Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

A Meta-analysis of the Relationship Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19

The angiotensin converting enzyme (ACE) 2 is a cell surface protein used for entry into type II pneumocytes and other tissues by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – the infective agent of COVID-19.[1] It has been demonstrated that ACE2 is upregulated on tissues by renin-angiotensin-aldosterone system (RAAS) inhibitors. This raised concerns that RAAS inhibitors may increase susceptibility and worsen prognosis in COVID-19. In contrast, ACE2 facilitates degradation of angiotensin II and has an anti-inflammatory function and may actually protect the lungs and other tissues from injury.[1] Thus, the effect of RAAS inhibitors on susceptibility and prognosis of COVID-19 continues to be the subject of much debate.[1] Individual observational studies in the area have yielded equivocal results; hence, we sought to conduct a meta-analysis of all available data to provide greater insight.

For this study, PubMed and Scopus were searched in May 2020 using the following keywords and their MeSH terms: "COVID-19," "hypertension," "ACE inhibitors (ACEIs)," and "Angiotensin receptor blockers (ARBs)." Studies were included if they:[1] they reported the risk of testing positive for COVID-19 and/or the risk of mortality in COVID-positive patients; and[2] compared hypertensive patients prescribed RAAS inhibitors to those not using these drugs. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) from each study were pooled using a random-effects model. A p-value <0.05 was considered significant.

Our initial search yielded 950 potential studies. After exclusions, eight studies[2–9] with a total of 62,706 patients (n = 20,316 ACEI/ARB users and n = 42,390 nonusers) remained for analysis. Study and baseline characteristics are provided in Table 1. Pooled analysis revealed no significant association between the likelihood of testing positive for COVID-19 and the use of ACEIs (OR 0.96 [0.88 to 1.04]; p = 0.29; $I^2 = 0\%$) (Figure 1) or ARBs (OR 0.99 [0.91 to 1.08]; p = 0.90; $I^2 = 5\%$) (Figure 1). Similarly, no significant difference was observed in mortality rate among hypertensive patients prescribed RAAS inhibitors compared with hypertensive patients not prescribed these medications (OR 0.74 [0.34 to 1.58]; p = 0.43; $I^2 = 65\%$) (Figure 1).

The results of the current meta-analysis suggest that neither ACEI nor ARB use is significantly associated with the odds of testing positive with COVID-19. This result can be considered robust, as it was derived from 3 large-scale studies[2,3,6] which adjusted for multiple potential confounding factors, including age, sex and co-morbidities. Our findings also show no significant association between RAAS inhibitor use and mortality in COVID-19 patients; however, this result must be viewed with caution as – due to the lack of data – we were unable to analyze ACEI users and ARB users separately, and adjusted data was reported by only one study. In this context, specific aspects of our analysis are notable. COVID-19 patients using RAAS inhibitors are older and have a higher burden of comorbidities, and this may have confounded our results. Adjustment for these factors could potentially shift the results in favor of RAAS inhibitors. Thus, our results support the consensus by multiple specialty societies, which recommend continued usage of RAAS inhibitors in COVID-19 patients and among the general public who have been prescribed these medications.

Table 1
Baseline and study characteristics

Study	Design	Country	Total patients	COVID-19 positive (%)	RAAS inhibitor group (Total, ACEi, ARB)	Non-RAAS inhibitor group (Total, non-ACEI, non-ARB)	Age	Male (%)	Adjustment
Studies reporting mortality									
Meng et al.	Cross-sectional	China	42	-	17, -, -	25, -, -	64.5 (55.80 - 69.00)	57.1	-
Richardson et al.	Retrospective	USA	2411	-	-, 140, 194	2077, -, -	63 (52 - 75)	60.3	-
Yang et al.	Retrospective	China	126	-	43, -, -	83, -, -	66 (61 - 73)	49.2	-
Yudong et al.	Retrospective	China	112	-	22, -, -	90, -, -	62	-	-
Zhang et al.	Retrospective	China	1128	-	188, -, -	940, -, -	-	ACEIARB - 53.2	-
Studies reporting risk of testing positive for COVID-19									
Mancia et al.	Case-control	Italy	37,031	16.9	15,375, 8071, 7304	21,656, -, -	68 ± 13	63	Multivariable adjustment for severity, sex, municipality, age at diagnosis, a number of treatment-related covariates and markers of patient clinical status
Mehta et al.	Cross-sectional	USA	18472	9.4	2285, 1322, 982	16187, 17150, 17490	ACEI - 63, ARB -64	ACEI - 49, ARB - 59	Propensity matched for age, sex, diabetes, coronary artery disease, hypertension, chronic obstructive pulmonary disease and heart failure
Reynolds et al.	Cross-sectional	USA	3384	46.8	1692, 954, 1057	1692, 954, 1057	ACEI - 64.7, ARB - 66	ACEI - 56, ARB - 50	Propensity matched for age; sex; race; ethnic group; body-mass index; smoking history; history of hypertension, myocardial infarction, heart failure, diabetes, chronic kidney disease, and obstructive lung disease (e.g., asthma and obstructive pulmonary diseases); and other classes of medication.

RAAS inhibitor = Renin-angiotensin-aldosterone system inhibitor; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

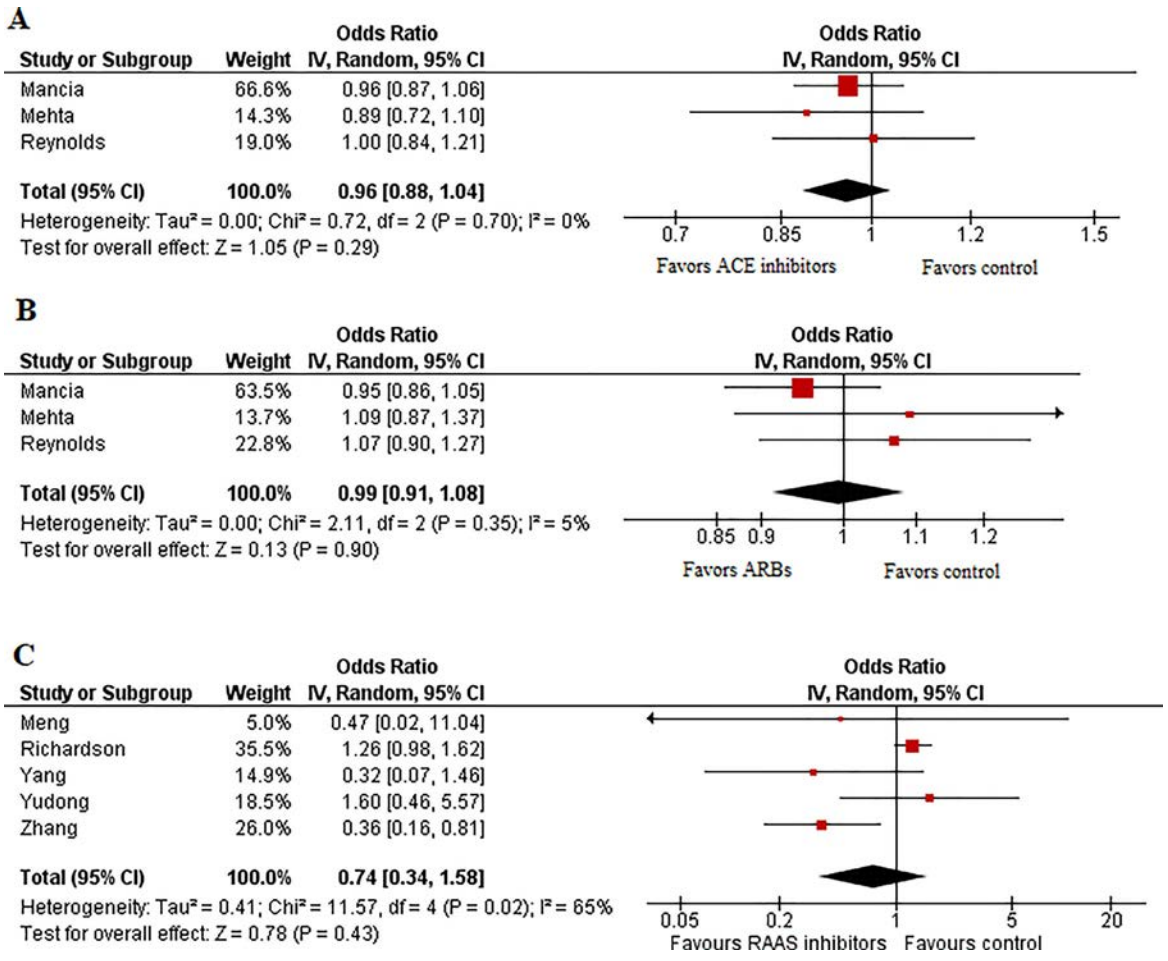

Figure 1. Forest plots displaying the odds of (A) testing positive for COVID-19 amongst patients using ACEI, compared to those not using ACEI; (B) testing positive for COVID-19 amongst patients using ARBs, compared to those not using ARBs; (C) mortality in COVID-19 patients using RAAS inhibitors, compared to those not using RAAS inhibitors.

Disclosures

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Angiotensin Converting Enzyme 2 May Mediate Disease Severity In COVID-19

Identification of vulnerability to *severe* coronavirus disease 2019 (COVID-19) is extremely important and might allow optimized shielding and easing of lockdown. The disease is attributed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which enters host cells through binding to angiotensin converting enzyme 2 (ACE2) on the cell surface. Clinical syndromes such as hypertension that display reduced ACE2 expression tend to correlate with a more severe disease course, whereas treatments which upregulate ACE2 such as the use of angiotensin converting enzyme inhibitors (ACE-i) appear to have a protective effect against COVID-19. Preclinical studies have shown that plasma soluble ACE2 could render SARS-CoV-2 inactive in a dose-dependent manner. The association of clinical syndromes or treatments that impact ACE2 expression and clinical severity of COVID-19 infection combined with the reduction in viral load with human recombinant serum ACE2 shown in preclinical studies indicate a key role for ACE2 in determining COVID-19 severity. In conclusion, we propose that measurement of ACE2 level may help identify individuals at risk of severe infection where targeted shielding can be used and could provide a novel therapeutic target.

Identification of vulnerability to *severe* COVID-19 is extremely important, and might allow optimized shielding and easing of lockdown. We propose a pathological role for soluble angiotensin converting enzyme (sACE2) modulating COVID-19 disease severity, which could be used in screening and treatment.

Hypertension, diabetes, and obesity are risk factors for severe disease.[1] SARS-CoV-2 enters the host cell through the spike (S) protein binding to ACE2,[2] and since ACE-inhibitors (ACE-i) and angiotensin-II receptor blockers (ARB) upregulate cellular ACE2 expression, this could theoretically facilitate SARS-CoV-2 binding and severe disease manifestation, whereas renin-angiotensin-aldosterone inhibition appears protective.[3]

After SARS-CoV-2 binds to host cells, ACE2 expression and enzymatic activity are significantly reduced through enhanced shedding, with the extracellular component of ACE2 cleaved and resultant soluble protein released. The resultant increased sACE2 may act as a "dummy" receptor, binding the S protein on circulating virus. Thus, higher numbers of ACE2 receptors expressed before first binding event may lead to higher sACE2 level and reduced circulating SARS-CoV-2 with "active" S protein sites, reduced numbers of affected host cells, and less systemic impact. Therefore, conditions that upregulate ACE2 may confer protection, whereas reduced ACE2 expression may result in more severe disease.

Clinical findings support such pathological role for reduced ACE2 levels in mediating disease severity. Patients with hypertension, exhibiting marked ACE up-regulation and ACE2 downregulation, are at higher risk of severe disease, whereas those taking ACE-i/ARB exhibit less disease severity and lower mortality.[3] The ACE2 gene is linked to metabolic syndrome and obesity.[4] ACE2 gene knockout leads to metabolic syndrome in mice. In patients with diabetic renal disease, ACE2 expression is reduced compared with patients with nondiabetic renal disease or controls. Lower ACE2 expression in obese patients and metabolic syndrome may explain worse outcomes with COVID-19.[1]

The ACE2 gene is located on the X-chromosome, and ACE2 activity and expression in rats was decreased by oophorectomy and restored by oestrogen. Thus, women would be expected to have higher ACE2 activity, which might explain better outcomes. Recent studies show that human recombinant sACE2 (hrsACE2) can bind and neutralise SARS-CoV-2 S protein,[5] reducing SARS-CoV-2 entry into cells in a dose-dependent manner.[2]

The association of clinical syndromes and treatments that impact ACE2 expression and the reduction in viral load with hrsACE2, indicate a key role for ACE2 in COVID-19 severity. We propose that measurement of ACE2 level may help identify individuals at risk of severe infection and provide a novel therapeutic target.

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