Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis

Maria Elena Flacco,1 Cecilia Acuti Martellucci,2 Francesca Bravi,3 Giustino Parruti,4 Rosaria Cappadona,1 Alfonso Mascitelli,5 Roberto Manfredini,6 Lorenzo G Mantovani,7,8 Lamberto Manzoli 1

ABSTRACT

Objective It has been hypothesised that the use of ACE inhibitors and angiotensin receptor blockers (ARBs) might either increase or reduce the risk of severe or lethal COVID-19. The findings from the available observational studies varied, and summary estimates are urgently needed to elucidate whether these drugs should be suspended during the pandemic, or patients and physicians should be definitely reassured. This meta-analysis of adjusted observational data aimed to summarise the existing evidence on the association between these medications and severe/lethal COVID-19.

Methods We searched MedLine, Scopus and preprint repositories up to 8 June 2020 to retrieve cohort or case–control studies comparing the risk of severe/fatal COVID-19 (either mechanical ventilation, intensive care unit admission or death), among hypertensive subjects treated with: (1) ACE inhibitors, (2) ARBs and (3) both, versus untreated subjects. Data were combined using a random-effect generic inverse variance approach.

Results Ten studies, enrolling 9890 hypertensive subjects were included in the analyses. Compared with untreated subjects, those using either ACE inhibitors or ARBs showed a similar risk of severe or lethal COVID-19 (summary OR: 0.90; 95% CI 0.65 to 1.26 for ACE inhibitors; 0.92; 95% CI 0.75 to 1.12 for ARBs). The results did not change when both drugs were considered together, when death was the outcome and excluding the studies with significant, divergent results.

Conclusion The present meta-analysis strongly supports the recommendation of several scientific societies to continue ARBs or ACE inhibitors for all patients, unless otherwise advised by their physicians who should thus be reassured.

INTRODUCTION

With the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, evidence is rapidly accumulating on the risk factors of severe COVID-19 and death. In the wake of some preliminary, unadjusted reports,1–4 individuals with pre-existing comorbidities such as hypertension, diabetes and cardiovascular diseases have been identified as those highly vulnerable.5 Notably, such chronic conditions frequently require prescription of ACE inhibitors and angiotensin II receptor blockers (ARBs).6 Animal studies showed that ACE inhibitors and ARBs upregulate ACE2 expression7 and, as coronaviruses bind their target cells through ACE2, concerns have been expressed that these therapies might facilitate infection with SARS-CoV-2 and increase the risk of severe or fatal COVID-19.6 8 In contrast, it has been suggested that ACE inhibitors and ARBs could benefit infected patients, as ACE2 converts angiotensin II (with known vasoconstrictive, proinflammatory and fibrotic effects) into angiotensin 1–7, which may protect lungs from acute injury, and upregulating ACE2 through therapy may enhance this process.9

In this uncertain scenario, some observational studies with multivariable analyses found no association between use of renin-angiotensin-aldosterone system (RAAS) inhibitors and COVID-19 severity.10–16 a few studies found a significant reduction in the risk of death or severe disease17–19 and one study found a increased risk of mechanical ventilation and admission to the intensive care unit (ICU).19 The magnitude of the association also varied across studies, which differed for patients’ characteristics, setting (inpatient or outpatient), population targeted by serological testing protocols and extent of measured confounding.

Summary estimates are urgently needed to elucidate whether these drugs, that are prescribed to tens of millions patients worldwide,20 should be suspended during the pandemic, or patients and physicians should be definitely reassured.7 We thus carried out a meta-analysis to summarise the existing evidence from adjusted analyses on the association between RAAS inhibitors and COVID-19.

METHODS

Bibliographic search, data extraction and quality assessment

We searched MEDLINE and Scopus databases, up to 11 May 2020, for studies evaluating the risk of severe and/or fatal COVID-19 among ACE inhibitors and/or ARBs users versus non-users. The following search strategy was adopted, without language restrictions: COVID-19 [Title/Abstract] OR Coronavirus [Title/Abstract] OR SARS-CoV-2 [Title/Abstract] AND angiotensin [Title/Abstract]. The reference lists of reviews and retrieved articles was also screened for additional pertinent papers. In the context of a public health emergency, there is urgency to make research findings available,21 and several relevant clinical data have been shared in public preprint repositories: we thus extended the search to include any relevant manuscript posted in MedRxiv. Inclusion criteria were: (A) cohort or...
The informed consent was not required, as the study did not enrol human subjects.

**RESULTS**

Of the 553 papers initially retrieved, five case-control and five cohort studies were included in the analyses. Overall, the studies included 9890 hypertensive subjects; four studies included only COVID-19 symptomatic patients requiring hospitalisation and two in the USA and two in China. The mean age ranged from 58 to 69 years, and the sample size ranged from 203 to 6272.

The methodological characteristics of the included studies are summarised in table 2: the selection of the cohort of patients, the ascertainment of the exposure and the evaluation of the comparability of subjects were adequate in all studies, while 8 out of 10 adequately addressed the items pertaining to outcome assessment and follow-up (length and missing data). One study had a high risk of misclassification bias, as the proportions of hypertensive subjects treated with ACE inhibitors (16.4%) or ARBs (13.2%) were particularly low.

**Risk of severe/lethal COVID-19**

A total of five studies, enrolling 7489 hypertensive patients, were included in the meta-analysis comparing the risk of severe/lethal COVID-19 between ACE inhibitors users versus non-users. Six studies were carried out in Europe, two in the USA and two in China. The mean age ranged from 58 to 69 years, and the sample size ranged from 203 to 6272.

Risk of death from COVID-19

The risk of death among RAAS inhibitors users versus non-users was compared in five studies, including a total of 2412 and ARBs users, versus non users, in predicting: (1) severe/lethal COVID-19 (presence of either ICU admission, mechanical ventilation or death) and (2) lethal COVID-19. When a study only reported separate estimates for ACE inhibitors or ARBs users, or for the different outcomes included in the definition of severe/lethal COVID-19 (eg, ICU admission and mechanical ventilation separately), the overall estimate of risk was computed from the separate relative risks using the fixed-effect model for generic inverse variance outcomes.

All meta-analyses were performed using RevMan software, V.5.3 (The Cochrane Collaboration, 2019).

**Ethics**

The informed consent was not required, as the study did not enrol human subjects.
**Table 1** Characteristics of the included studies

| N  | First author | Journal       | Country | Study design  | No. of infected patients (with severe/lethal COVID-19) | No. of hypertensive patients (under ACEi/ARBs) | Mean age (SD) | % males | Follow-up | Extracted outcome(s) | Method for adjustment |
|----|--------------|---------------|---------|---------------|------------------------------------------------------|-----------------------------------------------|--------------|---------|-----------|----------------------|----------------------|
| 1  | Bean12       | Submitted (MedRxiv) | UK      | Cohort        | 205 (53)                                             | 105 (38)                                       | 63.0 (20.0) | 51.7    | 7 days    | Severe/lethal COVID-19 (ICU and death). | Logistic regression adjusted for age, gender and comorbidities. |
| 2  | Bravi13      | Submitted     | Italy   | Case–control  | 1603 (192)                                           | 543 (450)                                     | 58.0 (20.9) | 47.3    | 24 days   | (1) Severe/lethal COVID-19 (mech. ventilation, ICU and death); (2) death. | Logistic regression adjusted for age, gender and comorbidities. |
| 3  | de Abajo14   | The Lancet    | Spain   | Case–control  | 1139 (393)*                                          | 6261 (3950)*                                  | 69.1 (15.4) | 61.0    | –         | Severe COVID-19 (hospital admission). | Logistic regression adjusted for age, gender, region (matching variables) and comorbidities. |
| 4  | Giorgi Rossi15 | Submitted (MedRxiv) | Italy   | Cohort        | 2653 (217)                                           | 430 (108)                                    | 63.2         | 50.1    | 14 days   | Death. | Cox proportional hazard analysis adjusted for age, gender and Charlson Index. |
| 5  | Liu16        | Submitted     | China   | Case–control  | 511 (381)                                            | 78 (22)                                      | 65.2 (10.7) | 55.2    | NR        | Severe/lethal COVID-19 (dyspnoea, resp. rate ≥30/min, SaO2 <89%, mech. ventilation). | Logistic regression adjusted for gender and medications. |
| 6  | Mancia17     | NEJM          | Italy   | Case–control  | 6272 (617)                                           | 3586 (1844)                                  | 68.0 (13.0) | 63.2    | –         | Severe COVID-19 (ICU and death). | Logistic regression adjusted for age, race, comorbidities and medications. |
| 7  | Mehra18      | NEJM          | Multicountry | Case–control | 8910 (515)                                           | 2346 (1326)                                  | 49.0 (16.0) | 60.0    | 40 days   | Death. | Logistic regression adjusted for age, gender and comorbidities. |
| 8  | Mehta9       | JAMA Cardiol  | USA     | Cohort        | 1735 (272)                                           | 682 (202)                                    | 64.0 (14.0) | 58.5    | NR        | Severe COVID-19 (ICU and mech. ventilation). | Logistic regression adjusted for age, gender and comorbidities. |
| 9  | Reynolds10   | NEJM          | USA     | Case-control  | 5894 (1002)                                          | 2573 (2141)                                  | 64.0 (15.6) | 50.8    | –         | Severe COVID-19 (mech. ventilation, ICU and death). | Analysis propensity score-matched for age, gender, race, BMI, smoke, and comorbidities. |
| 10 | Tedeschi11   | Clin Infect Dis | Italy   | Cohort        | 609 (179)                                            | 311 (175)                                    | 68.0 (18.5) | 68.0    | 6 days    | Death. | Cox proportional hazard analysis adjusted for age, gender and comorbidities. |
| 11 | Zhang12      | Circ Res      | China   | Cohort        | 1128 (99)                                            | 1128 (188)                                   | 64.0 (9.0)  | 53.3    | 28 days   | Death. | Analysis propensity score-matched for age, gender, comorbidities and in-hospital therapy. |

*Cases were COVID-19 patients; controls were SARS-CoV-2 negative subjects extracted from primary healthcare databases: as such, the number of hypertensive subjects includes both cases and controls and is higher than the number of COVID-19 patients.

†Number of patients with severe COVID-19 among only those with hypertension.

Included only in sensitivity analyses.

ARBs, Angiotensin receptor blockers; ICU, intensive care unit; mech., mechanical; NR, not reported; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2** Methodological quality of the included studies according to the Newcastle Ottawa Scale

| First author | Selection (max. score 4) | Comparability (max. score 2) | Outcome (max. score 3) |
|--------------|--------------------------|------------------------------|------------------------|
| Bean12       | 4                        | 2                            | 3                      |
| Bravi13      | 4                        | 2                            | 3                      |
| de Abajo14   | 4                        | 2                            | 3                      |
| Giorgi Rossi15 | 4                       | 2                            | 3                      |
| Liu13        | 4                        | 2                            | 1                      |
| Mancia14     | 4                        | 2                            | 3                      |
| Mehta19      | 3                        | 2                            | 1                      |
| Reynolds10   | 3                        | 2                            | 3                      |
| Tedeschi11   | 4                        | 2                            | 3                      |
| Zhang12      | 4                        | 2                            | 3                      |

**DISCUSSION**

Two main findings emerge from the present meta-analysis, which included the adjusted estimates of 10 observational studies and hypertensive subjects.10 12 16 18 Overall, no differences in risk emerged between the two groups, with a summary OR of 0.88 (95% CI 0.68 to 1.14; table 3, figure 5). A single study from China, enrolling 1128 hospitalised hypertensive patients, showed a significant risk reduction among treated subjects16; when its results were excluded from the analyses, the overall estimates did not change (pooled OR 0.95; 95% CI 0.76 to 1.18). Another study18 assessed the risk of death among ACE inhibitors/ARBs users versus non users and was initially included in the meta-analysis. However, this study was later retracted16; thus, it was excluded from the main analyses and included into a sensitivity analysis: with or without the study, the summary estimate did not change (pooled OR 0.85; 95% CI 0.81 to 1.03).
Cardiac risk factors and prevention

Table 3  Risk of severe/fatal COVID-19 or death among hypertensive subjects treated with RAAS inhibitors versus untreated subjects, overall and by drug class

| Outcomes                                                                 | No. of studies (sample) | Pooled OR (95% CI) | P value | I², % |
|---------------------------------------------------------------------------|-------------------------|--------------------|---------|-------|
| 1. Severe/fatal COVID-19*                                               |                         |                    |         |       |
| ACE inhibitors only                                                       | 5 (7489)                | 0.90 (0.65 to 1.26) | 0.6     | 80    |
| ARBs only                                                                 | 5 (7462)                | 0.92 (0.75 to 1.12) | 0.4     | 25    |
| ARBs/ACE inhibitors                                                       | 5 (11 334)              | 1.00 (0.84 to 1.18) | 0.9     | 50    |
| 2. Death from COVID-19                                                          |                         |                    |         |       |
| (in users vs non-users)                                                  |                         |                    |         |       |
| a. Main analysis:                                                          |                         |                    |         |       |
| ARBs/ACE inhibitors                                                       | 4 (2412)                | 0.88 (0.68 to 1.14) | 0.3     | 24    |
| b. Sensitivity analysis:                                                   |                         |                    |         |       |
| ARBs/ACE inhibitors                                                       | 5 (4758)                | 0.85 (0.71 to 1.03) | 0.10    | 12    |

All meta-analyses are based on a generic inverse variance approach.

*Including admission into intensive care unit, need for mechanical ventilation or death.

†Including one retracted study.25 26

ARBs, angiotensin receptor blockers; RAAs, renin–angiotensin–aldosterone.

Figure 2  Risk of severe/fatal COVID-19 among ACE inhibitors users versus non-users.

Figure 3  Risk of severe/fatal COVID-19 among ARB inhibitors users, versus non-users. ARBs, angiotensin receptor blockers.

Figure 4  Risk of severe/fatal COVID-19 among ACE inhibitors/ARBs users versus non-users. ARBs, angiotensin receptor blockers.

Figure 5  Risk of death among ACE inhibitors/ARBs users versus non-users. ARBs, angiotensin receptor blockers.

almost 10 000 hypertensive subjects: first, no significant differences in the risk of developing severe or fatal COVID-19 were observed between the subjects treated with either ACE inhibitors or ARBs, as compared with non-users. Second, and importantly, the results did not change after the exclusion of the three studies, which reported either a significantly higher or lower risk of severe illness among treated patients.

The present findings provide solid evidence from properly adjusted estimates across different countries on the absence of risk from RAAS inhibitors treatment during the pandemic, strongly supporting the statements of several experts27 28 and scientific societies, including the European Medicines Agency,29 the European Society of Cardiology30 and the American Heart Association,31 who recommend continuation of ARBs or ACE inhibitors medication. Although the present findings do not support the hypothesis of a beneficial effect from therapy during the pandemic,25 26 the results did not change after the exclusion of the three studies, which reported either a significantly higher or lower risk of severe illness among treated patients.

Acknowledging these caveats, the present meta-analysis, based on 10 studies and almost 10 000 hypertensive subjects, did not find any association between COVID-19 severity or mortality and treatment with ARBs, ACE inhibitors or both, strongly supporting the recommendation of several scientific societies to continue ARBs or ACE inhibitors medication for all patients, unless otherwise advised by their physicians, who should thus be reassured.

The following authors have contributed to the planning (MFE, CAM, RC, LGM and LaM), conduct (MFE, CAM, FB, GP, RC, AM, RM, LGM) and reporting (MFE, FB, GP, RAM, RM, LGM and LM) of the present work.

The authors declare no conflict of interest.
Some preliminary, unadjusted reports on severe acute respiratory syndrome coronavirus 2 positive subjects showed an increased mortality and morbidity among hypertensive patients, who were frequently treated with ACE inhibitors or angiotensin receptor blockers (ARBs). Recently, some observational studies with multivariable analyses found no association between these medications and COVID-19 severity, a few studies found a significant reduction in the risk of death or severe disease and one study found a increased risk of mechanical ventilation and admission to the intensive care unit. The magnitude of the association also varied across studies, which differed for patients’ characteristics, setting (inpatient or outpatient), population targeted by serological testing protocols and extent of measured confounding.

What might this study add?
► This meta-analysis is based on 10 adjusted observational studies (enrolling almost 10 000 hypertensive subjects), from different countries, and provides the first summary estimate on the association between ACE inhibitors or ARBs use and COVID-19 severity or mortality. All analyses showed a comparable risk of severe or fatal illness among treated and untreated subjects, either considering ACE inhibitors or ARBs separately, or combined.

How might this impact on clinical practice?
► Given that ACE inhibitors and ARBs are prescribed to tens of millions patients worldwide, summary estimates were strongly needed to elucidate whether these drugs should be suspended during the pandemic, or patients and physicians should be definitely reassured. These findings strongly support the recommendation of several scientific societies to continue ARBs or ACE inhibitors medication for all patients, unless otherwise advised by their physicians.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study complies with the Declaration of Helsinki. As a meta-analysis, the protocol and study did not require the approval from Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data are available from the corresponding author on request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Lamberto Manzoli http://orcid.org/0000-0002-8129-9344

REFERENCES
1 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.

2 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020.

3 Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020.

4 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

5 Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5.

6 Karakalusik G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020.

7 Vaduganathan M, Vardeny O, Michel T, et al. Renin-Angiotensin-Aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020.

8 Zheng YY, Ma YT, Zhang Y-J, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–60.

9 Bavishi C, Maddox TM, Messerli FH. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. JAMA Cardiol 2020. doi:10.1001/jama cardiol.2020.1282.

10 Bravi F, Flacco ME, Carandini T, et al. Predictors of severe or lethal COVID-19, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, in a sample of infected Italian citizens. Plos One 2020;15:e0235248.

11 de Abajo FJ, Rodríguez-Martín S, Lemco V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. Lancet 2020;395:1705–14.

12 Giorgi Rossi P, Marino M, Formisano D, et al. Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the province of Reggio Emilia, Italy. MedRxiv 2020.

13 Liu Y, Huang F, Xu J, et al. Anti-Hypertensive angiotensin II receptor blockers associated with mitigation of disease severity in elderly COVID-19 patients. MedRxiv 2020.

14 Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-Aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020;382:2431–40.

15 Reynolds HR, Adhikari S, Pulpaini C, et al. Renin-Angiotensin-Aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020.

16 Tedeschi S, Giannella M, Bartocletti M, et al. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for COVID-19. Clin Infect Dis 2020. doi:10.1093/cid/ciaa492.

17 Bean D, Kraljevic Z, Searle T, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-CoV-2 infection in a multi-site UK acute hospital Trust (Unpublished work). MedRxiv 2020.

18 Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020.

19 Mehta N, Kaifra A, Novacki AS, et al. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020.

20 WHO. COVID-19 and the use of angiotensin-converting enzyme inhibitors and receptor blockers - Scientific brief WHO. 2020.

21 Carr D. Sharing research data and findings relevant to the novel coronavirus (COVID-19) outbreak. secondary sharing research data and findings relevant to the novel coronavirus (COVID-19) outbreak, 2020. Available: https://wellcome.ac.uk/coronavirus-covid19-open-data.

22 Wells G, Shea B, O’Connell D, et al. The Newcast秾-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. secondary the Newcast秾-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2005. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

23 Manzoli L, Flacco ME, Boccia S, et al. Generic versus brand-name drugs used in cardiovascular diseases. Eur J Epidemiol 2016;31:351–68.

24 Manfredini R, Fabbian F, Cappadona R, et al. Daylight saving time and acute myocardial infarction: a meta-analysis. J Clin Res Cardiol 2019;8. doi:10.3390/jcrms0804004.

25 Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020.

26 Mehra MR, Desai SS, Kuy S, et al. Retraction: cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med.

27 Kuster GM, Osowski S. Switching antihypertensive therapy in times of COVID-19: why we should wait for the evidence. Eur Heart J 2020;41:1857.

28 Kuster GM, Pfister Q, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020;41:1801–3.

29 European Medicines Agency. Ema advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic, 2020. Available: https://www.ema.europa.eu/en/news/ema-advises-continued-use-medicines-hypertension-heart-kidney-disease-during-covid-19-pandemic [Accessed 20 Apr 2020].

30 European Society of Cardiology. Position statement of the ESC Council on hypertension on ACE-inhibitors and angiotensin receptor blockers, 2020. Available:
Cardiac risk factors and prevention

https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang [Accessed 20 Apr 2020].

31 American Hearth Association. Patients taking ACE-i and Arbs who contract COVID-19 should continue treatment, unless otherwise advised by their physician, 2020. Available: https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-people-to-continue-treatment-unless-otherwise-advised-by-their-physician?utm_campaign=science news19-20&utm_source=science news&utm_medium=phd-link&utm_content=phd03-17-20

32 Thomas LE, Bonow RO, Pencina MJ. Understanding observational treatment comparisons in the setting of coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020.

33 Page MJ, Forbes A, Chau M, et al. Investigation of bias in meta-analyses due to selective inclusion of trial effect estimates: empirical study. BMJ Open 2016;6:e011863.