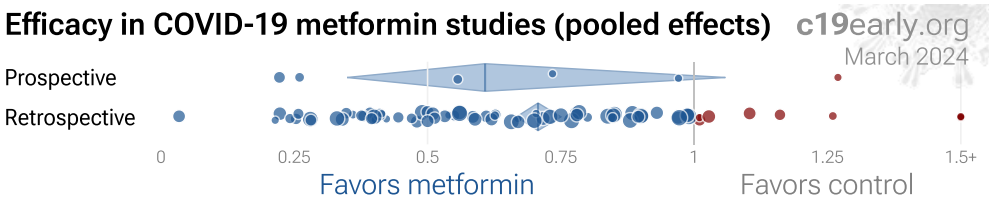


Figure 20. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 21 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

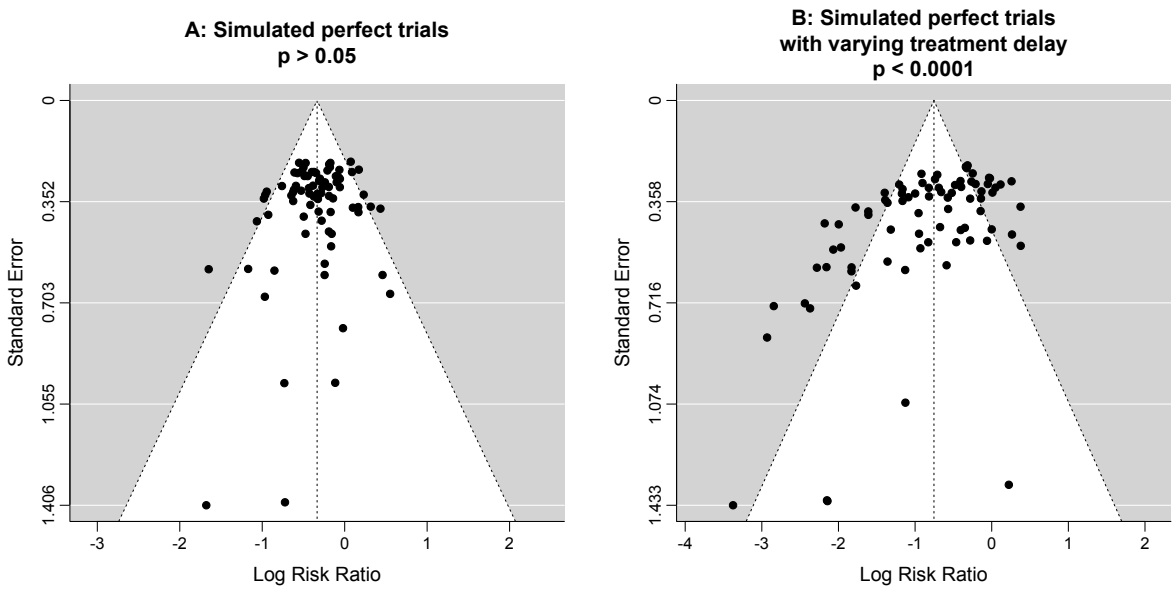


Figure 21. Example funnel plot analysis for simulated perfect trials.

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. Metformin for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 metformin 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 metformin 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 by specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

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

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

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

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

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

treatments.

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

No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes. 5 of the 84 studies compare against other treatments, which may reduce the effect seen. Other meta analyses show significant improvements with metformin for mortality *Hariyanto, Kan, Kow, Li, Lukito, Ma, Oscanoa, Parveen, Petrelli, Poly, Schlesinger, Yang*, hospitalization *Li*, progression *Yang*, and severity *Petrelli, Schlesinger*.

Reviews. Multiple reviews cover metformin for COVID-19, presenting additional background on mechanisms and related results, including *De Jesús-González, Halma, Petakh (B), Tseng, Zhang*.

Conclusion

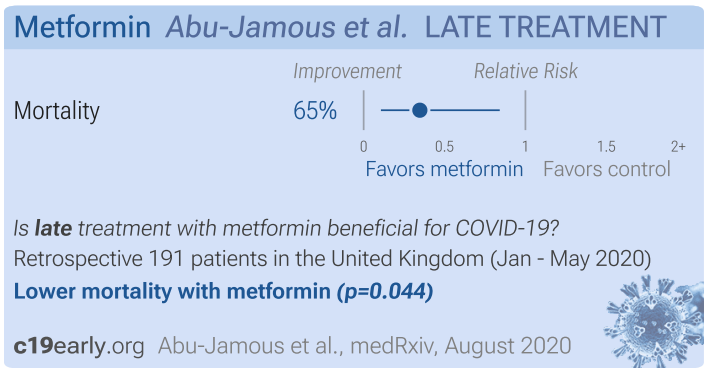
Statistically significant lower risk is seen for mortality, ventilation, ICU admission, hospitalization, progression, and recovery. 53 studies from 50 independent teams in 17 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 29% [25-33%] lower risk. Results are similar for higher quality and peer-reviewed studies and better for Randomized Controlled Trials. Results are robust — in exclusion sensitivity analysis 64 of 84 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Most studies analyze existing use with diabetic patients, and many results may be subject to confounding by indication — metformin is typically used early in the progression of type 2 diabetes. Prophylaxis results typically include continuing use after infection and hospitalization, and greater benefit is seen for more serious outcomes. The TOGETHER RCT shows 27% lower mortality. While not statistically significant, p = 0.53, this is consistent with the mortality results from all studies, 34% [29-39%].

Other meta analyses show significant improvements with metformin for mortality *Hariyanto, Kan, Kow, Li, Lukito, Ma, Oscanoa, Parveen, Petrelli, Poly, Schlesinger, Yang*, hospitalization *Li*, progression *Yang*, and severity *Petrelli, Schlesinger*.

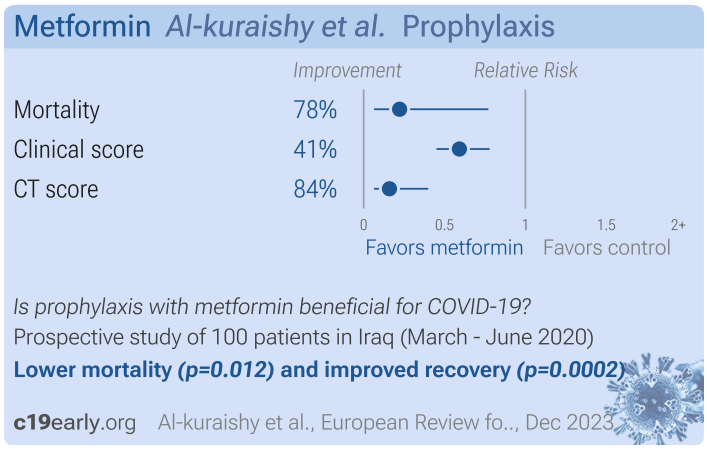
Study Notes

Abu-Jamous



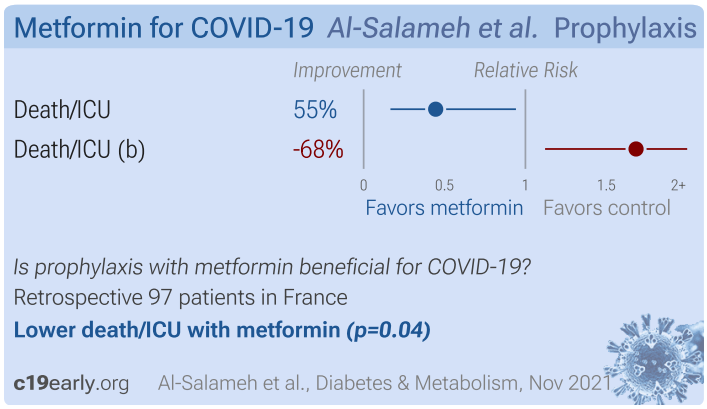
Abu-Jamous: Retrospective diabetes patients in the UK, showing lower mortality for metformin treatment (administered within 21 days after a positive PCR test).

Al-kuraishy



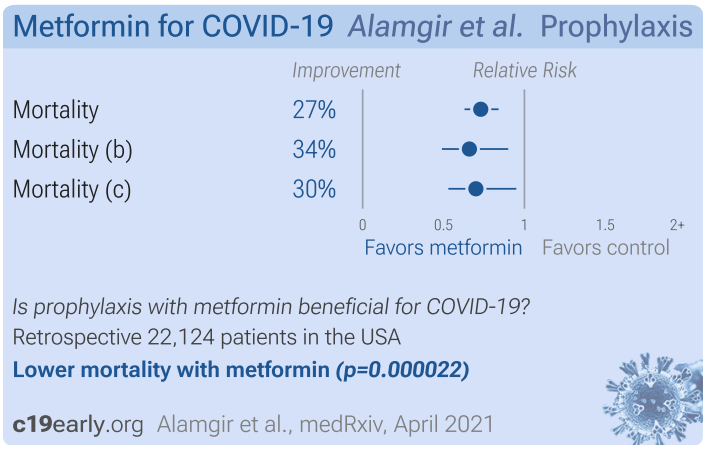
Al-kuraishy: Prospective study of 60 hospitalized type 2 diabetes patients with COVID-19 on metformin monotherapy compared to 40 patients on other diabetes treatments, showing significantly lower inflammatory biomarkers, oxidative stress, and mortality, and improvements in radiological and clinical outcomes with metformin. Confounding due to differences in baseline characteristics may be significant.

Al-Salameh



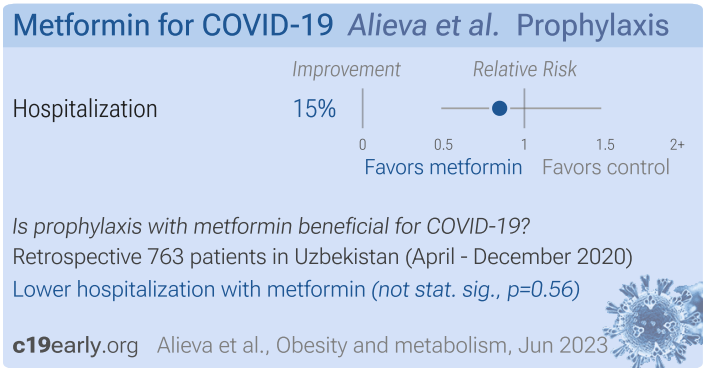
Al-Salameh: Retrospective 140 diabetic patients in France, showing lower mortality for patients where metformin use was continued after hospitalization.

Alamgir



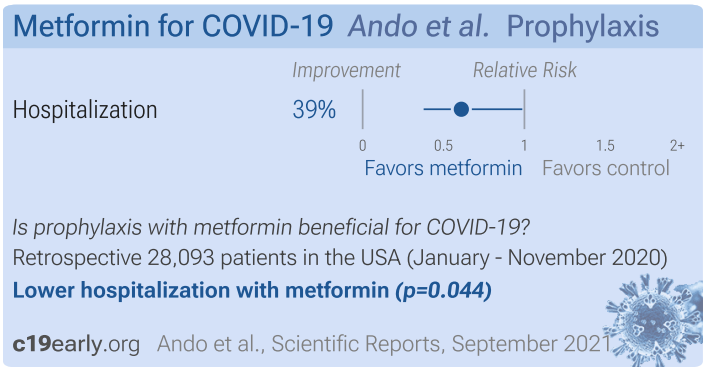
Alamgir: In Silico study followed by PSM analysis of the National COVID Cohort Collaborative data in the USA, showing 27% lower mortality with metformin use.

Alieva



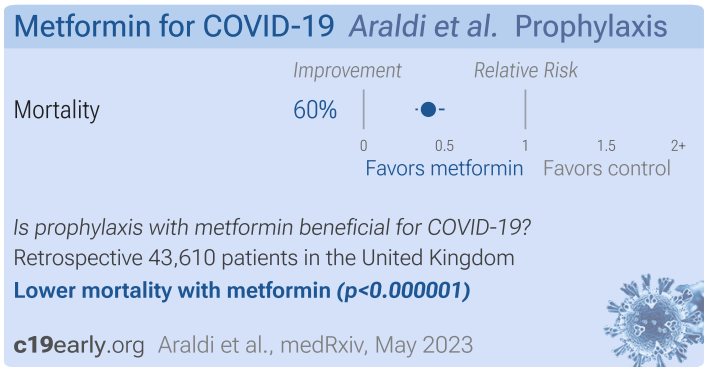
Alieva: Retrospective 763 COVID-19 patients with type 2 diabetes in Uzbekistan, showing lower hospitalization with metformin use in unadjusted results, without statistical significance.

Ando



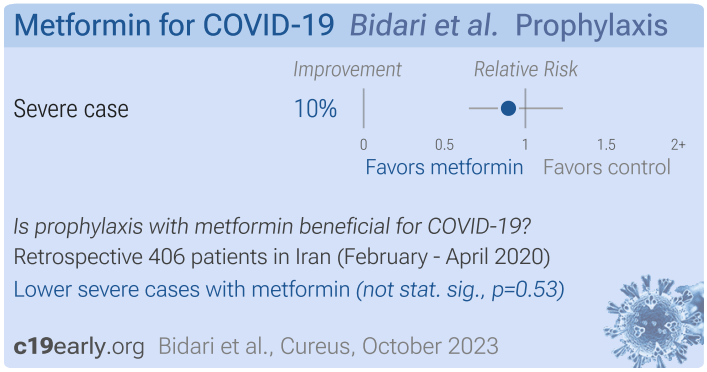
Ando: Retrospective 28,093 COVID+ patients in the USA, showing lower risk of hospitalization with metformin use.

Araldi



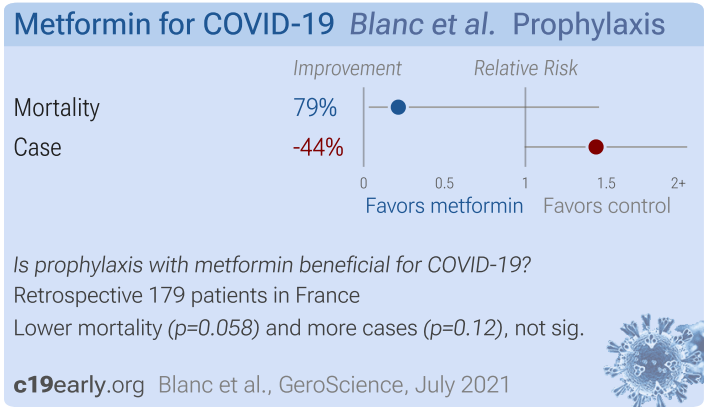
Araldi: UK Biobank retrospective including 43,610 type 2 diabetes patients, showing lower mortality with metformin use within matched type 2 diabetes patients.

Bidari



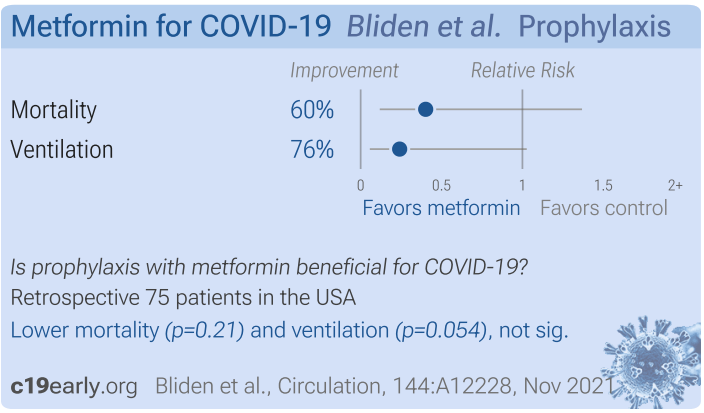
Bidari: Retrospective 406 COVID-19 patients in Iran, showing lower risk of severe cases with metformin use in unadjusted results, without statistical significance.

Blanc



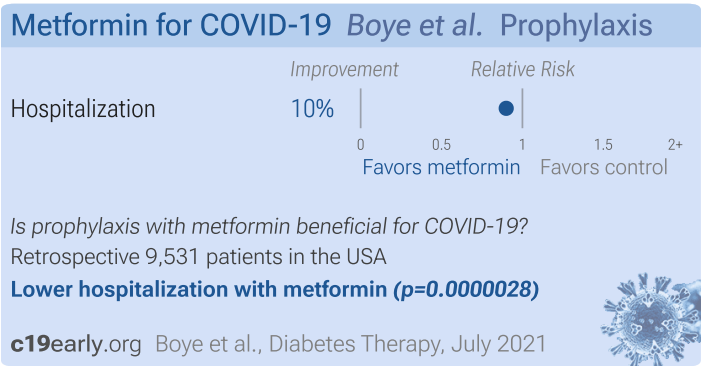
Blanc: Retrospective 179 patients in France exposed to COVID-19 showing, without statistical significance, a higher risk of cases, and a lower risk of mortality among cases with existing metformin treatment.

Bliden



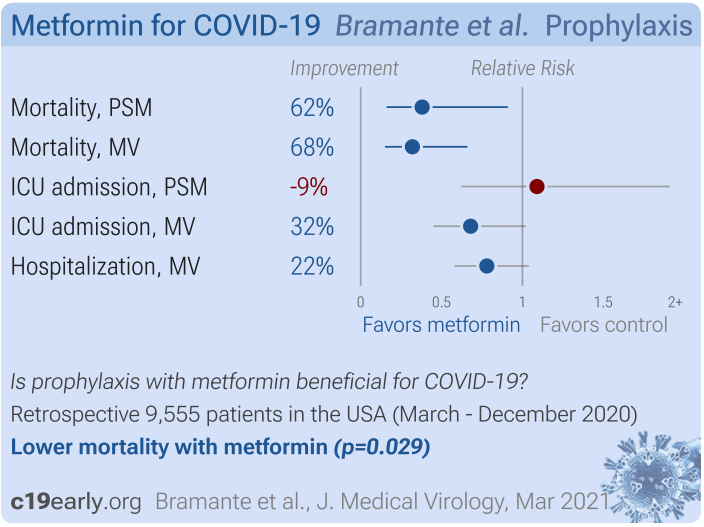
Bliden: Retrospective 75 diabetes patients, 34 on metformin, showing lower mortality with treatment in unadjusted results with minimal group details.

Boye



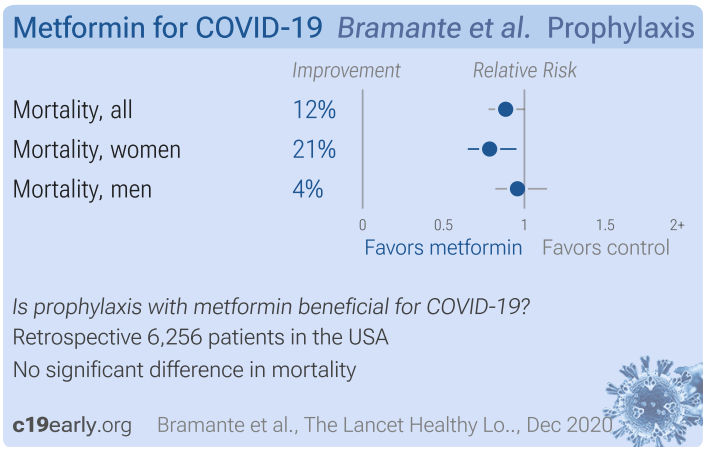
Boye: Retrospective 9531 COVID+ diabetes patients in the USA, showing lower risk of hospitalization with existing biguanides treatment (defined as mainly metformin in the abstract and entirely metformin in the text).

Bramante



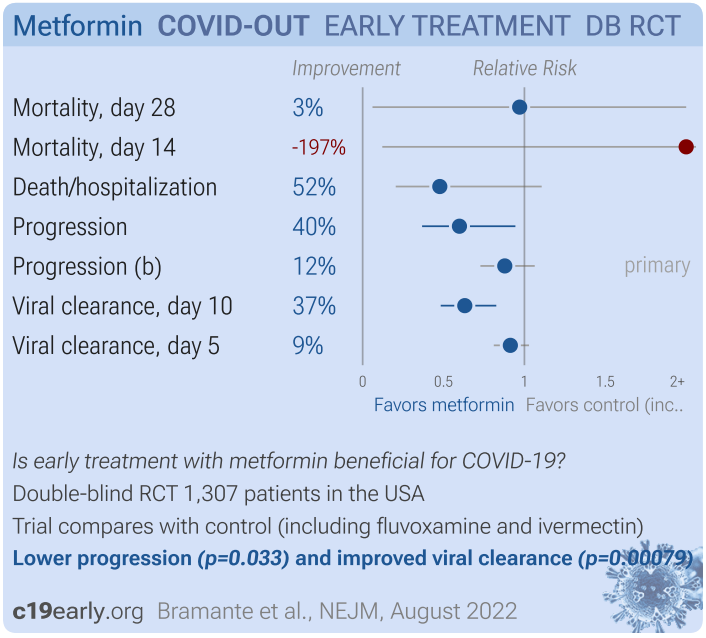
Bramante (B): Retrospective 17,396 PCR+ patients in the USA, showing lower mortality with metformin use.

Bramante



Bramante (C): Retrospective 6,256 COVID-19+ diabetes patients in the USA, showing lower mortality with existing metformin treatment, statistically significant only for women.

Bramante



COVID-OUT remotely operated RCT, showing lower combined ER/hospitalization/death with metformin. Results for other treatments are listed separately - ivermectin, fluvoxamine.

The "control" group includes patients receiving active treatments fluvoxamine and ivermectin.

Control arm results are very different between treatments, for example considering hospitalization/death, this was 1.0% for ivermectin vs. 2.7% for overall control, however it was 1.3% for the ivermectin-specific control. 394 control patients are shared. The rate for the non-shared 261 metformin control patients is 5%, compared to 1.3% for ivermectin control patients. The metformin arm started earlier, however it is unclear why the difference in outcomes is so large.

Results were delayed for 6 months with no explanation, with followup ending Feb 14, 2022.

Adherence was very low, with 77% overall reporting 70+% adherence. Numbers for 100% adherence are not provided.

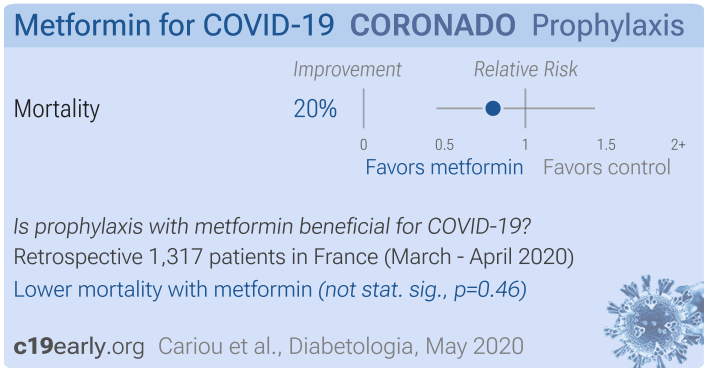
Multiple outcomes are missing, for example time to recovery (where ACTIV-6 showed superiority of ivermectin).

Treatment was 14 days for metformin and fluvoxamine, but only 3 days for ivermectin.

Trial outcomes were changed on January 20, 2022 clinicaltrials.gov, and again on March 2, 2022 clinicaltrials.gov (B). COVIDOUT.

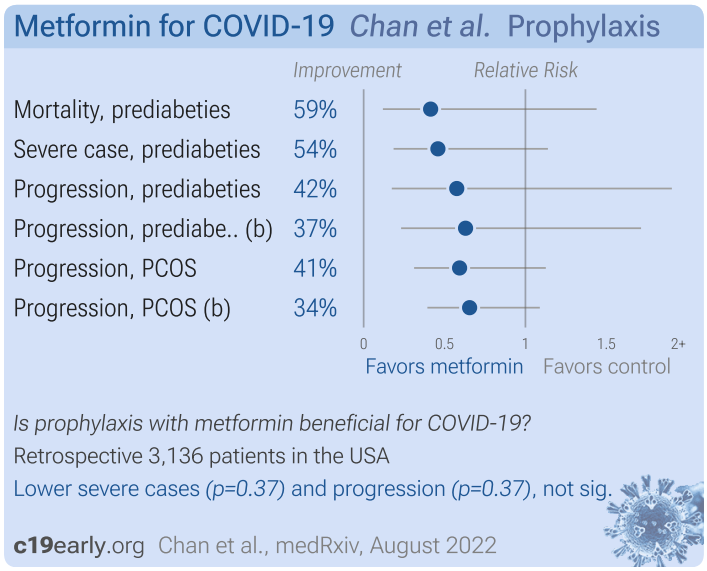
Medication delivery varied significantly over the trial. In this presentation vimeo.com, author indicates that delivery was initially local, later via FedEx, was much slower in August, there were delays due to team bandwidth issues, and they only realized they could use FedEx same day delivery in September.

Cariou



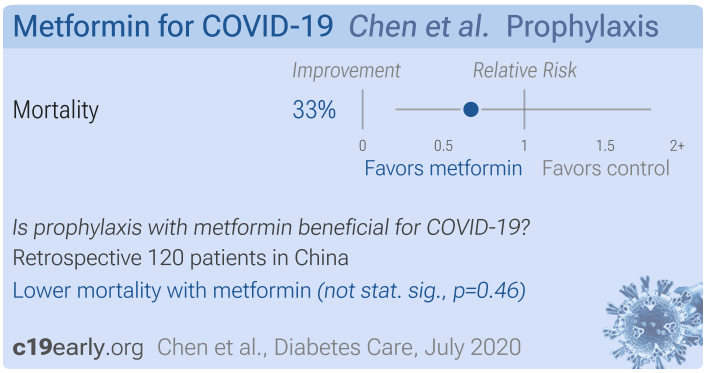
Cariou: Analysis of 1,317 hospitalized COVID-19 patients with diabetes showing lower mortality with metformin use, without statistical significance.

Chan



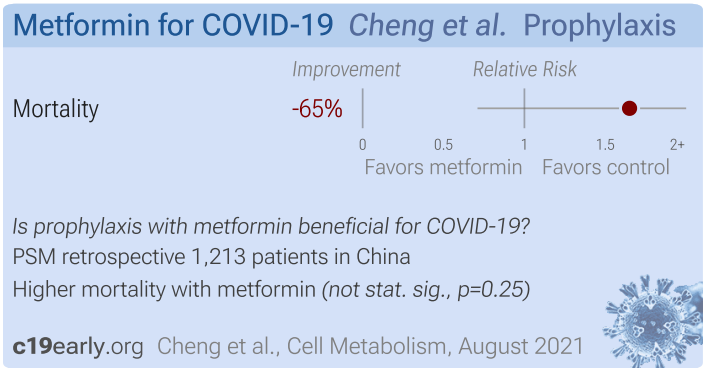
Chan: Retrospective 3,136 patients with prediabetes and 282 with PCOS, showing metformin associated with reduced COVID-19 severity.

Chen



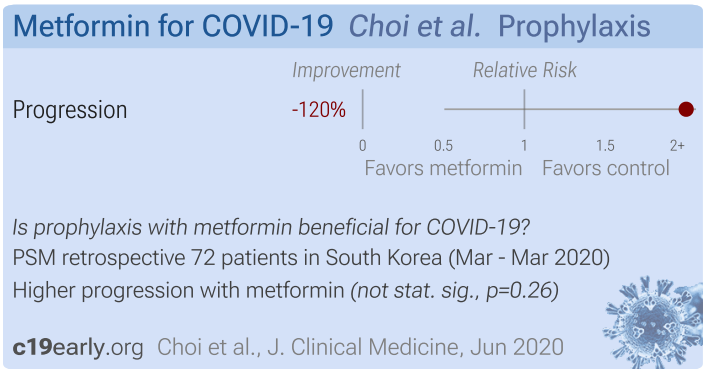
Chen: Retrospective 120 COVID-19 diabetes patients, showing non-statistically significantly lower mortality with existing metformin treatment.

Cheng



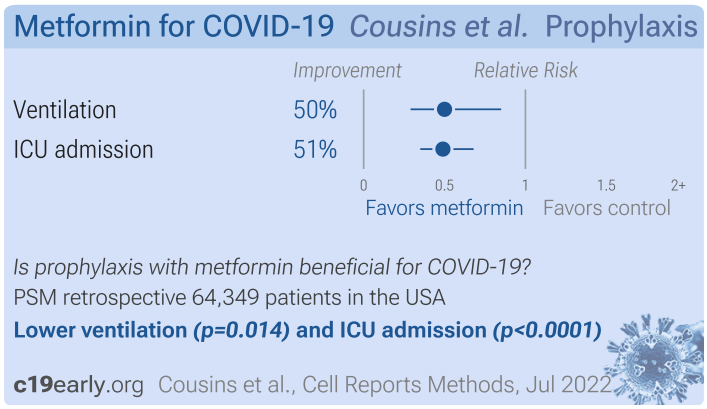
Cheng: Retrospective 1,213 hospitalized diabetic COVID-19 patients in China, showing no significant difference in mortality with pre-existing metformin use.

Choi



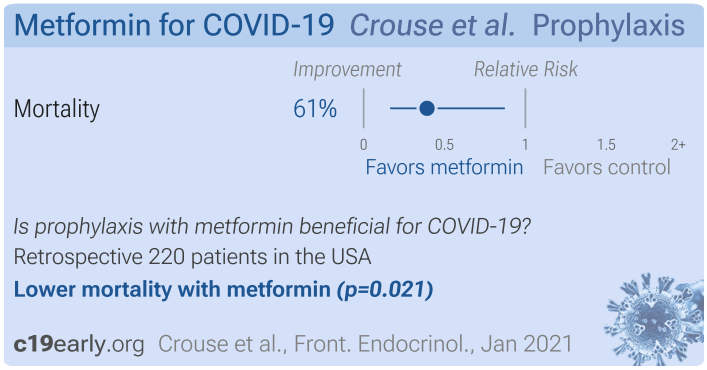
Choi: Retrospective 293 patients in South Korea, showing higher risk of progression with metformin use, without statistical significance.

Cousins



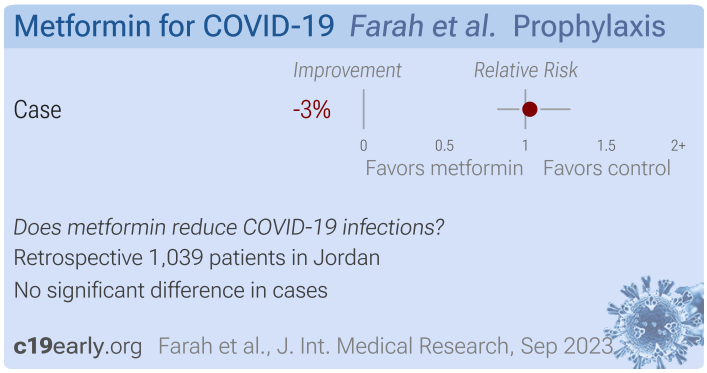
Cousins: PSM retrospective 64,349 COVID-19 patients in the USA, showing metformin associated with lower ICU admission and mechanical ventilation.

Crouse



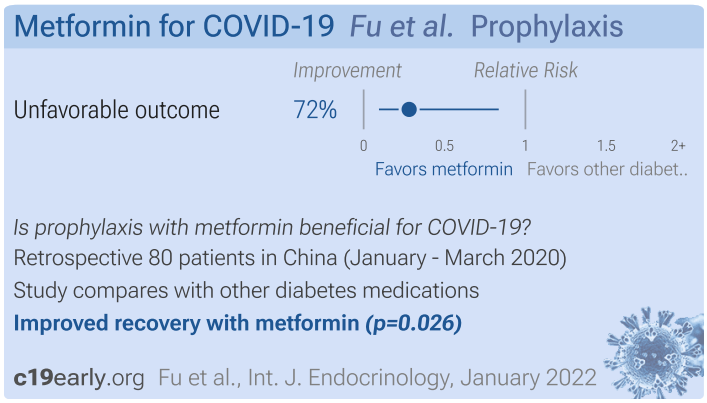
Crouse: Retrospective 219 COVID-19+ diabetes patients in the USA, showing lower mortality with existing metformin treatment.

Farah



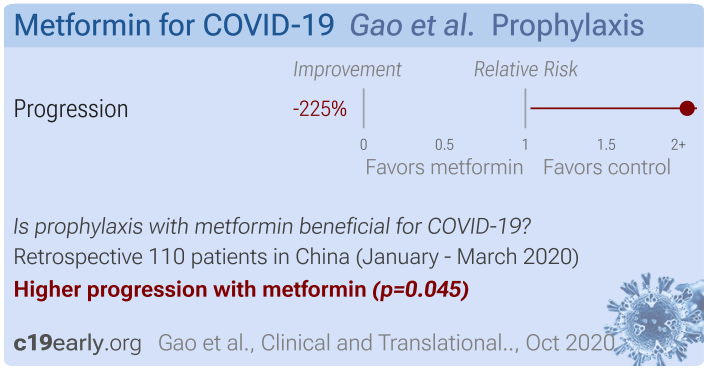
Farah: Retrospective 1,039 diabetes patients in Jordan, showing no significant difference in COVID-19 cases with metformin use in unadjusted results. Severity outcomes are not provided for metformin.

Fu



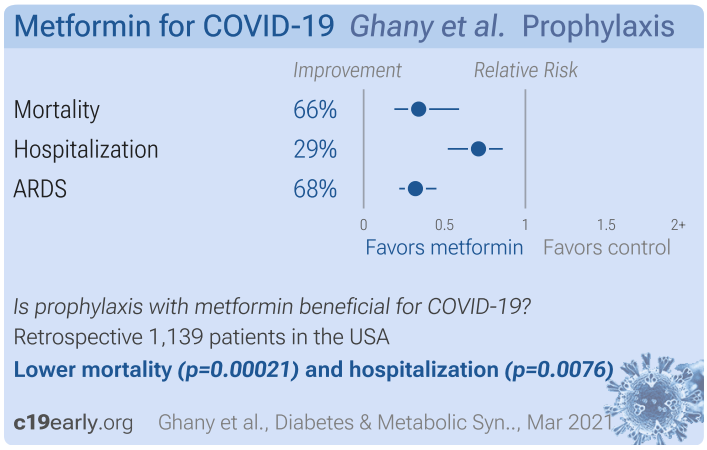
Fu: Retrospective 108 T2D patients hospitalized with COVID-19, showing lower risk of unfavorable outcomes with metformin use vs. other diabetic medications.

Gao



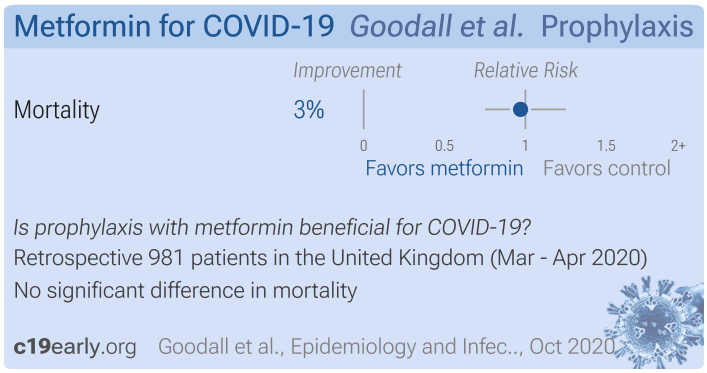
Gao: Retrospective 110 hospitalized COVID-19 patients with diabetes in China, showing increased risk of severity with metformin.

Ghany



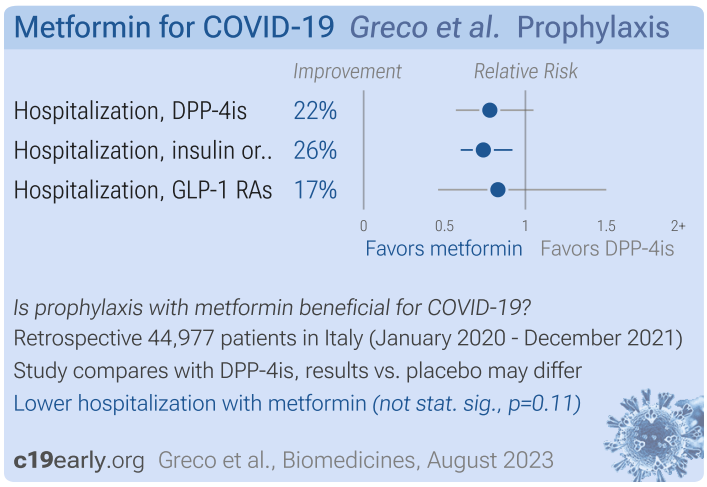
Ghany: Retrospective 1,139 elderly COVID+ patients in the USA, 392 with pre-existing metformin use, showing significantly lower mortality, hospitalization, and ARDS with treatment.

Goodall



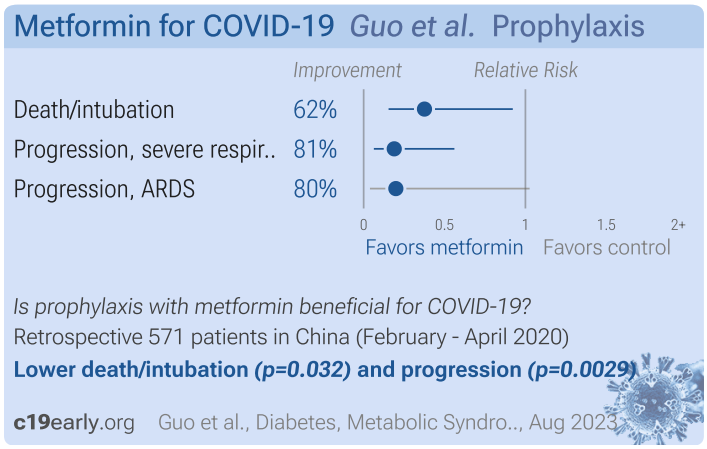
Goodall: Retrospective 981 hospitalized patients in the UK, showing no significant difference with metformin use.

Greco



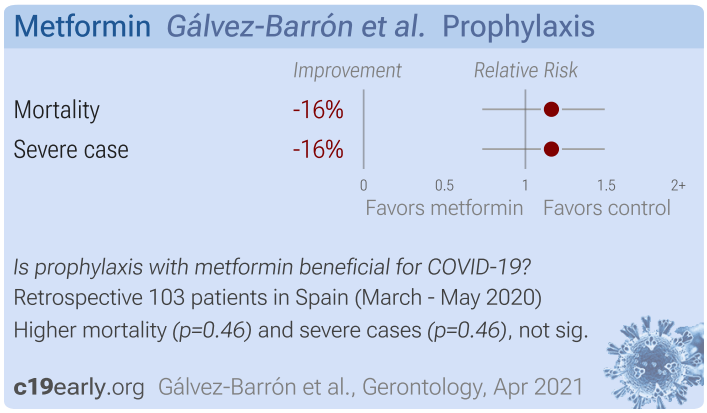
Greco: Retrospective 76,764 diabetes patients in Italy, showing that patients on metformin had lower rates of COVID-19 hospitalization compared to those on insulin/insulin secretagogues, GLP-1 receptor agonists, and DPP-4 inhibitors. Metformin vs. no metformin results are not provided. The most relevant result for COVID-19 and metformin may be the DPP-4i comparison, based on the DPP-4i group being the most similar to the metformin group in terms of baseline COVID-19 risk and confounders. Patients on insulin/secretagogues may have more severe or advanced diabetes.

Guo



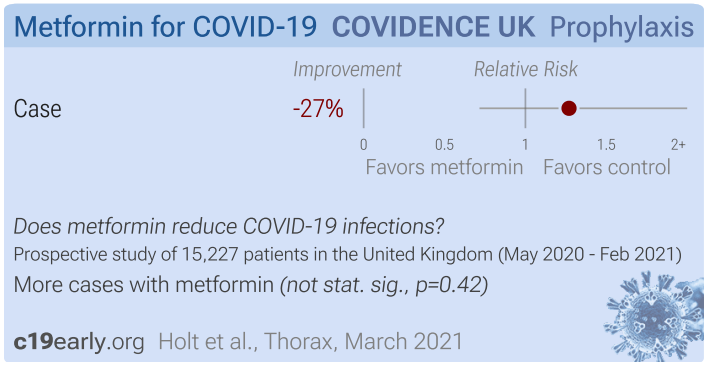
Guo: Retrospective 571 type 2 diabetes patients with COVID-19 in China, showing lower combined mortality/mechanical ventilation with metformin.

Gálvez-Barrón



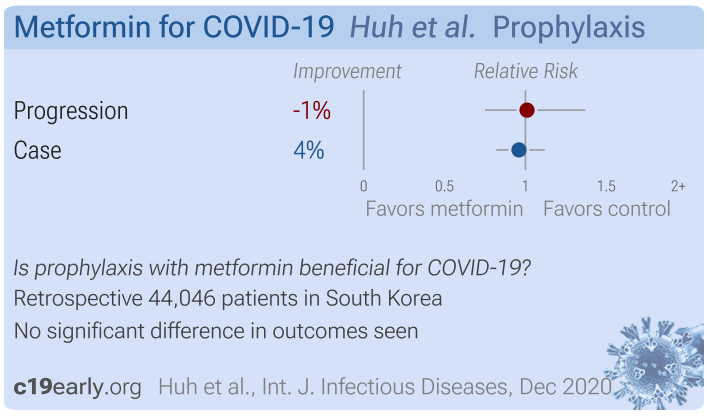
Gálvez-Barrón: Analysis of 103 elderly hospitalized COVID-19 patients in Spain, showing higher mortality with metformin, without statistical significance.

Holt



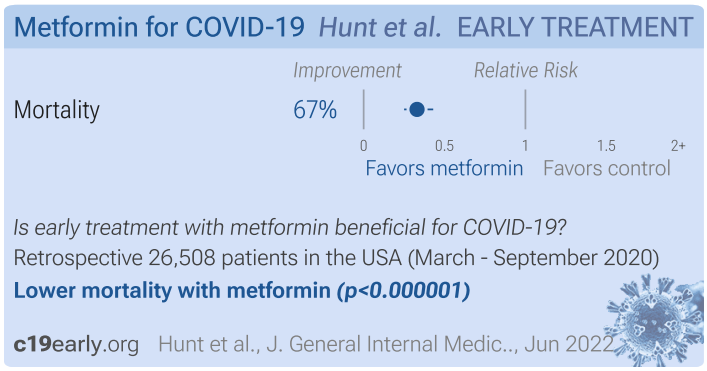
Holt: Prospective survey-based study with 15,227 people in the UK, showing lower risk of COVID-19 cases with vitamin A, vitamin D, zinc, selenium, probiotics, and inhaled corticosteroids; and higher risk with metformin and vitamin C. Statistical significance was not reached for any of these. Except for vitamin D, the results for treatments we follow were only adjusted for age, sex, duration of participation, and test frequency. NCT04330599. COVIDENCE UK.

Huh



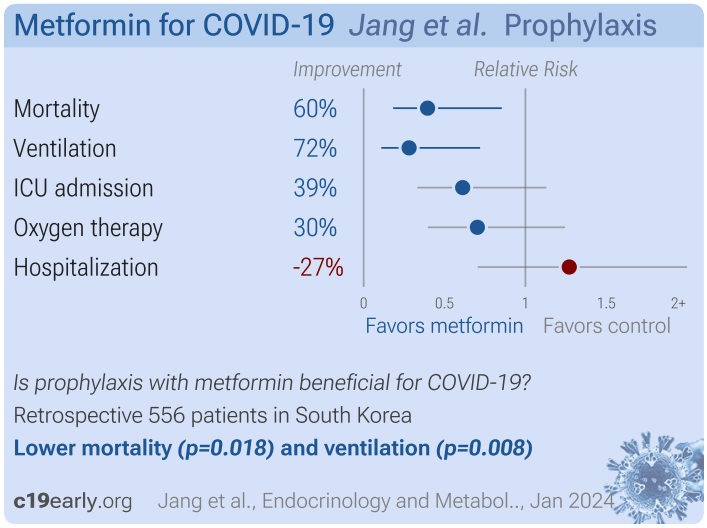
Huh: Retrospective database analysis showing no significant differences with pre-existing metformin use.

Hunt



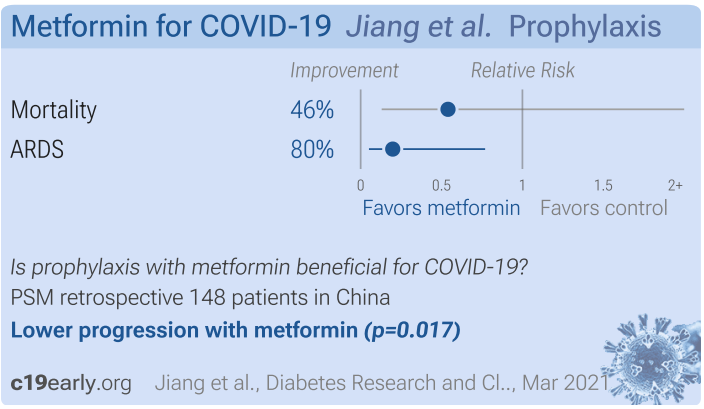
Hunt: Retrospective 26,508 consecutive COVID+ veterans in the USA, showing lower mortality with multiple treatments including metformin. Treatment was defined as drugs administered ≥50% of the time within 2 weeks post-COVID+, and may be a continuation of prophylactic treatment in some cases, and may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

Jang



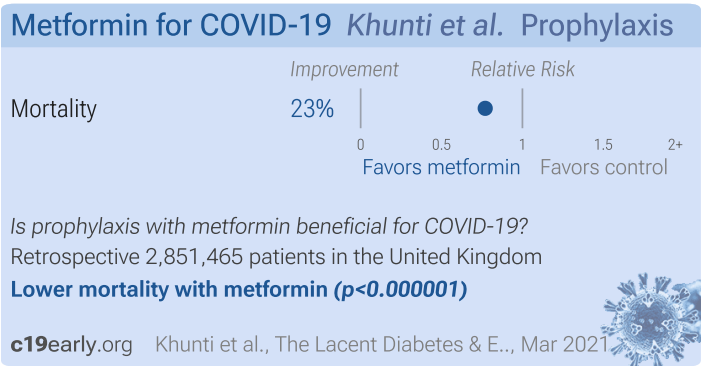
Jang: Retrospective 556 diabetic patients in South Korea with COVID-19 showing lower risk of mechanical ventilation and death with metformin, lower risks of oxygen treatment and death with DPP-4 inhibitors, and increased risk of mechanical ventilation with sulfonylureas. The study used nationwide data to analyze the impact of common antidiabetic medications on COVID-19 outcomes. Authors note that South Korea had a policy early in the pandemic of hospitalizing nearly all confirmed COVID-19 patients regardless of severity.

Jiang



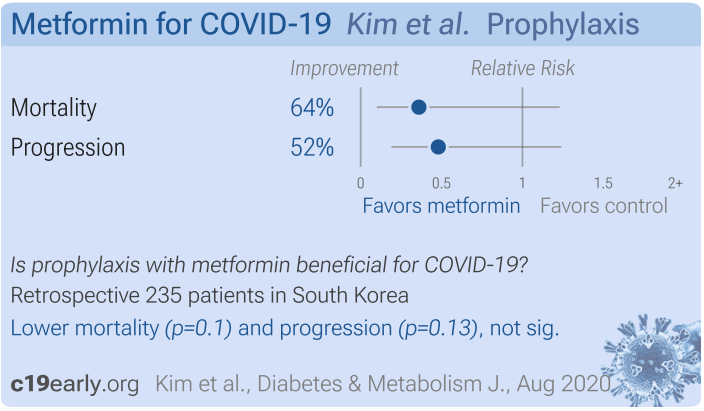
Jiang: Retrospective 328 COVID-19 patients with type 2 diabetes in China, showing significantly lower risk of ARDS with existing metformin use.

Khunti



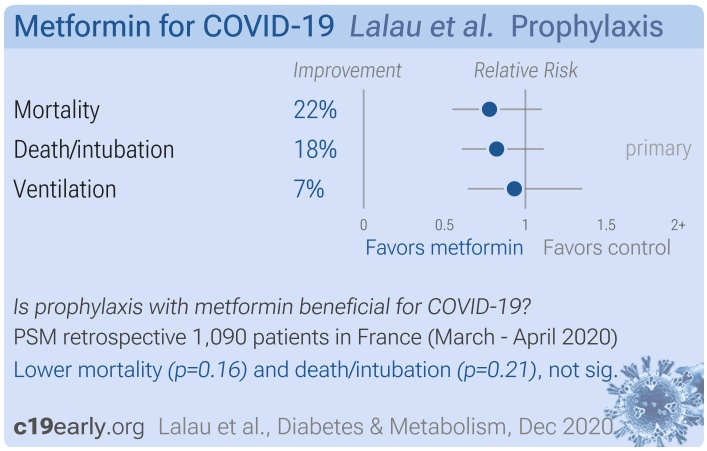
Khunti: Retrospective 2,851,465 people with type 2 diabetes in the UK, showing lower mortality with existing metformin use. Results are subject to confounding by indication because metformin is typically used early in the progression of type 2 diabetes.

Kim



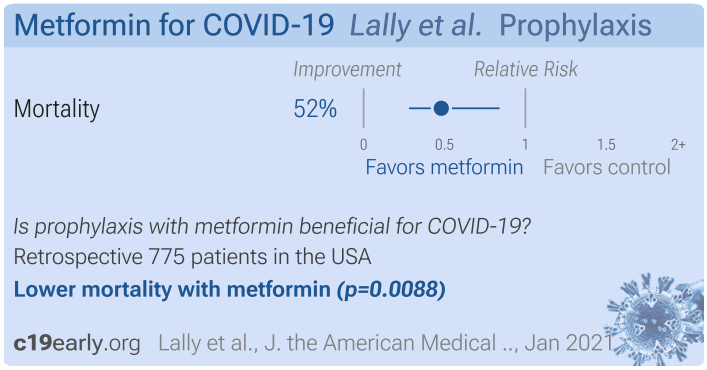
Kim: Retrospective 235 hospitalized diabetes patients in South Korea, showing lower mortality and lower progression to severe disease with metformin.

Lalau



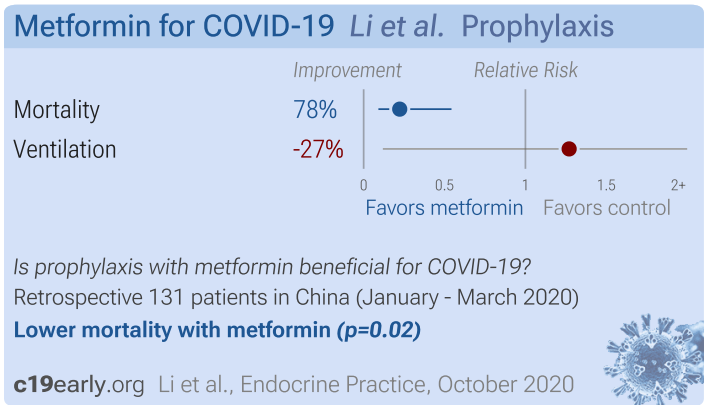
Lalau: Retrospective 2,449 hospitalized COVID-19 diabetes patients in France, 1,496 with existing metformin use, showing lower mortality with treatment. Statistical significance was reached in model 1 but not in models 2-4 which also adjust for HbA1c, eGFR, and diabetes duration, but have a lower number of patients. CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcomes).

Lally



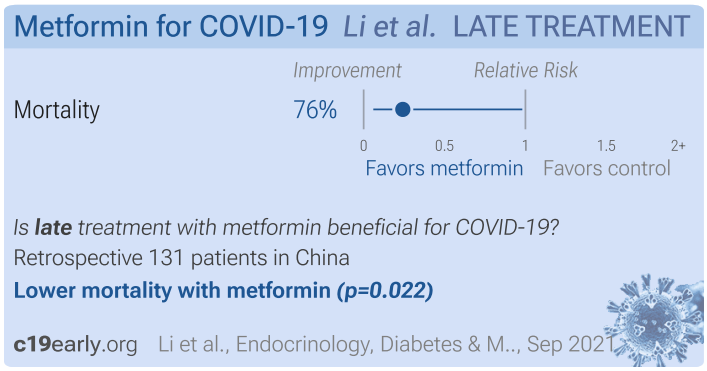
Lally: Retrospective 775 nursing home residents in the USA, showing lower mortality with existing metformin use.

Li



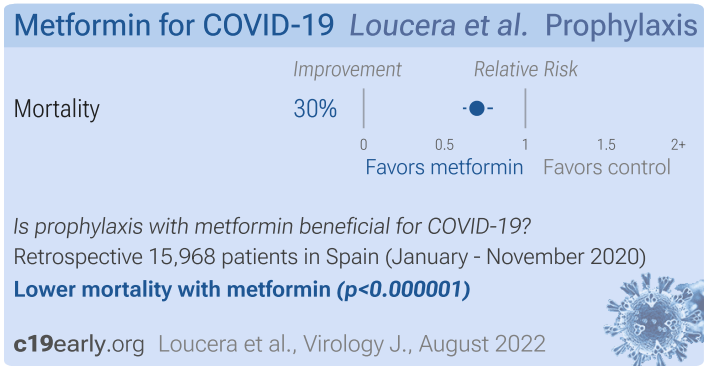
Li (C): Retrospective 131 type II diabetes patients with COVID pneumonia, showing lower mortality with existing metformin use. Acarbose (commonly used in China as an initial therapy for diabetes) did not have a similar association with mortality, suggesting that the result may not be explained by metformin being used early in type II diabetes.

Li



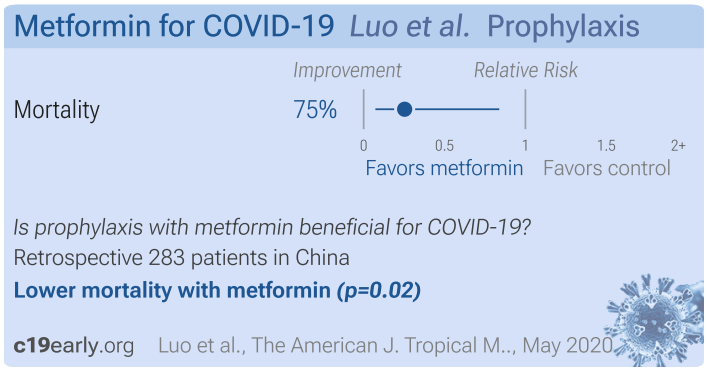
Li (B): Retrospective 131 hospitalized COVID-19 patients with type 2 diabetes, showing lower mortality with metformin treatment and acarbose treatment.

Loucera



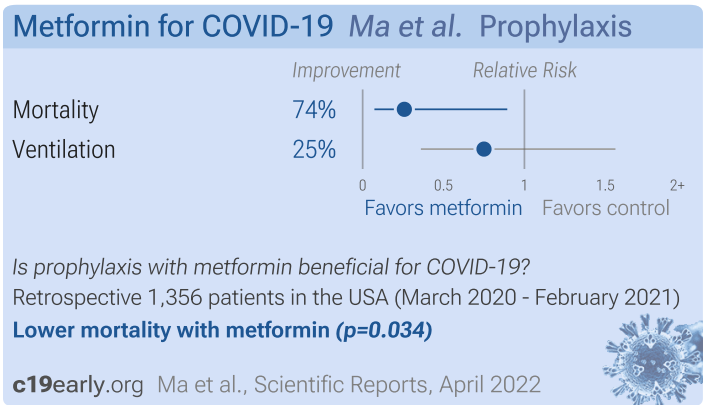
Loucera: Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different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

Luo



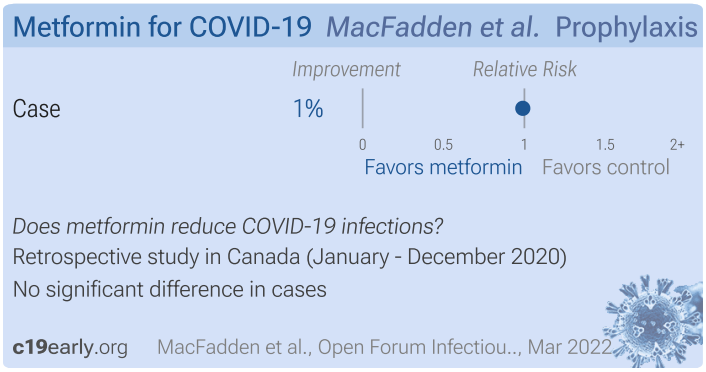
Luo: Retrospective 283 COVID-19+ diabetes patients in China, showing lower mortality with existing metformin treatment.

Ma



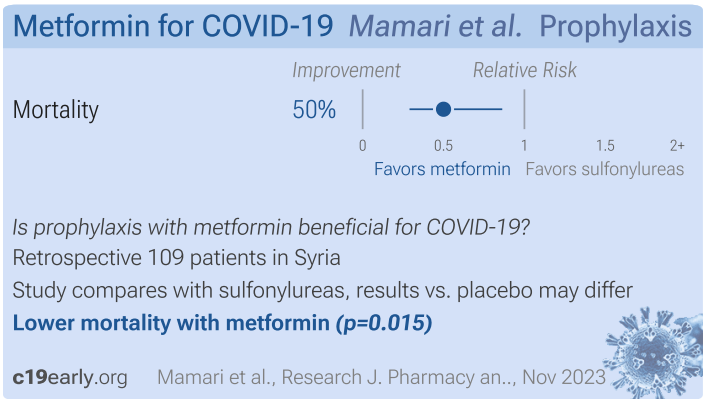
Ma (B): PSM/IPTW retrospective 1,356 hospitalized COVID-19 patients with type 2 diabetes in China, showing lower mortality/hospice with metformin use.

MacFadden



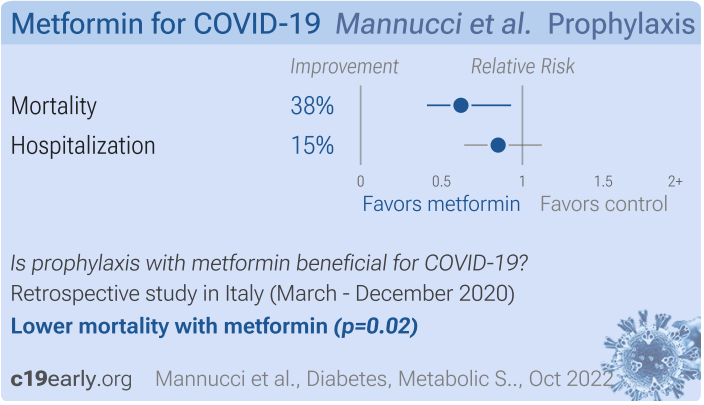
MacFadden: Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing no significant difference in cases with chronic use of metformin.

Mamari



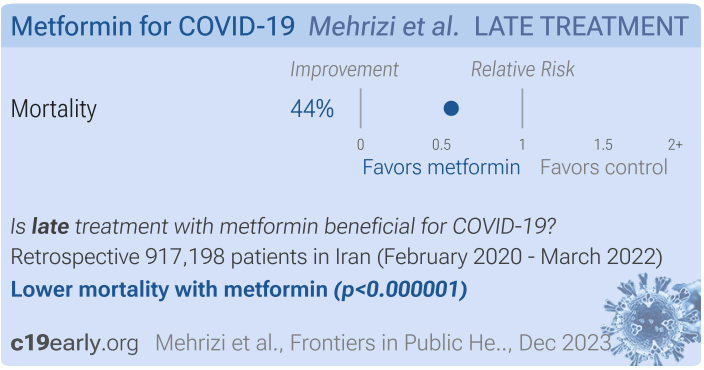
Mamari: Retrospective 109 hospitalized COVID-19 patients in Syria, 68 with diabetes, showing significantly lower mortality with metformin vs. sulfonylureas, and significantly higher mortality with discontinuation of metformin.

Mannucci



Mannucci: Retrospective 54,009 diabetes patients in Italy, showing lower mortality with metformin use.

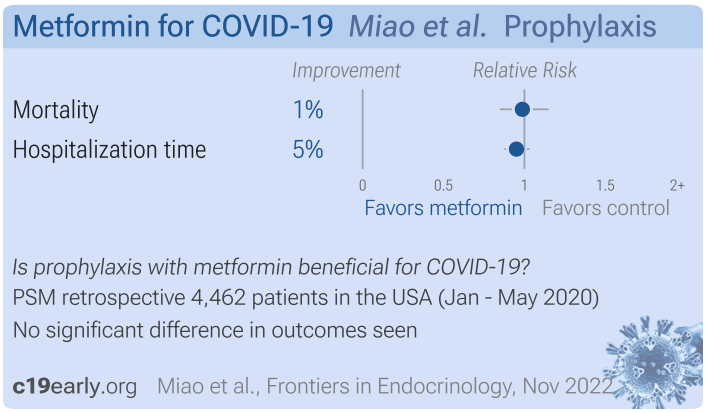
Mehrizi



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.

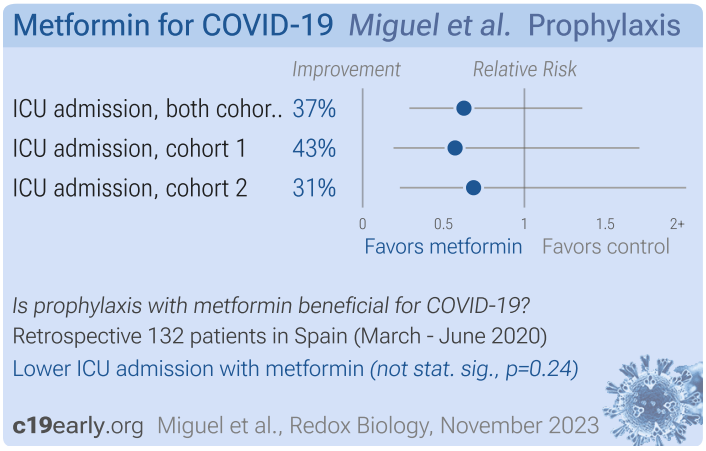
Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency,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

Miao



Miao: Retrospective 4,462 COVID+ diabetes patients in the USA, showing no significant difference in outcomes with metformin use.

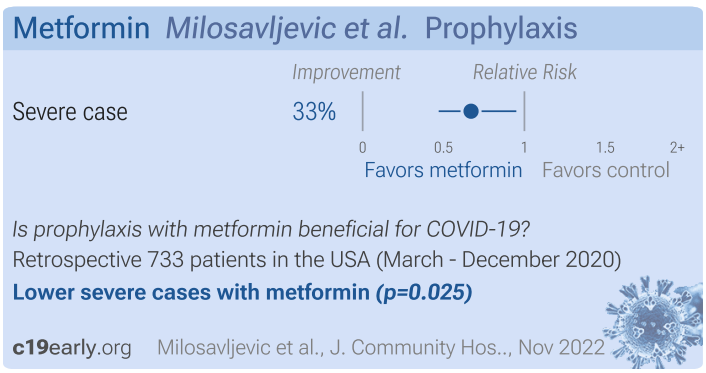
Miguel



Miguel: Mouse models showing reduced lung and kidney injury with metformin. Metformin minimized lung damage and fibrosis in a mouse model of LPS-induced ARDS, and reduced UUO and FAN-induced kidney fibrosis. In Vitro study showing that metformin increased mitochondrial function and decreased TGF-β-induced fibrosis, apoptosis, and inflammation markers in lung epithelial cells.

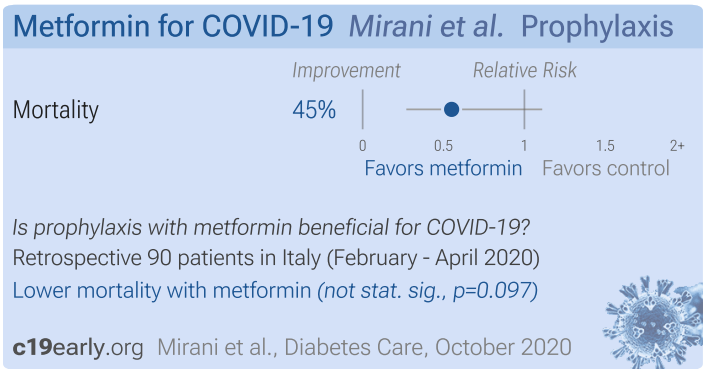
Authors also include a retrospective study showing lower ICU admission with metformin without statistical significance.

Milosavljevic



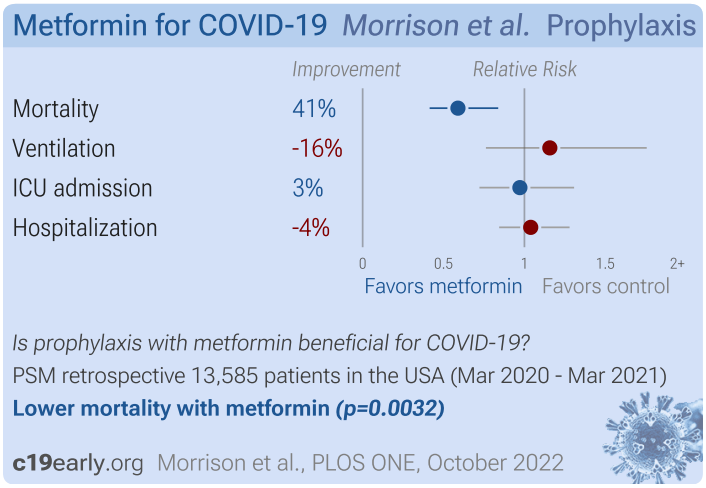
Milosavljevic: Retrospective 733 hospitalized COVID-19 patients with diabetes in the USA, showing lower risk of severity with metformin use.

Mirani



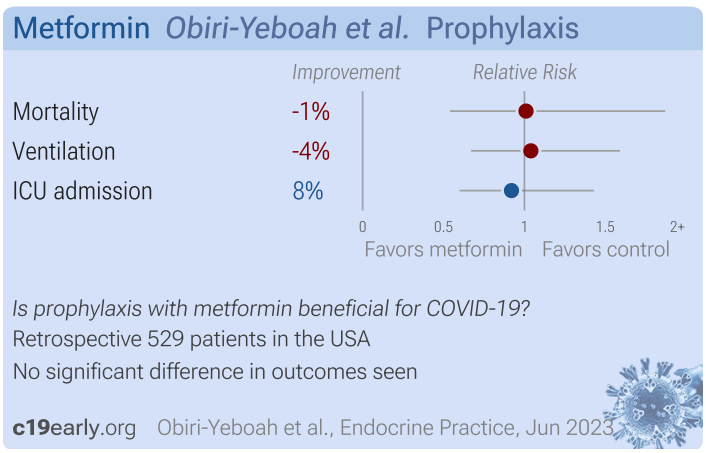
Mirani: Retrospective 90 hospitalized COVID-19 patients with diabetes in Italy, showing lower mortality with metformin use, without statistical significance.

Morrison



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

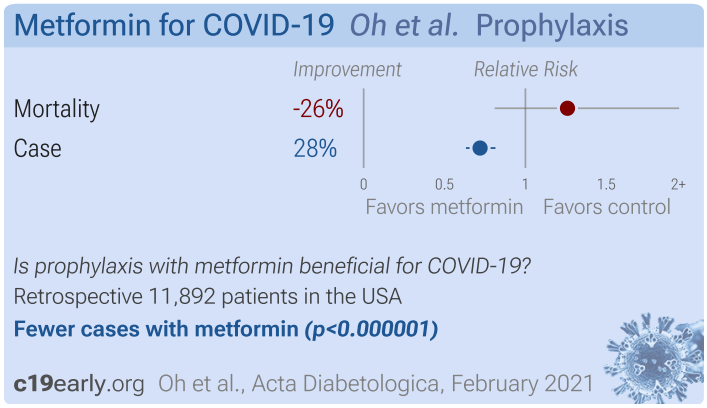
Obiri-Yeboah



Obiri-Yeboah: Retrospective 529 hospitalized COVID-19 patients with type 2 diabetes, showing no significant difference in outcomes with metformin use. This does not account for the different risk of being hospitalized based on metformin use.

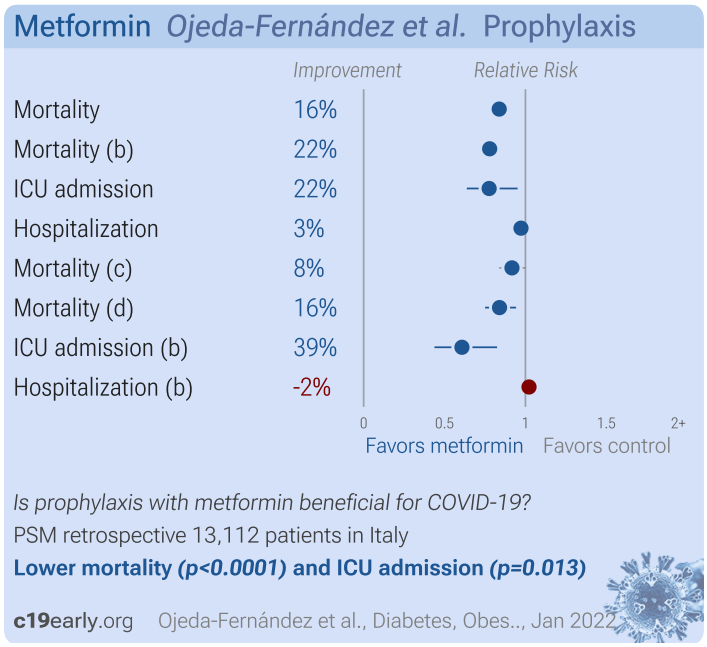
Authors note that *"there is a lower-than-expected proportion of metformin prescription in our population (28%) compared to the general US population"*, without noting that this may reflect the lower risk of being hospitalized for metformin patients, as shown in other studies [c19early.org (C)].

Oh



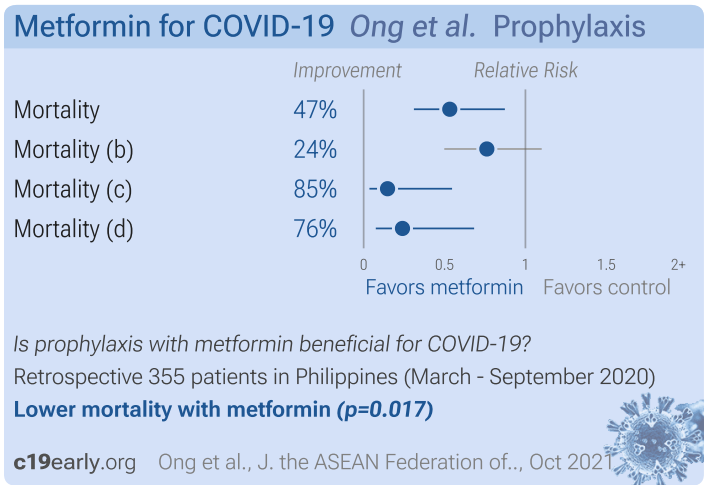
Oh: Retrospective 27,493 type II diabetes patients in the USA, 7,204 on metformin, showing significantly lower COVID-19 cases, but no significant difference in mortality.

Ojeda-Fernández



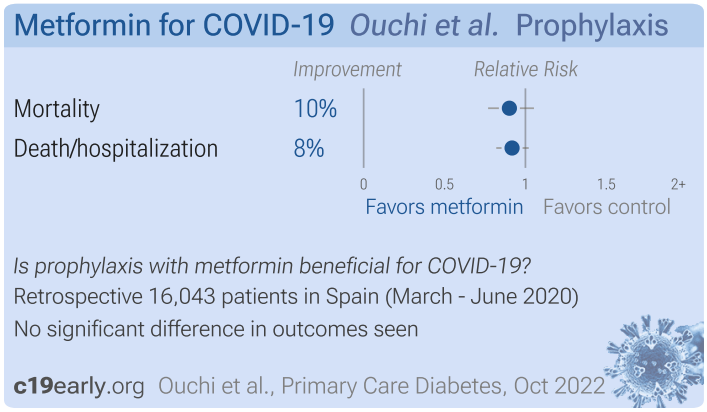
Ojeda-Fernández: Retrospective 31,966 COVID+ patients using anti-hyperglycemic drugs in Italy, showing lower mortality and ICU admission with metformin use.

Ong



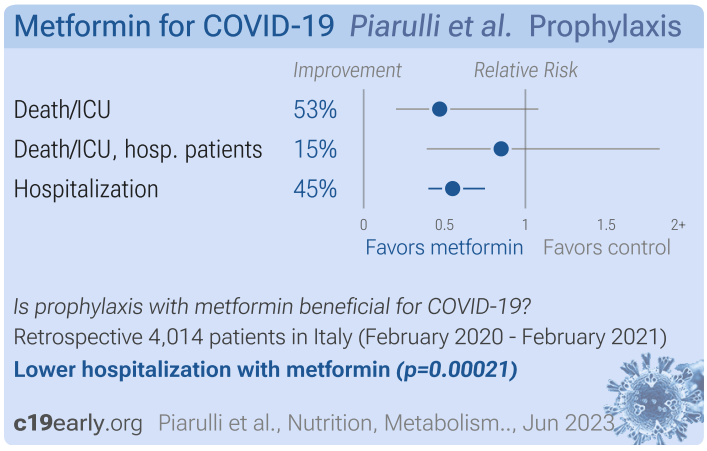
Ong: Retrospective 355 diabetic hospitalized COVID-19 patients in the Philippines, showing lower mortality with metformin use.

Ouchi



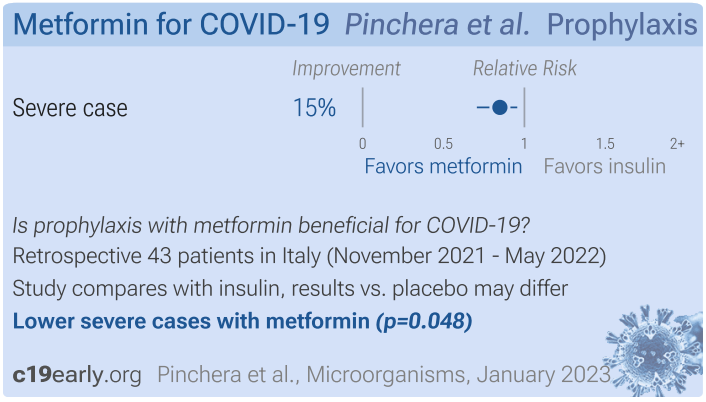
Ouchi: Retrospective 31,006 diabetic COVID-19 patients in Spain, showing lower mortality with metformin treatment, without statistical significance. Authors provide results for metformin compared with untreated patients rather than all non-metformin patients, which may increase confounding due to higher prevalence for treatment of patients with more severe disease.

Piarulli



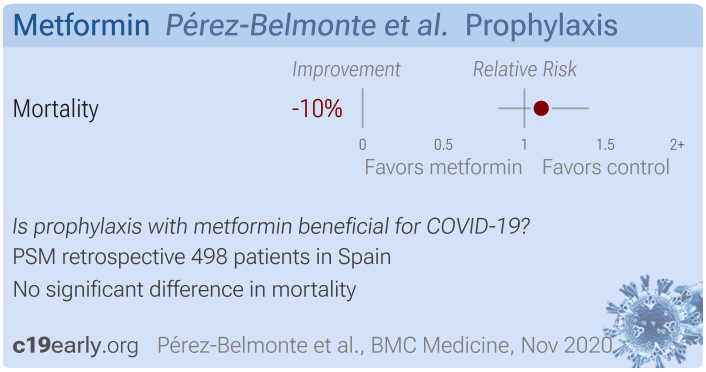
Piarulli: Retrospective diabetic COVID-19 patients in Italy, showing lower risk of hospitalization with metformin use.

Pinchera



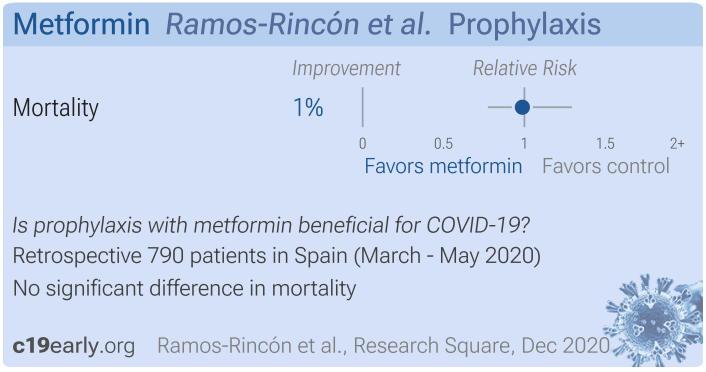
Pinchera: Retrospective 43 diabetes patients hospitalized for COVID-19 in Italy, showing lower risk of severe cases with metformin vs. insulin.

Pérez-Belmonte



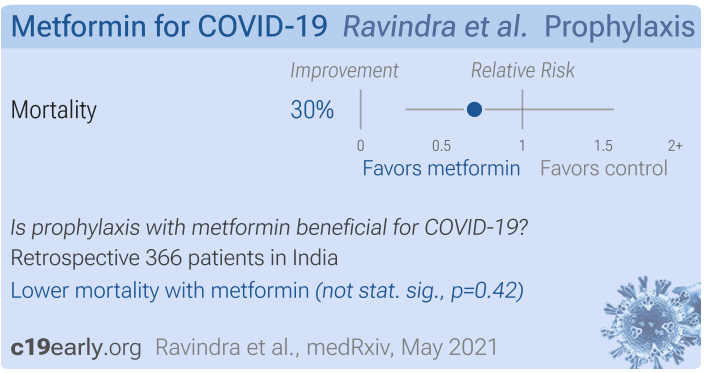
Pérez-Belmonte: Retrospective 2,666 type 2 diabetes COVID-19 patients in Spain, showing higher mortality with existing metformin use (not statistically significant).

Ramos-Rincón



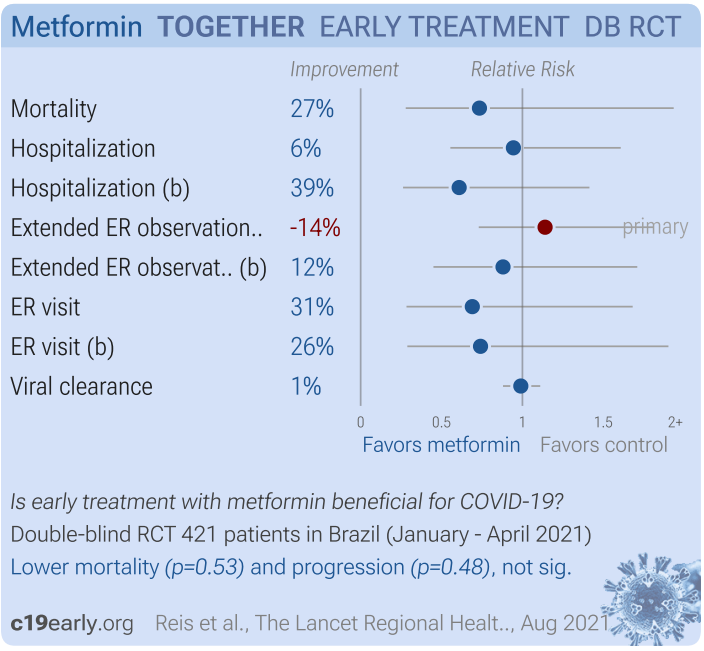
Ramos-Rincón: Retrospective 790 hospitalized type 2 diabetes patients ≥80 years old in Spain, showing no significant difference in mortality with existing metformin use.

Ravindra



Ravindra: Retrospective 1,035 hospitalized patients in India. Of 366 diabetic patients, there was lower mortality for the 53 that were on metformin.

Reis



SEE ALSO

TOGETHER Trial: Doin' Metformin Dirty
TOGETHER Trial & The Negative Number of Metformin Patients
TOGETHER Trial: Doin' Metformin Dirty, Part 3

Reis: Data for the primary outcome in this trial appears to be impossible *doyourownresearch.substack.com*. For example, considering the metformin arm and the ITT population: 24 were hospitalized and 8 had an ER visit (tables S2/S3), therefore the number for combined ER or hospitalization must be between 24 and 32. However, authors report 34 events for ER/hospitalization.

RCT with 215 patients treated with metformin and 203 controls, showing no significant difference with treatment.

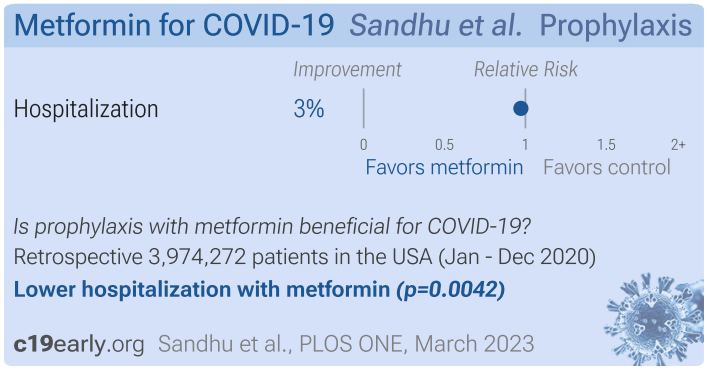
For multiple major issues with this trial see *doyourownresearch.substack.com, doyourownresearch.substack.com (B)*.

The hospitalization risk for off-protocol patients was several times higher in both arms, resulting in Simpson's paradox when combining per-protocol and off-protocol patients *twitter.com*.

750mg twice daily for 10 days.

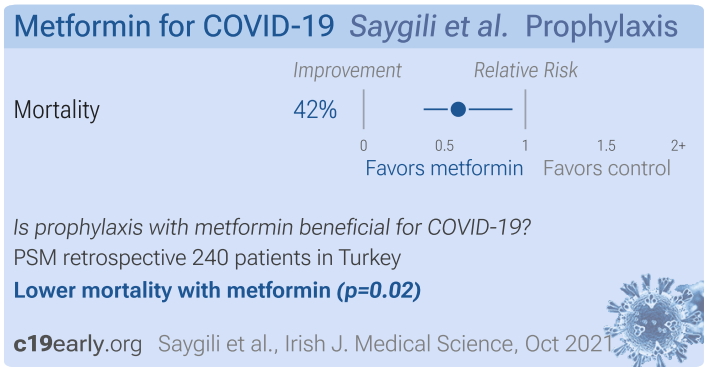
The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see *Reis (B), Reis (C), Reis (D), Reis (E), Reis (F)*.

Sandhu



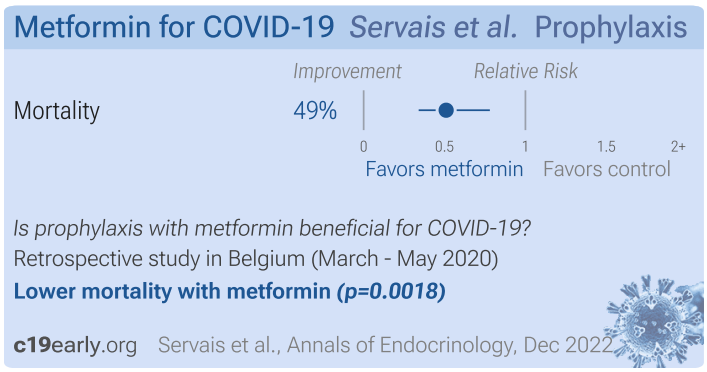
Sandhu: Retrospective 3,974,272 COVID-19 patients in the USA, showing 3% lower risk of hospitalization with pre-existing metformin use.

Saygili



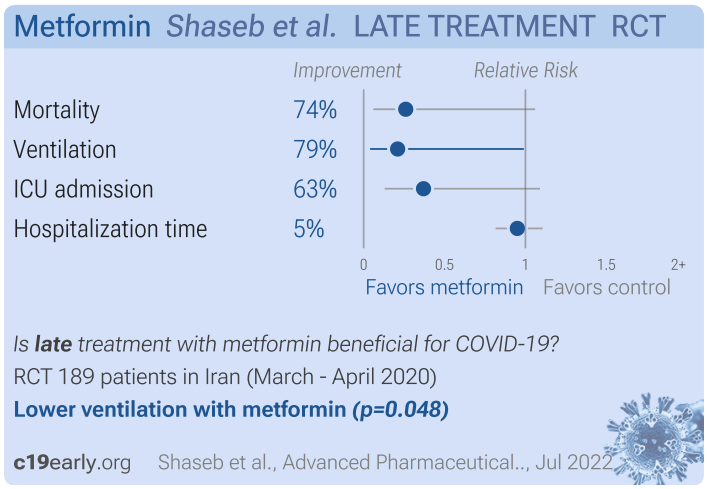
Saygili: Retrospective 586 diabetic hospitalized COVID-19 patients in Turkey, showing lower mortality with existing metformin use.

Servais



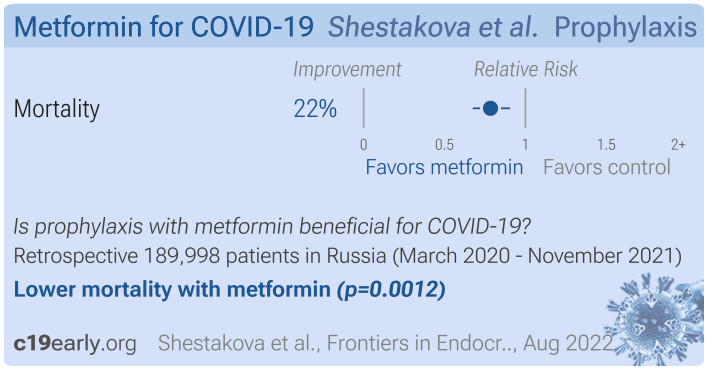
Servais: Retrospective 375 hospitalized diabetes patients in Belgium, showing lower risk of COVID-19 mortality with metformin use.

Shaseb



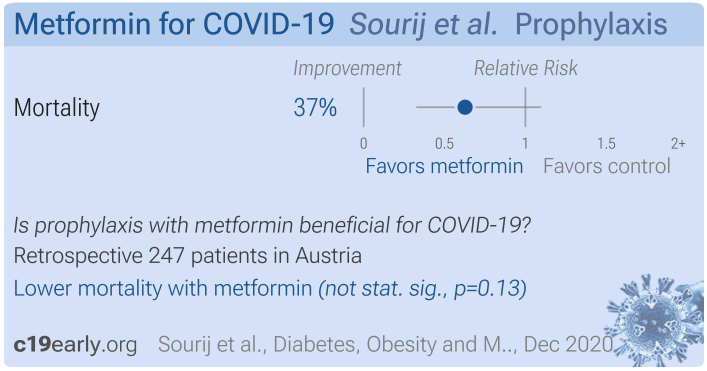
Shaseb: RCT 189 hospitalized patients showing lower mortality, ICU admission, and intubation with metformin, statistically significant only for intubation. Treatment patients may have also taken metformin prior to admission. Authors note that patients receiving metformin prior to the study were not matched, and diabetes and hyperlipidemia differed between groups.

Shestakova



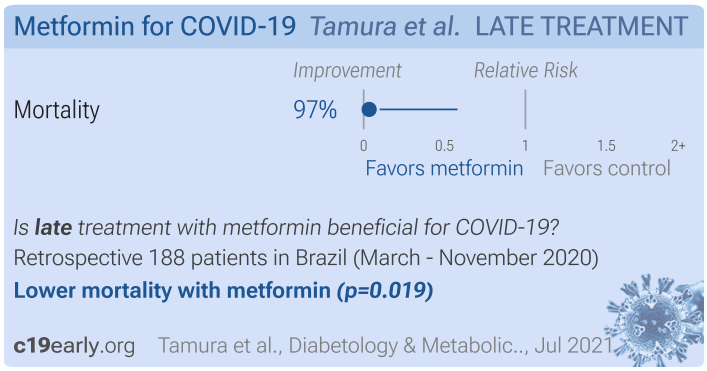
Shestakova: Retrospective 224,190 type 2 diabetes patients in Russia, showing lower mortality with metformin use.

Sourij



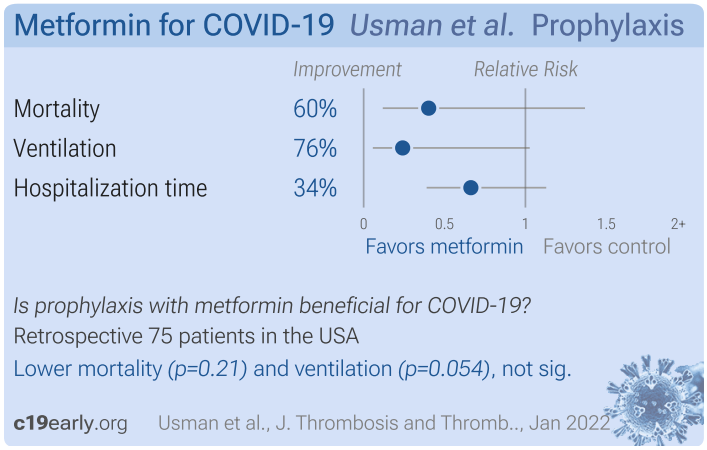
Sourij: Retrospective 247 hospitalized COVID-19 diabetes patients, showing lower mortality with metformin use in unadjusted results.

Tamura



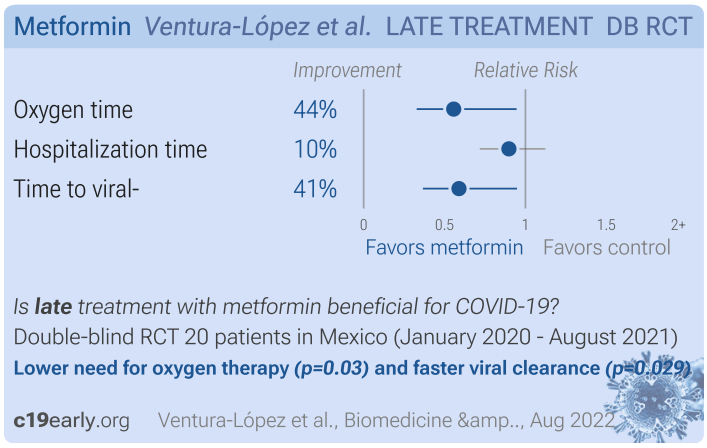
Tamura: Retrospective 188 hospitalized patients in Brazil, showing lower risk of mortality with metformin use. Authors note that, although pre-hospital metformin use improved clinical parameters at admission, continuous use during hospitalization is essential. Patients that used pre-hospital metformin therapy but interrupted the treatment during hospitalization showed higher mortality than those that continued metformin therapy.

Usman



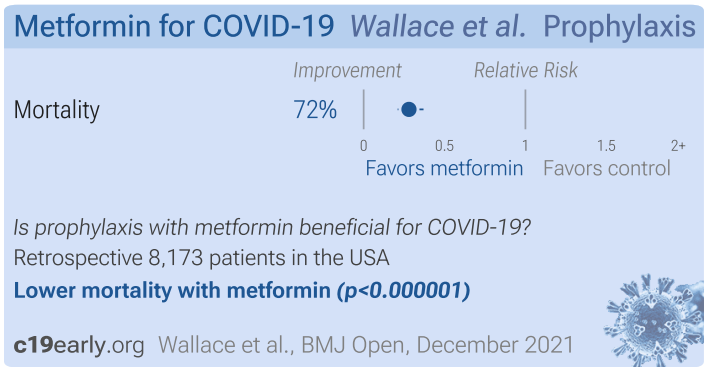
Usman: Retrospective 75 diabetes patients, 34 on metformin, showing improved clinical outcomes with treatment, without statistical significance.

Ventura-López



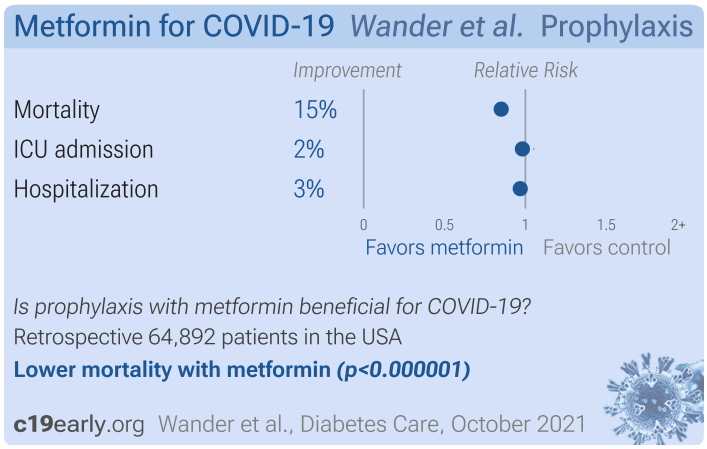
Ventura-López: RCT 20 hospitalized COVID-19 patients showing faster viral load reduction and lower oxygen use with metformin glycinate 620mg twice daily for 14 days compared to placebo. The in vitro portion demonstrated inhibition of viral replication and cytopathic effects with metformin glycinate pretreatment.

Wallace



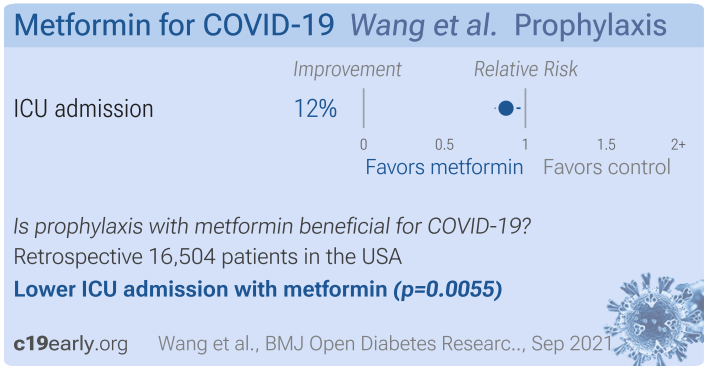
Wallace: Retrospective 9,532 hospitalized COVID+ veterans in the USA, showing lower mortality with metformin use. The study provides results for use before, after, and before+after. Before+after should more accurately represent prophylaxis up to COVID-19 infection (and continued use). Before included use up to 2 years before, and after included use up to 60 days later.

Wander



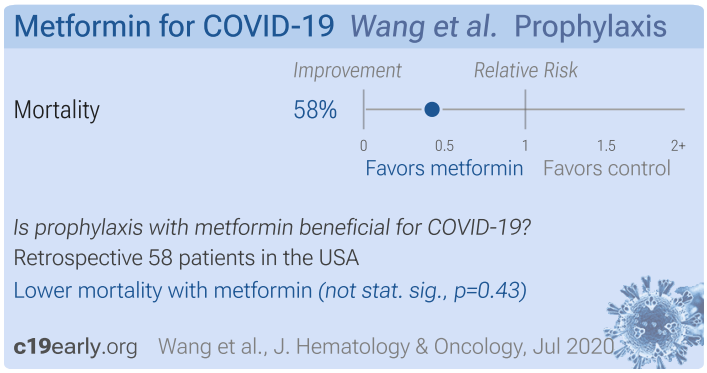
Wander: Retrospective 64,892 veterans with diabetes in the USA, showing lower mortality with existing metformin use.

Wang



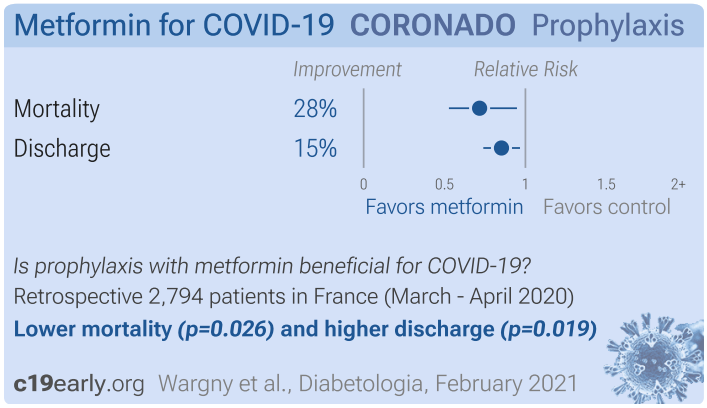
Wang (B): Retrospective 16,504 COVID-19 type 2 diabetes patients, showing lower risk of ICU admission with existing metformin use.

Wang



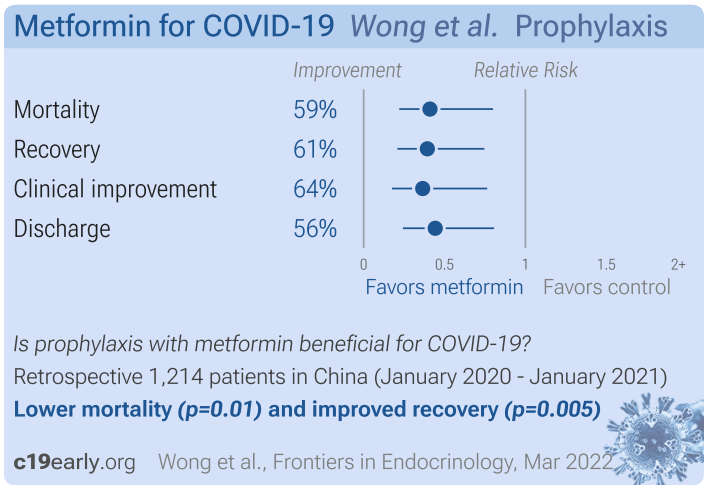
Wang (C): Retrospective 58 multiple myeloma COVID-19 patients in the USA, showing non-statistically significant lower mortality with metformin treatment.

Wargny



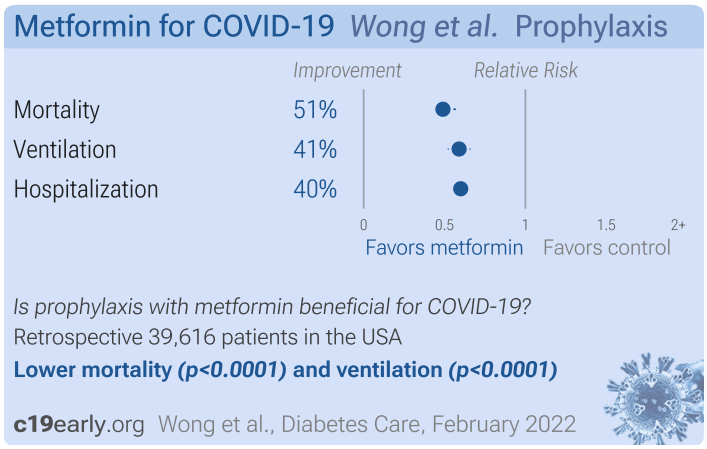
Wargny: Retrospective 2,796 hospitalized diabetes patients with COVID-19 in France, showing lower mortality with metformin use.

Wong



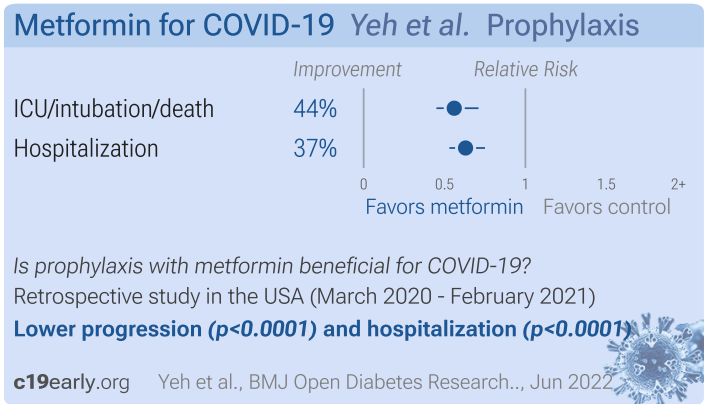
Wong: Retrospective 1,214 COVID+ type 2 diabetes patients in Hong Kong, showing lower mortality and improved recovery with metformin use.

Wong



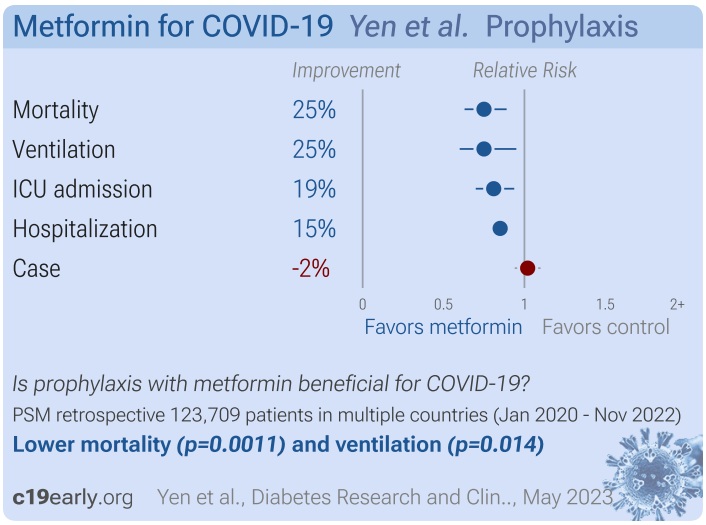
Wong (B): N3C retrospective 39,616 COVID-19 patients with diabetes in the USA, showing lower mortality, ventilation, and hospitalization with metformin use.

Yeh



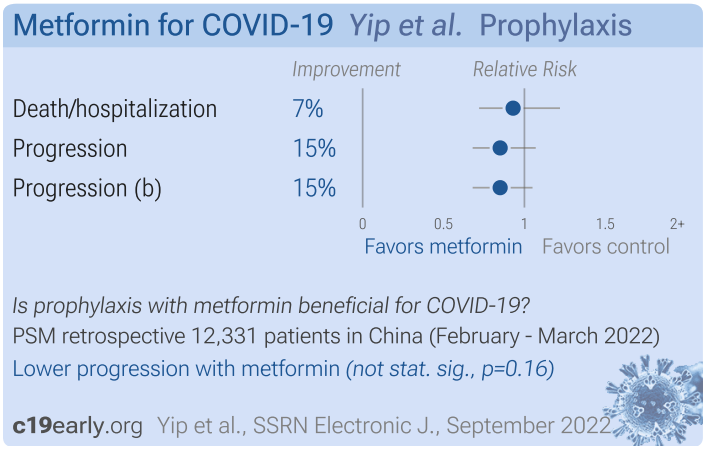
Yeh: Retrospective 4,944 COVID-19 patients with type 2 diabetes in the USA, showing lower risk of hospitalization and combined ICU/intubation/death with metformin use.

Yen



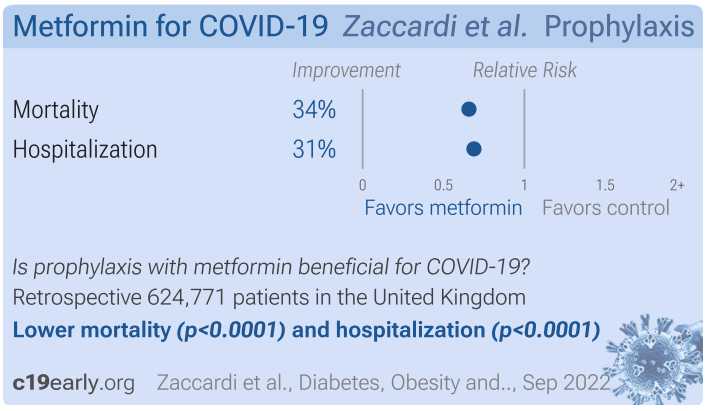
Yen: TriNetX retrospective 123,709 vaccinated patients with type 2 diabetes, showing significantly lower risk of COVID-19 mortality, mechanical ventilation, and hospitalization with metformin use. There was no significant difference for cases. The increasing benefit for more serious outcomes matches the results of studies to date.

Yip



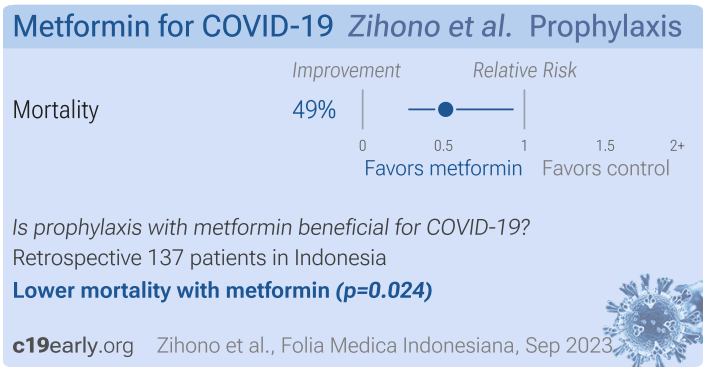
Yip: Retrospective 12,331 diabetes patients in Hong Kong, showing no significant difference in outcomes with metformin use.

Zaccardi



Zaccardi: Retrospective 624,771 people with type 2 diabetes in the UK, showing lower COVID-19 mortality and hospitalization with metformin use.

Zihono



Zihono: Retrospective 137 hospitalized mild to moderate COVID-19 patients with type 2 diabetes in Indonesia, showing a significantly lower mortality with metformin 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 metformin 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 metformin 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 (B)*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only

report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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

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

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

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

Bramante, 8/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 3 authors, average treatment delay 4.8 days, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04510194 (history) (COVID-OUT).	risk of death, 2.9% lower, RR 0.97, $p = 1.00$, treatment 1 of 408 (0.2%), control 1 of 396 (0.3%), NNT 13464, day 28.
	risk of death, 197.1% higher, RR 2.97, $p = 1.00$, treatment 1 of 408 (0.2%), control 0 of 396 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 14.
	risk of death/hospitalization, 52.3% lower, RR 0.48, $p = 0.09$, treatment 8 of 652 (1.2%), control 18 of 655 (2.7%), NNT 66, odds ratio converted to relative risk.
	risk of progression, 40.2% lower, RR 0.60, $p = 0.03$, treatment 27 of 652 (4.1%), control 48 of 655 (7.3%), NNT 31, odds ratio converted to relative risk, combined ER, hospitalization, death.
	risk of progression, 12.1% lower, RR 0.88, $p = 0.18$, treatment 154 of 652 (23.6%), control 179 of 653 (27.4%), NNT 26, odds ratio converted to relative risk, combined hypoxemia, ER, hospitalization, death, primary outcome.
	risk of no viral clearance, 36.9% lower, RR 0.63, $p < 0.001$, treatment 72 of 504 (14.3%), control 112 of 495 (22.6%), NNT 12, day 10.

	risk of no viral clearance, 8.7% lower, RR 0.91, $p = 0.15$, treatment 251 of 504 (49.8%), control 270 of 495 (54.5%), NNT 21, day 5.
Hunt, 6/29/2022, retrospective, USA, peer-reviewed, 8 authors, study period 1 March, 2020 - 10 September, 2020.	**risk of death, 67.0% lower, RR 0.33, $p < 0.001$**, treatment 73 of 3,956 (1.8%), control 1,539 of 22,552 (6.8%), NNT 20, adjusted per study, day 30.
Reis, 8/31/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 23 authors, study period 15 January, 2021 - 3 April, 2021, impossible data, see notes, trial NCT04727424 (history) (TOGETHER).	**risk of death, 26.6% lower, RR 0.73, $p = 0.53$**, treatment 7 of 215 (3.3%), control 9 of 203 (4.4%), NNT 85, day 28.
	risk of hospitalization, 5.6% lower, RR 0.94, $p = 0.88$, treatment 24 of 215 (11.2%), control 24 of 203 (11.8%), NNT 152, ITT.
	risk of hospitalization, 39.1% lower, RR 0.61, $p = 0.28$, treatment 8 of 168 (4.8%), control 14 of 179 (7.8%), NNT 33, PP.
	risk of extended ER observation or hospitalization, 14.0% higher, RR 1.14, $p = 0.58$, treatment 34 of 215 (15.8%), control 28 of 203 (13.8%), ITT, primary outcome.
	risk of extended ER observation or hospitalization, 12.0% lower, RR 0.88, $p = 0.72$, treatment 14 of 168 (8.3%), control 17 of 179 (9.5%), NNT 86, PP.
	risk of ER visit, 31.0% lower, RR 0.69, $p = 0.48$, treatment 8 of 216 (3.7%), control 11 of 205 (5.4%), NNT 60, ITT.
	risk of ER visit, 25.9% lower, RR 0.74, $p = 0.62$, treatment 7 of 171 (4.1%), control 10 of 181 (5.5%), NNT 70, PP.
	risk of no viral clearance, 1.0% lower, RR 0.99, $p = 0.85$, treatment 215, control 203, adjusted per study.

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.

Abu-Jamous, 8/23/2020, retrospective, United Kingdom, preprint, 7 authors, study period 1 January, 2020 - 27 May, 2020.	**risk of death, 65.3% lower, RR 0.35, $p = 0.04$**, treatment 4 of 23 (17.4%), control 94 of 168 (56.0%), NNT 2.6, odds ratio converted to relative risk.
Li (B), 9/29/2021, retrospective, China, peer-reviewed, 13 authors.	**risk of death, 75.8% lower, RR 0.24, $p = 0.02$**, treatment 2 of 37 (5.4%), control 21 of 94 (22.3%), NNT 5.9.
Mehrizi, 12/18/2023, retrospective, Iran, peer-reviewed, 10 authors, study period 1 February, 2020 - 20 March, 2022.	**risk of death, 44.0% lower, OR 0.56, $p < 0.001$**, RR approximated with OR.
Shaseb, 7/2/2022, Randomized Controlled Trial, Iran, peer-reviewed, 26 authors, study period 20 March, 2020 - 5 April, 2020, trial IRCT20160310026998N10.	**risk of death, 74.0% lower, OR 0.26, $p = 0.06$**, treatment 85, control 104, RR approximated with OR.

	risk of mechanical ventilation, 79.0% lower, OR 0.21, $p = 0.048$, treatment 85, control 104, RR approximated with OR.
	risk of ICU admission, 63.0% lower, OR 0.37, $p = 0.07$, treatment 85, control 104, RR approximated with OR.
	hospitalization time, 5.0% lower, relative time 0.95, $p = 0.52$, treatment 85, control 104.
Tamura, 7/13/2021, retrospective, Brazil, peer-reviewed, 4 authors, study period 10 March, 2020 - 13 November, 2020.	**risk of death, 96.6% lower, OR 0.03, $p = 0.02$**, treatment 115, control 73, adjusted per study, in-hospital use, multivariable, RR approximated with OR.
Ventura-López, 8/31/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, mean age 47.5, 14 authors, study period January 2020 - August 2021.	**oxygen time, 44.3% lower, relative time 0.56, $p = 0.03$**, treatment mean 5.9 (±4.6) n=10, control mean 10.6 (±6.2) n=10.
	hospitalization time, 10.2% lower, relative time 0.90, $p = 0.35$, treatment mean 8.8 (±6.1) n=10, control mean 9.8 (±5.4) n=10.
	time to viral-, 41.1% lower, relative time 0.59, $p = 0.03$, treatment mean 3.3 (±2.16) n=10, control mean 5.6 (±0.89) n=10.

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.

Al-kuraishy, 12/1/2023, prospective, Iraq, peer-reviewed, 10 authors, study period March 2020 - June 2020, excluded in exclusion analyses: unadjusted results with significant baseline differences.	**risk of death, 77.8% lower, RR 0.22, $p = 0.01$**, treatment 3 of 60 (5.0%), control 9 of 40 (22.5%), NNT 5.7.
	relative clinical score, 40.8% better, RR 0.59, $p < 0.001$, treatment 57, control 31.
	relative CT score, 84.0% better, RR 0.16, $p < 0.001$, treatment 57, control 31.
Al-Salameh, 11/30/2021, retrospective, France, peer-reviewed, 4 authors.	**risk of death/ICU, 55.5% lower, RR 0.45, $p = 0.04$**, treatment 9 of 47 (19.1%), control 22 of 50 (44.0%), NNT 4.0, adjusted per study, odds ratio converted to relative risk, metformin continued, multivariable.
	risk of death/ICU, 68.4% higher, RR 1.68, $p = 0.02$, treatment 34 of 43 (79.1%), control 22 of 50 (44.0%), adjusted per study, odds ratio converted to relative risk, metformin discontinued, multivariable.
Alamgir, 4/6/2021, retrospective, database analysis, USA, preprint, 11 authors.	**risk of death, 27.0% lower, OR 0.73, $p < 0.001$**, treatment 11,062, control 11,062, all patients, RR approximated with OR.
	risk of death, 34.0% lower, OR 0.66, $p = 0.007$, treatment 5,369, control 5,369, diabetic patients with CCI≤3, RR approximated with OR.

	risk of death, 30.0% lower, OR 0.70, $p = 0.02$, treatment 2,525, control 2,525, non-diabetic patients with CCI≤3, RR approximated with OR.
Alieva, 6/6/2023, retrospective, Uzbekistan, peer-reviewed, 9 authors, study period April 2020 - December 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of hospitalization, 15.3% lower, OR 0.85, $p = 0.56$, treatment 375, control 388, RR approximated with OR.
Ando, 9/9/2021, retrospective, USA, peer-reviewed, 6 authors, study period 1 January, 2020 - 30 November, 2020.	risk of hospitalization, 39.0% lower, HR 0.61, $p = 0.04$, treatment 19 of 663 (2.9%), control 1,056 of 27,430 (3.8%), adjusted per study, multivariable, Cox proportional hazards.
Araldi, 5/19/2023, retrospective, United Kingdom, preprint, 3 authors.	risk of death, 60.0% lower, HR 0.40, $p < 0.001$, treatment 107 of 2,598 (4.1%), control 263 of 2,598 (10.1%), NNT 17, adjusted per study, type 2 diabetes patients, matched cohort, multivariable, Cox proportional hazards.
Bidari, 10/19/2023, retrospective, Iran, peer-reviewed, 8 authors, study period February 2020 - April 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of severe case, 10.5% lower, RR 0.90, $p = 0.53$, treatment 29 of 80 (36.2%), control 132 of 326 (40.5%), NNT 24.
Blanc, 7/17/2021, retrospective, France, peer-reviewed, 22 authors.	risk of death, 78.6% lower, RR 0.21, $p = 0.06$, treatment 1 of 14 (7.1%), control 25 of 75 (33.3%), NNT 3.8, COVID+.
	risk of case, 43.7% higher, RR 1.44, $p = 0.12$, treatment 11 of 16 (68.8%), control 78 of 163 (47.9%).
Bliden, 11/8/2021, retrospective, USA, preprint, 9 authors, excluded in exclusion analyses: unadjusted results with minimal group details.	risk of death, 59.8% lower, RR 0.40, $p = 0.21$, treatment 3 of 34 (8.8%), control 9 of 41 (22.0%), NNT 7.6.
	risk of mechanical ventilation, 75.9% lower, RR 0.24, $p = 0.05$, treatment 2 of 34 (5.9%), control 10 of 41 (24.4%), NNT 5.4.
Boye, 7/18/2021, retrospective, USA, peer-reviewed, 14 authors.	risk of hospitalization, 10.0% lower, RR 0.90, $p < 0.001$, treatment 2,067 of 4,250 (48.6%), control 3,196 of 5,281 (60.5%), NNT 8.4, odds ratio converted to relative risk.
Bramante (B), 3/23/2021, retrospective, USA, peer-reviewed, 18 authors, study period 4 March, 2020 - 4 December, 2020.	risk of death, 62.0% lower, OR 0.38, $p = 0.03$, treatment 342, control 342, propensity score matching, RR approximated with OR.
	risk of death, 68.0% lower, OR 0.32, $p = 0.003$, treatment 676, control 8,879, adjusted per study, multivariable, RR approximated with OR.
	risk of ICU admission, 9.0% higher, OR 1.09, $p = 0.78$, treatment 342, control 342, propensity score matching, RR approximated with OR.
	risk of ICU admission, 32.0% lower, OR 0.68, $p = 0.06$, treatment 676, control 8,879, adjusted per study, multivariable, RR approximated with OR.

	risk of hospitalization, 22.0% lower, OR 0.78, p = 0.10, treatment 676, control 8,879, adjusted per study, multivariable, RR approximated with OR.
Bramante (C), 12/3/2020, retrospective, database analysis, USA, peer-reviewed, 17 authors.	risk of death, 11.6% lower, HR 0.88, p = 0.65, treatment 394 of 2,333 (16.9%), control 791 of 3,923 (20.2%), NNT 31, adjusted per study, multivariable, Cox proportional hazards.
	risk of death, 21.5% lower, HR 0.79, p = 0.01, treatment 1,129, control 2,173, adjusted per study, women, multivariable, Cox proportional hazards.
	risk of death, 4.3% lower, HR 0.96, p = 0.69, treatment 1,204, control 1,750, adjusted per study, men, multivariable, Cox proportional hazards.
Cariou, 5/29/2020, retrospective, France, peer-reviewed, mean age 69.8, 41 authors, study period 10 March, 2020 - 10 April, 2020, trial NCT04324736 (history) (CORONADO).	risk of death, 20.0% lower, OR 0.80, p = 0.46, treatment 746, control 571, adjusted per study, multivariable, RR approximated with OR.
Chan, 8/30/2022, retrospective, USA, preprint, 15 authors.	risk of death, 58.6% lower, OR 0.41, p = 0.66, treatment 400, control 2,736, adjusted per study, mortality/hospice, multivariable, prediabeties, RR approximated with OR.
	risk of severe case, 54.1% lower, OR 0.46, p = 0.37, treatment 400, control 2,736, adjusted per study, multivariable, prediabeties, RR approximated with OR.
	risk of progression, 42.4% lower, RR 0.58, p = 0.37, treatment 51 of 400 (12.8%), control 798 of 2,736 (29.2%), NNT 6.1, adjusted per study, odds ratio converted to relative risk, moderate, multivariable, prediabeties.
	risk of progression, 37.0% lower, OR 0.63, p = 0.37, treatment 400, control 2,736, adjusted per study, mild ER, multivariable, prediabeties, RR approximated with OR.
	risk of progression, 40.7% lower, OR 0.59, p = 0.22, treatment 196, control 86, adjusted per study, moderate, multivariable, PCOS, RR approximated with OR.
	risk of progression, 34.5% lower, OR 0.66, p = 0.20, treatment 196, control 86, adjusted per study, mild ER, multivariable, PCOS, RR approximated with OR.
Chen, 7/31/2020, retrospective, China, peer-reviewed, 12 authors.	risk of death, 33.0% lower, RR 0.67, p = 0.46, treatment 4 of 43 (9.3%), control 15 of 77 (19.5%), NNT 9.8, adjusted per study, odds ratio converted to relative risk.
Cheng, 8/20/2021, retrospective, propensity score matching, China, peer-reviewed, 35 authors.	risk of death, 65.0% higher, HR 1.65, p = 0.25, treatment 678, control 535, after PSM.
Choi, 6/23/2020, retrospective, South Korea, peer-reviewed, median age 29.0, 8 authors, study period 5 March, 2020 - 18 March, 2020.	risk of progression, 120.0% higher, OR 2.20, p = 0.26, treatment 6 of 36 (16.7%) cases, 3 of 36 (8.3%) controls, case control OR, propensity score matching.

Cousins, 7/6/2022, retrospective, propensity score matching, USA, peer-reviewed, 10 authors.	risk of mechanical ventilation, 50.0% lower, OR 0.50, $p = 0.01$, treatment 2,463, control 2,463, propensity score matching, RR approximated with OR.
	risk of ICU admission, 51.0% lower, OR 0.49, $p < 0.001$, treatment 2,463, control 2,463, propensity score matching, RR approximated with OR.
Crouse, 1/13/2021, retrospective, USA, peer-reviewed, 6 authors.	risk of death, 60.8% lower, RR 0.39, $p = 0.02$, treatment 8 of 76 (10.5%), control 34 of 144 (23.6%), NNT 7.6, adjusted per study, odds ratio converted to relative risk, multiple logistic regression.
Farah, 9/20/2023, retrospective, Jordan, peer-reviewed, mean age 59.5, 10 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of case, 2.7% higher, RR 1.03, $p = 0.87$, treatment 267 of 821 (32.5%), control 69 of 218 (31.7%).
Fu, 1/17/2022, retrospective, China, peer-reviewed, median age 63.0, 14 authors, study period 8 January, 2020 - 7 March, 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of unfavorable outcome, 71.9% lower, RR 0.28, $p = 0.03$, treatment 4 of 49 (8.2%), control 9 of 31 (29.0%), NNT 4.8, unfavorable outcome, metformin vs. other treatments.
Gao, 10/19/2020, retrospective, China, peer-reviewed, 7 authors, study period 31 January, 2020 - 20 March, 2020.	risk of progression, 225.0% higher, RR 3.25, $p = 0.045$, treatment 16 of 56 (28.6%), control 4 of 54 (7.4%), odds ratio converted to relative risk, progression to life threatening complications.
Ghany, 3/31/2021, retrospective, USA, peer-reviewed, 8 authors.	risk of death, 66.0% lower, HR 0.34, $p < 0.001$, treatment 392, control 747, adjusted per study, multivariable, Cox proportional hazards.
	risk of hospitalization, 29.0% lower, HR 0.71, $p = 0.008$, treatment 392, control 747, adjusted per study, multivariable, Cox proportional hazards.
	risk of ARDS, 68.0% lower, HR 0.32, $p < 0.001$, treatment 392, control 747, adjusted per study, multivariable, Cox proportional hazards.
Goodall, 10/13/2020, retrospective, United Kingdom, peer-reviewed, 7 authors, study period 12 March, 2020 - 15 April, 2020.	risk of death, 3.0% lower, HR 0.97, $p = 0.81$, treatment 74 of 210 (35.2%), control 280 of 771 (36.3%), NNT 93.
Greco, 8/18/2023, retrospective, Italy, peer-reviewed, 8 authors, study period January 2020 - December 2021, this trial compares with another treatment - results may be better when compared to placebo.	risk of hospitalization, 22.0% lower, OR 0.78, $p = 0.11$, treatment 30,238, control 2,264, DPP-4is, RR approximated with OR.
	risk of hospitalization, 26.0% lower, OR 0.74, $p = 0.006$, treatment 30,238, control 14,739, insulin or insulin secretagogues, RR approximated with OR.
	risk of hospitalization, 17.0% lower, OR 0.83, $p = 0.54$, treatment 30,238, control 317, GLP-1 RAs, RR approximated with OR.

Guo, 8/24/2023, retrospective, China, peer-reviewed, median age 65.0, 8 authors, study period 4 February, 2020 - 11 April, 2020.	risk of death/intubation, 62.4% lower, HR 0.38, $p = 0.03$, treatment 241, control 330, adjusted per study, multivariable, Cox proportional hazards.
	risk of progression, 81.1% lower, HR 0.19, $p = 0.003$, treatment 241, control 330, adjusted per study, severe respiratory failure, multivariable, Cox proportional hazards.
	risk of progression, 80.1% lower, HR 0.20, $p = 0.05$, treatment 241, control 330, adjusted per study, ARDS, multivariable, Cox proportional hazards.
Gálvez-Barrón, 4/14/2021, retrospective, Spain, peer-reviewed, mean age 86.8, 13 authors, study period 12 March, 2020 - 2 May, 2020.	risk of death, 16.1% higher, RR 1.16, $p = 0.46$, treatment 20, control 83, odds ratio converted to relative risk, control prevalance approximated with overall prevalence.
	risk of severe case, 16.1% higher, RR 1.16, $p = 0.46$, treatment 20, control 83, odds ratio converted to relative risk, control prevalance approximated with overall prevalence.
Holt, 3/30/2021, prospective, United Kingdom, peer-reviewed, 34 authors, study period 1 May, 2020 - 5 February, 2021, trial NCT04330599 (history) (COVIDENCE UK), excluded in exclusion analyses: significant unadjusted confounding possible.	risk of case, 27.0% higher, RR 1.27, $p = 0.42$, treatment 12 of 429 (2.8%), control 434 of 14,798 (2.9%), adjusted per study, odds ratio converted to relative risk, minimally adjusted, group sizes approximated.
Huh, 12/19/2020, retrospective, database analysis, South Korea, peer-reviewed, 8 authors.	risk of progression, 1.0% higher, RR 1.01, $p = 0.11$, treatment 104 of 272 (38.2%), control 774 of 2,533 (30.6%), adjusted per study, multivariable.
	risk of case, 4.0% lower, RR 0.96, $p = 0.82$, treatment 329 of 1,874 (17.6%), control 7,012 of 42,172 (16.6%), adjusted per study, multivariable.
Jang, 1/29/2024, retrospective, South Korea, peer-reviewed, 6 authors.	risk of death, 60.5% lower, OR 0.40, $p = 0.02$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of mechanical ventilation, 71.9% lower, OR 0.28, $p = 0.008$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of ICU admission, 38.8% lower, OR 0.61, $p = 0.12$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of oxygen therapy, 29.7% lower, OR 0.70, $p = 0.23$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 27.1% higher, OR 1.27, $p = 0.42$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.

Jiang, 3/31/2021, retrospective, China, peer-reviewed, 12 authors.	risk of death, 46.0% lower, HR 0.54, $p = 0.40$, treatment 3 of 74 (4.1%), control 10 of 74 (13.5%), adjusted per study, mixed effect Cox, propensity score matching.
	risk of ARDS, 80.2% lower, RR 0.20, $p = 0.02$, treatment 8 of 74 (10.8%), control 17 of 74 (23.0%), NNT 8.2, adjusted per study, odds ratio converted to relative risk, mixed effect Cox, propensity score matching.
Khunti, 3/30/2021, retrospective, population-based cohort, United Kingdom, peer-reviewed, 15 authors.	risk of death, 23.0% lower, HR 0.77, $p < 0.001$, adjusted per study.
Kim, 8/12/2020, retrospective, South Korea, peer-reviewed, 32 authors.	risk of death, 64.0% lower, OR 0.36, $p = 0.10$, treatment 113, control 122, adjusted per study, multivariable, RR approximated with OR.
	risk of progression, 52.0% lower, OR 0.48, $p = 0.13$, treatment 113, control 122, adjusted per study, multivariable, RR approximated with OR.
Lalau, 12/10/2020, retrospective, France, peer-reviewed, 33 authors, study period 10 March, 2020 - 10 April, 2020.	risk of death, 22.2% lower, OR 0.78, $p = 0.16$, treatment 671, control 419, day 28, model 2, propensity score matching, RR approximated with OR.
	risk of death/intubation, 17.8% lower, OR 0.82, $p = 0.21$, treatment 671, control 419, day 28, model 2, propensity score matching, primary outcome, RR approximated with OR.
	risk of mechanical ventilation, 6.8% lower, OR 0.93, $p = 0.72$, treatment 671, control 419, day 28, model 2, propensity score matching, RR approximated with OR.
Lally, 1/31/2021, retrospective, USA, peer-reviewed, 6 authors.	risk of death, 52.0% lower, HR 0.48, $p = 0.009$, treatment 16 of 127 (12.6%), control 144 of 648 (22.2%), NNT 10, adjusted per study, multivariable regression.
Li (C), 10/1/2020, retrospective, China, peer-reviewed, 16 authors, study period 23 January, 2020 - 19 March, 2020.	risk of death, 77.7% lower, HR 0.22, $p = 0.02$, treatment 2 of 37 (5.4%), control 21 of 94 (22.3%), NNT 5.9, adjusted per study, multivariable.
	risk of mechanical ventilation, 27.0% higher, RR 1.27, $p = 1.00$, treatment 1 of 37 (2.7%), control 2 of 94 (2.1%).
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	risk of death, 30.0% lower, HR 0.70, $p < 0.001$, treatment 1,896, control 14,072, Cox proportional hazards, day 30.
Luo, 5/21/2020, retrospective, China, peer-reviewed, 9 authors.	risk of death, 74.7% lower, RR 0.25, $p = 0.02$, treatment 3 of 104 (2.9%), control 22 of 179 (12.3%), NNT 11, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariate.
Ma (B), 4/1/2022, retrospective, USA, peer-reviewed, 4 authors, study period 16 March, 2020 - 15 February, 2021.	risk of death, 74.2% lower, RR 0.26, $p = 0.03$, treatment 3 of 361 (0.8%), control 40 of 995 (4.0%), NNT 31, odds ratio converted to relative risk, in-hospital death or hospice, propensity score weighting.

	risk of mechanical ventilation, 25.0% lower, RR 0.75, p = 0.44, treatment 12 of 360 (3.3%), control 16 of 360 (4.4%), NNT 90, propensity score matching.
MacFadden, 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	risk of case, 1.0% lower, OR 0.99, p = 0.45, RR approximated with OR.
Mamari, 11/30/2023, retrospective, Syria, peer-reviewed, 2 authors, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 50.0% lower, RR 0.50, p = 0.01, treatment 11 of 34 (32.4%), control 22 of 34 (64.7%), NNT 3.1.
Mannucci, 10/31/2022, retrospective, Italy, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 December, 2020.	risk of death, 38.0% lower, OR 0.62, p = 0.02, RR approximated with OR.
	risk of hospitalization, 15.0% lower, OR 0.85, p = 0.25, RR approximated with OR.
Miao, 11/9/2022, retrospective, USA, peer-reviewed, 6 authors, study period 1 January, 2020 - 7 May, 2020.	risk of death, 1.3% lower, RR 0.99, p = 0.91, treatment 233 of 796 (29.3%), control 236 of 796 (29.6%), NNT 265, propensity score matching.
	hospitalization time, 4.9% lower, relative time 0.95, p = 0.23, treatment 796, control 796, propensity score matching.
Miguel, 11/17/2023, retrospective, Spain, peer-reviewed, 19 authors, study period March 2020 - June 2020.	risk of ICU admission, 37.4% lower, RR 0.63, p = 0.24, treatment 49, control 40, both cohorts combined.
	risk of ICU admission, 42.9% lower, RR 0.57, p = 0.34, treatment 3 of 15 (20.0%), control 14 of 40 (35.0%), NNT 6.7.
	risk of ICU admission, 31.4% lower, RR 0.69, p = 0.52, treatment 6 of 49 (12.2%), control 5 of 28 (17.9%), NNT 18.
Milosavljevic, 11/9/2022, retrospective, USA, peer-reviewed, mean age 67.4, 7 authors, study period 1 March, 2020 - 31 December, 2020.	risk of severe case, 33.0% lower, OR 0.67, p = 0.03, treatment 377, control 356, RR approximated with OR.
Mirani, 10/6/2020, retrospective, Italy, peer-reviewed, median age 66.0, 8 authors, study period 20 February, 2020 - 9 April, 2020.	risk of death, 45.0% lower, HR 0.55, p = 0.10, treatment 25 of 69 (36.2%), control 13 of 21 (61.9%), NNT 3.9, adjusted per study, Cox proportional hazards.
Morrison, 10/10/2022, retrospective, USA, peer-reviewed, mean age 62.5, 3 authors, study period March 2020 - March 2021.	risk of death, 41.1% lower, OR 0.59, p = 0.003, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.
	risk of mechanical ventilation, 15.7% higher, OR 1.16, p = 0.49, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.
	risk of ICU admission, 2.8% lower, OR 0.97, p = 0.85, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.

	risk of hospitalization, 3.9% higher, OR 1.04, $p = 0.72$, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.
Obiri-Yeboah, 6/8/2023, retrospective, USA, peer-reviewed, mean age 67.0, 8 authors.	**risk of death, 1.0% higher, OR 1.01, $p = 0.98$**, treatment 148, control 381, RR approximated with OR.
	risk of mechanical ventilation, 4.0% higher, OR 1.04, $p = 0.87$, treatment 148, control 381, RR approximated with OR.
	risk of ICU admission, 8.0% lower, OR 0.92, $p = 0.72$, treatment 148, control 381, RR approximated with OR.
Oh, 2/13/2021, retrospective, USA, peer-reviewed, 2 authors.	**risk of death, 26.0% higher, OR 1.26, $p = 0.30$**, treatment 5,946, control 5,946, adjusted per study, multivariable, RR approximated with OR.
	risk of case, 28.0% lower, RR 0.72, $p < 0.001$, treatment 390 of 5,946 (6.6%), control 541 of 5,946 (9.1%), NNT 39, adjusted per study, odds ratio converted to relative risk, propensity score matching.
Ojeda-Fernández, 1/10/2022, retrospective, Italy, peer-reviewed, 11 authors.	**risk of death, 16.2% lower, RR 0.84, $p < 0.001$**, treatment 1,476 of 6,556 (22.5%), control 1,787 of 6,556 (27.3%), NNT 21, odds ratio converted to relative risk, propensity score matching.
	risk of death, 22.1% lower, RR 0.78, $p < 0.001$, treatment 968 of 6,556 (14.8%), control 1,261 of 6,556 (19.2%), NNT 22, odds ratio converted to relative risk, in-hospital mortality, propensity score matching.
	risk of ICU admission, 22.4% lower, RR 0.78, $p = 0.01$, treatment 166 of 6,556 (2.5%), control 212 of 6,556 (3.2%), NNT 143, odds ratio converted to relative risk, propensity score matching.
	risk of hospitalization, 2.7% lower, RR 0.97, $p = 0.11$, treatment 3,551 of 6,556 (54.2%), control 3,670 of 6,556 (56.0%), NNT 55, odds ratio converted to relative risk, propensity score matching.
	risk of death, 8.3% lower, RR 0.92, $p = 0.06$, treatment 793 of 3,297 (24.1%), control 876 of 3,297 (26.6%), NNT 40, odds ratio converted to relative risk, excluding patients previously treated with insulin, propensity score matching.
	risk of death, 16.0% lower, RR 0.84, $p = 0.003$, treatment 512 of 3,297 (15.5%), control 618 of 3,297 (18.7%), NNT 31, odds ratio converted to relative risk, excluding patients previously treated with insulin, in-hospital mortality, propensity score matching.
	risk of ICU admission, 39.2% lower, RR 0.61, $p = 0.002$, treatment 64 of 3,297 (1.9%), control 102 of 3,297 (3.1%), NNT 87, odds ratio converted to relative risk, excluding patients previously treated with insulin, propensity score matching.

	risk of hospitalization, 2.2% higher, RR 1.02, p = 0.36, treatment 1,822 of 3,297 (55.3%), control 1,792 of 3,297 (54.4%), odds ratio converted to relative risk, excluding patients previously treated with insulin, propensity score matching.
Ong, 10/30/2021, retrospective, Philippines, peer-reviewed, 6 authors, study period 1 March, 2020 - 30 September, 2020.	**risk of death, 46.8% lower, RR 0.53, p = 0.02**, treatment 33 of 186 (17.7%), control 57 of 169 (33.7%), NNT 6.3, adjusted per study, odds ratio converted to relative risk, combined pre-existing and in-hospital use.
	risk of death, 23.9% lower, RR 0.76, p = 0.16, treatment 28 of 109 (25.7%), control 57 of 169 (33.7%), NNT 12, odds ratio converted to relative risk, pre-existing use, unadjusted.
	risk of death, 85.2% lower, RR 0.15, p = 0.002, treatment 2 of 40 (5.0%), control 57 of 169 (33.7%), NNT 3.5, odds ratio converted to relative risk, in-hospital use, unadjusted.
	risk of death, 76.0% lower, RR 0.24, p = 0.005, treatment 3 of 37 (8.1%), control 57 of 169 (33.7%), NNT 3.9, odds ratio converted to relative risk, mixed pre-existing/in-hospital use, unadjusted.
Ouchi, 10/4/2022, retrospective, Spain, peer-reviewed, mean age 71.5, 5 authors, study period March 2020 - June 2020.	**risk of death, 9.9% lower, OR 0.90, p = 0.19**, treatment 6,168, control 9,875, inverted to make OR<1 favor treatment, metformin monotherapy vs. untreated, RR approximated with OR.
	risk of death/hospitalization, 8.3% lower, OR 0.92, p = 0.12, treatment 6,168, control 9,875, inverted to make OR<1 favor treatment, metformin monotherapy vs. untreated, RR approximated with OR.
Piarulli, 6/24/2023, retrospective, Italy, peer-reviewed, 7 authors, study period February 2020 - February 2021.	**risk of death/ICU, 53.0% lower, OR 0.47, p = 0.08**, treatment 1,444, control 1,009, adjusted per study, for all patients, combined odds of hospitalization and ICU/death for hospitalized patients, multivariable, RR approximated with OR.
	risk of death/ICU, 15.0% lower, OR 0.85, p = 0.68, treatment 209, control 180, adjusted per study, among hospitalized patients, multivariable, RR approximated with OR.
	risk of hospitalization, 45.0% lower, OR 0.55, p < 0.001, treatment 1,444, control 1,009, adjusted per study, multivariable, RR approximated with OR.
Pinchera, 1/6/2023, retrospective, Italy, peer-reviewed, 9 authors, study period November 2021 - May 2022, this trial compares with another treatment - results may be better when compared to placebo.	**risk of severe case, 15.2% lower, RR 0.85, p = 0.048**, treatment 5 of 19 (26.3%), control 14 of 24 (58.3%), NNT 3.1, adjusted per study, odds ratio converted to relative risk, multivariable.
Pérez-Belmonte, 11/16/2020, retrospective, propensity score matching, Spain, peer-reviewed, 26 authors.	**risk of death, 10.4% higher, RR 1.10, p = 0.48**, treatment 79 of 249 (31.7%), control 79 of 249 (31.7%), adjusted per study, odds ratio converted to relative risk, mixed effect logistic regression, propensity score matching.

Ramos-Rincón, 12/28/2020, retrospective, Spain, preprint, 25 authors, study period 1 March, 2020 - 29 May, 2020.	risk of death, 1.3% lower, RR 0.99, $p = 0.78$, treatment 206 of 420 (49.0%), control 179 of 370 (48.4%), adjusted per study, odds ratio converted to relative risk, multivariable.
Ravindra, 5/5/2021, retrospective, India, peer-reviewed, 14 authors, excluded in exclusion analyses: minimal details provided.	risk of death, 29.6% lower, RR 0.70, $p = 0.42$, treatment 5 of 53 (9.4%), control 57 of 313 (18.2%), adjusted per study, odds ratio converted to relative risk.
Sandhu, 3/31/2023, retrospective, USA, peer-reviewed, mean age 50.7, 7 authors, study period 1 January, 2020 - 31 December, 2020.	risk of hospitalization, 2.8% lower, OR 0.97, $p = 0.004$, RR approximated with OR.
Saygili, 10/29/2021, retrospective, Turkey, peer-reviewed, 5 authors.	risk of death, 41.5% lower, RR 0.58, $p = 0.02$, treatment 120, control 120, overall mortality, Cox regression in matched group, propensity score matching.
Servais, 12/7/2022, retrospective, Belgium, peer-reviewed, median age 73.0, 21 authors, study period 1 March, 2020 - 6 May, 2020.	risk of death, 49.0% lower, HR 0.51, $p = 0.002$, adjusted per study, multivariable.
Shestakova, 8/9/2022, retrospective, Russia, peer-reviewed, 6 authors, study period 20 March, 2020 - 25 November, 2021.	risk of death, 21.6% lower, RR 0.78, $p = 0.001$, treatment 21,471 of 139,637 (15.4%), control 12,721 of 50,361 (25.3%), adjusted per study, odds ratio converted to relative risk, Table S2, multivariable.
Sourij, 12/4/2020, retrospective, Austria, peer-reviewed, mean age 71.1, 24 authors.	risk of death, 37.3% lower, RR 0.63, $p = 0.13$, treatment 14 of 77 (18.2%), control 44 of 161 (27.3%), NNT 11, odds ratio converted to relative risk.
Usman, 1/18/2022, retrospective, USA, peer-reviewed, 10 authors.	risk of death, 59.8% lower, RR 0.40, $p = 0.21$, treatment 3 of 34 (8.8%), control 9 of 41 (22.0%), NNT 7.6.
	risk of mechanical ventilation, 75.9% lower, RR 0.24, $p = 0.05$, treatment 2 of 34 (5.9%), control 10 of 41 (24.4%), NNT 5.4.
	hospitalization time, 33.7% lower, relative time 0.66, $p = 0.13$, treatment 34, control 41.
Wallace, 12/31/2021, retrospective, database analysis, USA, peer-reviewed, 6 authors.	risk of death, 72.0% lower, HR 0.28, $p < 0.001$, treatment 103 of 1,203 (8.6%), control 1,536 of 6,970 (22.0%), NNT 7.4, adjusted per study, before+after, propensity score weighting, Cox proportional hazards.
Wander, 10/6/2021, retrospective, database analysis, USA, peer-reviewed, 8 authors.	risk of death, 15.0% lower, RR 0.85, $p < 0.001$, treatment 29,685, control 35,207, odds ratio converted to relative risk, logistic regression, within 30 days of diagnosis, control prevalance approximated with overall prevalence.
	risk of ICU admission, 1.9% lower, RR 0.98, $p = 0.62$, treatment 29,685, control 35,207, odds ratio converted to relative risk, logistic regression, within 30 days of diagnosis, control prevalance approximated with overall prevalence.
	risk of hospitalization, 3.2% lower, RR 0.97, $p = 0.09$, treatment 29,685, control 35,207, odds ratio converted to relative risk, logistic regression, within 30 days of diagnosis, control

	prevalance approximated with overall prevalence.
Wang (B), 9/7/2021, retrospective, USA, peer-reviewed, 4 authors.	risk of ICU admission, 12.0% lower, RR 0.88, $p = 0.005$, treatment 6,504, control 10,000, Cox proportional hazards.
Wang (C), 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.
Wargny, 2/17/2021, retrospective, France, peer-reviewed, 43 authors, study period 10 March, 2020 - 10 April, 2020, trial NCT04324736 (history) (CORONADO).	risk of death, 28.3% lower, RR 0.72, $p = 0.03$, treatment 247 of 1,553 (15.9%), control 330 of 1,241 (26.6%), NNT 9.4, adjusted per study, odds ratio converted to relative risk, multivariable, day 28.
	risk of no hospital discharge, 14.8% lower, RR 0.85, $p = 0.02$, treatment 690 of 1,553 (44.4%), control 702 of 1,241 (56.6%), NNT 8.2, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable, day 28.
Wong, 3/7/2022, retrospective, China, peer-reviewed, 11 authors, study period 21 January, 2020 - 31 January, 2021.	risk of death, 59.0% lower, OR 0.41, $p = 0.01$, treatment 786, control 428, adjusted per study, propensity score weighting, multivariable, RR approximated with OR.
	risk of no recovery, 60.6% lower, OR 0.39, $p = 0.005$, treatment 786, control 428, adjusted per study, inverted to make OR<1 favor treatment, propensity score weighting, multivariable, RR approximated with OR.
	clinical improvement, 63.5% better, OR 0.36, $p = 0.009$, treatment 786, control 428, adjusted per study, inverted to make OR<1 favor treatment, propensity score weighting, multivariable, RR approximated with OR.
	risk of no hospital discharge, 55.8% lower, OR 0.44, $p = 0.009$, treatment 786, control 428, adjusted per study, inverted to make OR<1 favor treatment, propensity score weighting, multivariable, RR approximated with OR.
Wong (B), 2/24/2022, retrospective, USA, peer-reviewed, 15 authors.	risk of death, 51.0% lower, HR 0.49, $p < 0.001$, treatment 10,408, control 29,208, Cox proportional hazards.
	risk of mechanical ventilation, 41.0% lower, OR 0.59, $p < 0.001$, treatment 10,408, control 29,208, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 40.0% lower, OR 0.60, $p < 0.001$, treatment 10,408, control 29,208, adjusted per study, multivariable, RR approximated with OR.
Yeh, 6/9/2022, retrospective, USA, peer-reviewed, mean age 62.3, 9 authors, study period 1 March, 2020 - 28 February, 2021, trial NCT02788903 (history).	ICU/intubation/death, 44.0% lower, OR 0.56, $p < 0.001$, RR approximated with OR.
	risk of hospitalization, 37.0% lower, OR 0.63, $p < 0.001$, RR approximated with OR.

Yen, 5/6/2023, retrospective, multiple countries, peer-reviewed, 4 authors, study period 1 January, 2020 - 22 November, 2022.	**risk of death, 25.0% lower, HR 0.75, $p = 0.001$**, treatment 232 of 20,894 (1.1%), control 295 of 20,894 (1.4%), NNT 332, propensity score matching, Kaplan–Meier.
	risk of mechanical ventilation, 25.0% lower, HR 0.75, $p = 0.01$, treatment 133 of 20,894 (0.6%), control 168 of 20,894 (0.8%), NNT 597, propensity score matching, Kaplan–Meier.
	risk of ICU admission, 19.0% lower, HR 0.81, $p = 0.005$, treatment 332 of 20,894 (1.6%), control 390 of 20,894 (1.9%), NNT 360, propensity score matching, Kaplan–Meier.
	risk of hospitalization, 15.0% lower, HR 0.85, $p < 0.001$, treatment 2,820 of 20,894 (13.5%), control 3,139 of 20,894 (15.0%), NNT 65, propensity score matching, Kaplan–Meier.
	risk of case, 2.0% higher, HR 1.02, $p = 0.63$, treatment 1,467 of 20,894 (7.0%), control 1,364 of 20,894 (6.5%), propensity score matching, Kaplan–Meier.
Yip, 9/21/2022, retrospective, China, peer-reviewed, mean age 69.0, 10 authors, study period 16 February, 2022 - 31 March, 2022.	**risk of death/hospitalization, 7.0% lower, HR 0.93, $p = 0.61$**, treatment 8,604, control 3,727, propensity score matching, Cox proportional hazards.
	risk of progression, 15.0% lower, HR 0.85, $p = 0.16$, treatment 8,604, control 3,727, ER/hosp./death, propensity score matching, Cox proportional hazards.
	risk of progression, 15.0% lower, HR 0.85, $p = 0.13$, treatment 8,604, control 3,727, hypoxemia/ER/hosp./death, propensity score matching, Cox proportional hazards.
Zaccardi, 9/13/2022, retrospective, United Kingdom, peer-reviewed, 11 authors.	**risk of death, 34.3% lower, RR 0.66, $p < 0.001$**, meta analysis of 6 groups reported.
	risk of hospitalization, 31.2% lower, RR 0.69, $p < 0.001$, meta analysis of 6 groups reported.
Zihono, 9/10/2023, retrospective, Indonesia, peer-reviewed, 6 authors.	**risk of death, 48.7% lower, RR 0.51, $p = 0.02$**, treatment 11 of 56 (19.6%), control 31 of 81 (38.3%), NNT 5.4.

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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