INPLASY PROTOCOL

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Conflicts of interest:
None.

The use of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor on severity or mortality in patients with COVID-19: A Meta-analysis

Zhang, G[1]; Wu, Y[2].

Review question / Objective: **P: Patients with ACEI/ARB use. C: Patients with Non-ACEI/ARB use. O: The primary outcome was mortality (non-survivor) in patients with COVID-19 pneumonia. The secondary outcome was severe COVID-19, acute respiratory distress syndrome (ARDS), the need for mechanical ventilation, the need for dialysis, transfer to intensive unit care (ICU), length of hospital stay and hospitalization due to COVID-19. S: the observational cohort study.**
Condition being studied: **In December 2019, a series of unexplained pneumonia appeared in Wuhan, China. Sequencing analysis of lower respiratory tract samples suggested that it was a new coronavirus and was named 2019 novel coronavirus (2019- nCoV) by WHO on 12 January 2020.1 On 11 February 2020, WHO officially named the disease caused by 2019- nCoV as COVID-19. Previous studies suggest that the expression of ACE2 may be increased by chronic treatment with ACEi or ARB. The issue is controversial because ACEi/ARB may potentially be beneficial in severe lung injury by reducing activation of the renin angiotensin system (RAS). Furthermore, increased levels of ACE2 itself have been shown to be protective during severe lung injury. Whether or not treatment with ACEi/ARB increases the risk of severe COVID19 disease is a very important question in view of the large numbers of patients potentially on these drugs.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 September 2020 and was last updated on 15 September 2020 (registration number INPLASY202090067).

INTRODUCTION

Review question / Objective: **P: Patients with ACEI/ARB use. C: Patients with Non-ACEI/ARB use. O: The primary outcome was mortality (non-survivor) in patients with COVID-19 pneumonia. The secondary outcome was severe COVID-19, acute**

respiratory distress syndrome (ARDS), the need for mechanical ventilation, the need for dialysis, transfer to intensive unit care (ICU), length of hospital stay and hospitalization due to COVID-19. S: the observational cohort study.

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METHODS

Search strategy: The literature search included all studies published since the COVID-19 outbreak began (December 2019) until September 8, 2020, with no country restrictions imposed. We methodically searched the PubMed, Cochrane Library, Web of Science and EMBASE. The search terms were as follows:((((("Angiotensin Receptor Antagonists"[Mesh]) OR ((((((Antagonists, Angiotensin Receptor[Title/Abstract]) OR (Receptor Antagonists, Angiotensin[Title/Abstract])) OR (Angiotensin Receptor Blockers[Title/Abstract])) OR (Receptor Blockers, Angiotensin[Title/Abstract])) OR (Angiotensin II Receptor Antagonists[Title/Abstract])) OR (Angiotensin II Receptor Blockers[Title/Abstract]))) OR (("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR ((((((((((((((((Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR (Inhibitors, Kininase II[Title/Abstract])) OR (Kininase II Antagonists[Title/Abstract])) OR (Kininase II Inhibitors[Title/Abstract])) OR (Angiotensin I-Converting Enzyme Inhibitors[Title/Abstract])) OR (Angiotensin I Converting Enzyme Inhibitors[Title/Abstract])) OR (Antagonists, Angiotensin-Converting Enzyme[Title/Abstract])) OR (Antagonists, Angiotensin Converting Enzyme[Title/Abstract])) OR (Antagonists, Kininase II[Title/Abstract])) OR (Inhibitors, ACE[Title/Abstract])) OR (ACE Inhibitors[Title/Abstract])) OR (Inhibitors, Angiotensin-Converting Enzyme[Title/Abstract])) OR (Enzyme Inhibitors, Angiotensin-Converting[Title/Abstract])) OR (Inhibitors, Angiotensin Converting Enzyme[Title/Abstract])) OR (Angiotensin-Converting Enzyme Antagonists[Title/Abstract])) OR (Angiotensin Converting Enzyme Antagonists[Title/Abstract])) OR (Enzyme Antagonists, Angiotensin-Converting[Title/Abstract]))))) AND ((("COVID-19" [Supplementary Concept]) OR ((((((((((2019 novel coronavirus disease[Title/Abstract]) OR (COVID19[Title/Abstract])) OR (COVID-19 pandemic[Title/Abstract])) OR (SARS-CoV-2 infection[Title/Abstract])) OR (COVID-19 virus disease[Title/Abstract])) OR (2019 novel coronavirus infection[Title/Abstract])) OR (2019-nCoV infection[Title/Abstract])) OR (coronavirus disease 2019[Title/Abstract])) OR (coronavirus disease-19[Title/Abstract])) OR (2019-nCoV disease[Title/Abstract])) OR (COVID-19 virus infection[Title/Abstract])))) AND (("Cardiovascular Diseases"[Mesh]) OR (((Cardiovascular Disease[Title/Abstract]) OR (Disease, Cardiovascular[Title/Abstract])) OR (Diseases, Cardiovascular[Title/Abstract])))))) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]).

Participant or population: All adult inpatients (ARBs/ACEIs exposure) testing positive for SARS-Cov2 by RT-PCR. (part of

the participants with preexisting hypertension).

Intervention: The exposure of interest was patients' use of ACEI/ARBs.COVID-19 patients were retrospectively allocated into two groups, ARBs/ACEIs and non-ARBs/ACEIs group, according to their usage of antihypertensive drugs prior to admission and during hospital stay.

Comparator: All adult inpatients (Non-ARBs/ACEIs exposure) testing positive for SARS-Cov2 by RT-PCR.(part of the participants with preexisting hypertension).

Study designs to be included: The retrospective cohort study.

Eligibility criteria: (1) Study design: the observational cohort studies; (2) Grouping method: ACEI/ARB use versus non-ACEI/ARB use; (3) Sufficient information to calculate odds ratio (OR) or the adjusted data were provided in the publication. Editorials, correspondences, conference abstracts and commentary articles were excluded in our study.

Information sources: Data extracted from publications includes: (1) Research information: author name, country, publication journal, study design, study population, sample source, confounder adjustments and study quality. (2) Participant information: age, gender and ACEI/ARB use. (3) Outcomes: The primary outcome was mortality (non-survivor) in patients with COVID-19 pneumonia. The secondary outcome was severe COVID-19, acute respiratory distress syndrome (ARDS), the need for mechanical ventilation, the need for dialysis, transfer to intensive unit care (ICU), length of hospital stay and hospitalization due to COVID-19.

Main outcome(s): The primary outcome was mortality (non-survivor) in patients with COVID-19 pneumonia.

Additional outcome(s): The secondary outcome was severe COVID-19, acute respiratory distress syndrome (ARDS), the need for mechanical ventilation, the need for dialysis, transfer to intensive unit care (ICU), length of hospital stay and hospitalization due to COVID-19.

Quality assessment / Risk of bias analysis: Newcastle Ottawa Scale (NOS) was used to assess article quality. Any disagreement in quality assessment was resolved through consensus. Studies scoring >7 were considered at low risk of bias, scores of 5–7 indicated moderate risk of bias and scores of <5 indicated high risk of bias.

Strategy of data synthesis: Meta-analysis was performed using Stata 16.0 software. Heterogeneity was assessed using the I^2 statistics. χ^2 test statistic were used to assess the homogeneity between studies. Random-effects models were used for pooled analysis, regardless of heterogeneity. To provide a quantitative estimate of the association between ACEI/ARB use and outcomes in COVID-19 patients, the odds ratios (ORs) and the corresponding 95 % CIs were extracted from published articles. When the ORs were not given, tabular data were used to calculate the corresponding OR.

Subgroup analysis: Due to the participants differ in whether they have hypertension across the studies, subgroup analyses were performed.

Sensibility analysis: None.

Country(ies) involved: China.

Keywords: 2019 novel coronavirus disease, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Antagonists.

Contributions of each author:

Author 1 - Guoyue Zhang - Author1 participated in data extraction, quality evaluation, statistical analysis and article writing.

Author 2 - Yue Wu - Author1 participated in data extraction, quality evaluation, statistical analysis and article writing.