Renin-angiotensin system inhibitors and severity of SARS-CoV-2 infection: a meta-analysis

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Abstract

Introduction

The mechanism of entry of SARS-CoV-2 into the human host cell is through the ACE2 receptor. During the pandemic, a hypothesis has been proposed that Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARBs) could be risk factors for the development of severe SARS-CoV-2 infection.

Objective

To conduct a meta-analysis of the association between ACEi or ARB use and SARS-CoV-2 infection severity or mortality.

Data Sources

We searched PubMed, EMBASE, Google scholar and the Cochrane Database of Systematic Reviews for observational studies published between December 2019 and April 24, 2020

Study Selection: Studies were included if they contained data on ACEi or ARB use and SARS-CoV-2 infection severity or mortality. Effect statistics were pooled using random-effects models. The quality of included studies was assessed with the Newcastle–Ottawa Scale (NOS).

Data Extraction

Data on study design, study location, year of publication, study design, number of participants, sex, age at baseline, outcome definition, exposure definition, follow-up, effect estimates and 95% CIs.

Results

Thirteen observational studies were identified for inclusion, combining to a total sample of 14364 participants. Mean age was 59.2 (SD 7.3) years and 53.5% were men. Mean follow-up was 28.3 (14.2) days. The mean NOS score of included studies was 7.8 (range: 7-9). Results suggested that ACEi or ARB use did not increase the risk of severe disease or mortality from SARS-CoV-2 infection (OR=0.72, 95% CI 0.47-1.11, $p=0.138$).

Conclusions

At present, the limited evidence available does not support the hypothesis of increased SARS-CoV-2 risk with ACEi or ARB drugs. However, more evidence needs to accumulate before this controversy can be resolved.

Introduction

It had not been anticipated that a phenomenon such as the appearance of the new SARS-CoV-2 pandemic would affect the world in such a short time and lead to serious health and economic consequences. Scientists around the world are in a race against time in the search for effective treatment approaches. Among the many questions that need urgent clarification is that of the possible drug-disease interactions in patients taking Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin II receptor blockers (ARBs). These are among the most widely used antihypertensive drug classes in the world [1].

The Renin-Angiotensin system (RAS) has the function of maintaining homeostasis of blood pressure, fluid and salt in the human body. RAS contains two homologous enzymes belonging to the Angiotensin converting enzyme (ACE) dipeptidyl carboxypeptidase family, with different functions: the Angiotensin I converting enzyme 1 (ACE1) converts Angiotensin I to Angiotensin II; and the Angiotensin I converting enzyme 2 (ACE2) decreases the level of Angiotensin II and negatively regulates the RAS system. Thus, ACE2 reduces the effects of vasoconstriction, sodium retention and fibrosis. ACE2 is expressed in various organs such as the heart, kidneys and especially in alveolar epithelial cells of the lung [2]. Under normal conditions, circulating levels of soluble ACE2 are low and its function at the lung level is minimal [3].

The mechanism of entry of SARS-CoV-2 into the human host cell is through the ACE2 receptor. SARS-CoV-2 has an envelope made up of glycoproteins, called S1 (Spike) and S2, the former binding to ACE2 on the cell surface and the latter with the cell membrane[4]. While this mechanism is similar to that of another coronavirus that caused the SARS epidemic in 2002-2003 [5,6], SARS-CoV-2 has a higher affinity for ACE2 [7]. Although their three-dimensional structure is similar, SARS-CoV and SARS-CoV-2 differ in about 28% of the amino acid sequence in the receptor binding domains; SARS-CoV-2 has a distinct loop with flexible glycyl residues replacing rigid prolyl residues, which makes its structure less rigid and may explain its greater affinity for the ACE2 receptor [7].

ACE2 was involved in the pathophysiology of SARS-CoV infection [8] and it is feared that in SARS-CoV-2 infection, this effect could be of greater magnitude. In addition, prior to the pandemic it had been reported that ACEi/ARBs could increase mRNA expression of ACE2 at the cardiac level [9]. Hence, it has been hypothesized that ACEi and/or ARBs could be risk factors for the development of severe forms of SARS-CoV-2 infection [10,11] In the midst of the COVID-19 pandemic crisis, this simple hypothesis was, without clinical or research evidence to support it, widely disseminated by the media, which in turn caused great concern to patients who were taking these medications. Official statements rapidly followed recommending that these medications continue to be taken [12] in view of the absence of evidence to support the hypothesis. However, the absence of evidence does not mean evidence of absence and there is still an urgent need for clarification. In that light, we conducted a meta-analysis of the association between ACEi or ARB use and SARS-CoV-2 infection severity or mortality.

Methods

This study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[13].

Search strategy

Two independent investigators performed a systematic search in PubMed, EMBASE, Google scholar and the Cochrane Database of Systematic Reviews for observational studies published between December 2019 and April 24, 2020. In addition, we conducted a secondary search based on the reference list of retrieved articles. The PubMed search strategy is detailed in Supplementary Table A.

Eligibility criteria

We searched for randomized controlled trials (RCTs) or observational studies reporting data on ACEi or ARB use and SARS-CoV-2 infection severity or mortality. We included studies in English or other languages (all ages) meeting the following criteria: a) COVID-19 patients were diagnosed according to the interim guidance of the World Health Organization [14]; b) the study presented data on hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) with confidence intervals (CIs) or offered enough data to allow these to be calculated (including via email correspondence with original authors if necessary); and c) SARS-CoV-2 infection severity criteria were described.

Quality assessment

The quality of observational studies (cohort and case-control studies) and RCTs were assessed according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [15] and the Cochrane Risk of Bias Assessment Tool [16], respectively. Two investigators evaluated the quality of the studies independently. Conflicting results were resolved by discussion and involvement of a third reviewer if necessary.

Data extraction

The following data were extracted from each study: authors, study location, year of publication, study design, number of participants, sex, age at baseline, outcome definition, exposure definition, follow-up, effect estimates and 95% CIs.

Statistical analyses

Primary analyses evaluated the association (HRs, RRs or ORs) between use of ACEi or ARB and SARS-CoV-2 infection severity or mortality. We used random effects with an inverse variance method to calculate the pooled RRs and 95% CIs according to the heterogeneity between studies [17]. The overall estimates in the pooled analysis were obtained using using Stata 13 software (StataCorp LP, College Station, TX).

Results

After screening 343 citations, 13 observational studies were included (Figure 1) [18–30], combining to a total sample of 14,364 participants. The characteristics of included studies are summarized in Table 1. Ten studies were from China, with the other three being from UK, USA and Korea. Overall, mean age was 59.2 (SD 7.5) years and 53.5% were men. Mean follow-up was 28.3 (14.2) days. The mean NOS score of included studies was 7.8 (range: 7-9). The outcomes reported in the included studies are presented in Table 1.

For the meta-analysis, we used the combined outcome of severe disease and/or mortality. As shown in Figure 2, the meta-analysis suggested that ACEi or ARB use did not increase the risk of severe disease or mortality from SARS-CoV-2 infection (OR=0.72, 95% CI 0.47-1.11, $p=0.138$). Subgroup analyses were conducted to assess ACEi and ARB effects separately (Table 2) but no significant associations were found. Subgroup analyses were also negative for the effects of age (<60 vs. 60+) or sex (Table 2).

Discussion

Our study found no evidence to support the hypothesis of increased SARS-CoV-2 risk with ACEi or ARB drugs. This would seem at odds with a previous finding that chronic use of ACEi and ARBs was high among intensive care unit patients with non-COVID-19 sepsis [31]. However, it is possible that ACEIs/ARBs could be a marker of underlying comorbidities rather than being causal in SARS-CoV-2 severity or mortality.

Prior to the SARS-CoV-2 pandemic, Shinohara *et al.* published a meta-analytic study where they found a decreased risk of post-stroke pneumonia in patients treated with ACEi compared to other antihypertensive drugs (RR: 0.61, 95% CI 0.51–0.75; $P<0.001$) [32]. In another meta-analysis, Liu *et al.* found that ARBs were associated with a decreased risk of pneumonia morbidity (OR = 0.55, 95% CI; 0.43-0.70, $p<0.01$) and mortality (OR = 0.55, 95% CI; 0.44-0.69, $p<0.01$) [21]. These findings could however be seen from the perspective that the prescription of ACEi/ARBs may be a marker of good general medical care, given the well-evidenced preventative role of these medications in many cardiovascular and metabolic diseases.

The basis for the hypothesis of a probable ACEi/ARB-induced increase in ACE2 expression has been recently revised, evaluating the results of 12 animal and 11 human studies [33]. In animal studies, no significant changes in ACE2 expression were found, and in those where it was evidenced, it was when models of acute injury were used or at higher doses than those used in humans; furthermore, no increase in ACE2 expression induced by ACEi/ARBs was evidenced in human studies [33].

It has been proposed that ARBs may have protective effects on severity and mortality in SARS-CoV-2 infection through increasing the production of Angiotensin 1-7, reducing Angiotensin II and contributing towards lung protection [34]. Recently, Liu *et al.* found that Angiotensin II levels in the plasma of COVID-19 infected patients was markedly elevated and linearly associated to viral load and lung injury [35]. However, this may be a marker of general physiological stress during severe acute illness and not have specific drug-disease implications.

Our study is limited in that it only relies on observational studies and not RCTs and includes a relatively small number of participants. It would be important that future, more powered studies, re-evaluate the possible relevance of age (young vs. old), sex, and possible different roles of ACEi and ARB drugs. It would also be important to assess the risk of specific comorbidities (e.g. diabetes, hypertension, cerebrovascular disease, ischemic heart disease) in the absence of ACEi/ARB drugs. For example, Feng *et al.* showed that hypertension without ACEi/ARB therapy was an independent risk factor for developing severe pneumonia irrespective of age[20].

In conclusion, the limited evidence available at present does not support the hypothesis of increased SARS-CoV-2 risk with ACEi or ARB drugs. However, more evidence needs to accumulate before this controversy can be resolved; in the meantime, clinicians may adopt a tailored, pragmatic approach that is supported by official recommendations [12,35].

Declarations

Competing interests

Author	Competing interests
Teodoro J. Oscanoa	declare no competing interests
Xavier Vidal	declare no competing interests
Alfonso Carvajal	declare no competing interests
Roman Romero-Ortuno	declare no competing interests

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Tables

Table 1. Characteristics of the 12 studies included in the meta-analysis.

Study (year)	Country	Study design	Total Sample size	Mean age (SD)	Male sex (%)	Follow-up (SD) days	OR (95% CI)	Outcome	Type of RAS inhibitor	NOS
Guo T et al. (2020)	China	CC	187	58.5 (14.7)	48.7	26.3 (9.0)	1.70 (0.63-4.58)	Mortality	ACEi/ARB	8
Liu Y et al. (2020)	China	CC	511	>65	55.1	No data	0.34 (0.13-0.92)	Severe disease	ARB	8
							0.57 (0.14-2.34)	Severe disease	ACEi	
Peng Y et al. (2020)	China	CC	112	62.0	47.3	No data	1.32 (0.38-4.52)	Mortality	ACEi/ARB	8
Meng J et al. (2020)	China	CC	417	64.5	57.1	20	0.33 (0.09-1.31)	Severity/mortality	ACEi/ARB	8
Bean D et al. (2020)	UK	CC	205	63.0	51.7	7	0.29 (0.1-0.75)	Mortality/ required critical care	ACEi	7
							2.4 (0.62-9.30)	Mortality/ required critical care	ARB	
Yang G et al. (2020)	China	CC	462	67	49.4	35.2 (12.8)	0.32 (0.07-1.51)	Mortality	ACEi/ARB	9
							0.3455 (0.11-1.10)	Critical vs. noncritical		
Feng Y et al. (2020)	China	CC	476	Median (IQR) 53 (40-64)	56.9	16 (range: 12-24)	0.18 (0.06-0.57)	Severity (severe and critical vs moderate)	ACEi/ARB	8
							0.26 (0.08 -0.84)	Severity (severe and critical vs moderate)	ARB	
							0.27 (0.03-2.27)	Severity (severe and critical vs moderate)	ACEi	
Feng Z et al. (2020)	China	CC	564	47 (36-58)	50.4	No data	0.41 (0.05-3.19)	Severe pneumonia	ACEi/ARB	8
Rentsch C. et al (2020)	USA	CC	585	Median (IQR) 66 (60-71)	95.4	No data	1.66 (0.94-2.93)	Intensive care	ACEi/ARB	7
							1.28 (0.76-2.16)		ARB	
							2.01 (1.32-3.05)		ACEi	
Zeng Z et al. (2020)	China	CC	274	67	47	20 (14-27)	2.46 (0.94-6.40)	Severe vs non severe pneumonia	ACEi/ARB	8
							0.65 (0.12-3.58)	Mortality	ACEi/ARB	
Lee H et al. (2020)	Korea	CC	8266	44.4 (19.1)	38.5	60	HR=1.07 (0.68-1.65)	Mortality	ACEi/ARB	7
							HR=1.09 (0.70-1.70)	Mortality	ARB	
							HR=0.72 (0.17-3.04)	Mortality	ACEi	
Zhang P et al. (2020)	China	CC	1128	Median (IQR) 64 (55-68)	53.2	28	HR=0.36 (0.16-0.78)	Mortality	ACEi/ARB	7
Li J. et al (2020)	China	Case-control study	1178	55.5 years (interquartile range, 38-67 years)	46.3%	27	1.1 1 (0.72-1.73)	Severity	ACEi/ARB	8
							1.2 3(0.75-2.01)	Severity	ARB	

							0.91 (0.45-1.84)	Severity	ACEi	
							0.76 (0.44-1.33)	Mortality	ACEi/ARB	
							0.77 (0.421-1.44)	Mortality	ARB	
							0.92 (0.39-2.19)	Mortality	ACEi	

SD: standard deviation. CI: confidence interval. RAS: Renin-Angiotensin system. NOS: Newcastle-Ottawa Scale. CC: case control.

Table 2. Summary of subgroup analyses.

Subgroup	Studies (n)	Adjusted OR (95% CI)	P
Mean age (years)			
<60	4	0.68 (0.27-1.76)	0.429
≥60	9	0.72 (0.42-1.23)	0.232
% male sex			
<55	9	0.77 (0.47-1.26)	0.292
≥55	4	0.57 (0.19-1.68)	0.308
Type of Renin-angiotensin system inhibitors (RAS)			
ARB	7	0.83 (0.52-1.33)	0.436
ACEi	6	0.74 (0.35-1.57)	0.430

Figures

Figure 1

Flowchart of included studies.

Figure 2

Forest plot of the meta-analysis of the association between ACEi or ARB use and SARS-CoV-2 infection severity or mortality. Analysis model: random effect. OD: Odd ratio. CI: confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarydata.docx](#)