RAAS Inhibitors for Hypertensive Patients during Covid-19 Infection – A Metanalysis

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ABSTRACT

Inhibition of the Renin Angiotensin Aldosterone system (RAAS) is the leading form of anti-hypertensive treatment, through blockade of the angiotensin-converting enzyme 2 receptor (ACE2-r) by angiotensin enzyme inhibitors (ACE-is) and angiotensin receptor blockers (ARBs). However, the ACE-r has been found to be a functional receptor for the viral entry of SARS-CoV-2, and increased upregulation of ACE2 by inhibitors could increase the severity of infection. Previous to the SARS-CoV-2 outbreak, typical practice in patients with risk of infection would be to withhold ACE inhibitors due to evidence of renal failure. This thesis reviews the impact of RAAS inhibitor use in COVID-19 patients, and if withholding ACE inhibitors could affect the clinical outcome of patients. A total of 22 studies were located form database searching (PubMed, MedRxiv, Google scholar), 15,784 hypertensive COVID-19 patients were documented, with 8,035 taking ACE-is/ARBs treatment in comparison to 7,024 without. RAAS inhibitors were found to decrease likelihood of mortality (OR 0.68 [0.51, 0.90], p = 0.008), but there was no statistically significant difference between RAAS and Non-RAAS in severity (OR 0.91 [0.63, 1.31], p= 0.62). Following these results there would not be sufficient evidence to remove longstanding RAAS inhibitor medication in COVID-19 patients. Rapid data collected during observational trials can now be utilised in long term randomised controlled studies currently ongoing, such as BRACE-CORONA. This allows the opportunity for further analyses of the association between the RAAS system, new variants, genetic polymorphism and the maintenance of blood pressure.

Introduction

In late 2019, a cluster of unknown pneumonia cases were linked to a Seafood market in Wuhan, Hubei province, China (Zhu et al., 2020). On 12th January 2020 the World Health Organisation (WHO) reported an update of a new novel type of Coronavirus named the SARS-CoV-2 outbreak. The WHO reported 41 confirmed patients with the novel virus with no evidence that the virus was easily passed from person to person (World Health Organization, 2020). 3rd of May 2021, there have been 152,933,322 cases of COVID-19 reported globally (World Health Organization, 2021). SARS-CoV-2 is transmitted through airborne droplets by a contagious individual coughing or sneezing (Abboah-offei et al., 2021). The majority of patients are asymptomatic or develop mild to moderate symptoms. However, approximately 15% develop severe pneumonia with 5% of cases advancing to acute respiratory distress syndrome (ARDS) , septic shock and multiple organ failure (Cao, 2020). Older patients and those with cardiovascular comorbidities such as hypertension, diabetes and coronary heart disease had elevated risk of infection, severity of lung injury and mortality. Patients with existing hypertension constitute 20-30% of all patients hospitalised, 58.3% of Intensive care unit (ICU) patients and 60.9% of deaths caused by COVID-19 (Li, Hu and Zhang, 2020). Given that hypertensive patients are overrepresented in COVID-19mortality statistics, there is an urgent need to gather evidence as to how hypertension and anti-hypertensive medications influence the disease process. The Renin-angiotensin-aldosterone system (RAAS) plays a key role in the regulation of fluid volume and as a result in blood pressure regulation (Cooper et al., 1997). Inhibitors such angiotensin enzyme inhibitors (ACEi) and Angiotensin receptor blockers (ARBs) are the leading treatments used to block the angiotensin-converting enzyme 2 (ACE2) receptor reducing the effects of an overactive RAAS and therefore hypertension (Van

Vark et al., 2012). The Angiotensin-converting enzyme 2 receptor (ACE2-r) has been found to be a functional receptor for SARS-CoV-2 infection in the lung to enter cells (Casucci, Acanfora and Incalzi, 2020). Current research shows that RAAS inhibitors influence the expression of ACE2 in the heart kidney and plasma, however it is unclear if inhibitors can alter the expression of ACE2 in airway epithelial cells which would affect the virulence of the virus (Li, Hu and Zhang, 2020). Therefore, it is possible that increased expression of ACE2 without blockers could advance the proliferation of SARS-CoV-2 and intensify its capability for infection (Li, Hu and Zhang, 2020). Due to SARS-CoV-2 having a higher affinity to ACE2-r, which enables its capability of human-to-human transmission, concerns that increased upregulation of ACE2 by inhibitors will increase the severity of infection (Khashkhusha, Chan and Harky, 2020). Before the SARS-CoV-2 outbreak, typical practice in patients with risk of infection would withhold ACE inhibitors due to evidence of renal failure (Stirling et al., 2003). Therefore, it is vital to understand the impact of ARB/ACEi use in COVID-19 patients, and if withholding use of ACE inhibitors could improve the clinical outcome of patients.

Materials and Methods

Search strategy and selection

Studies were identified through searching the following databases PubMed, MedRxiv, Google scholar and Web of Science. Sources were identified through the key terms of "COVID-19, SARS-CoV-2, RAAS inhibitor, ACE-i, ARB, Mortality, Severity and hypertension". The initial search for literature was carried out in phases during the 18th of January 2021 and the 22nd of March 2021. All studies identified during this period were then considered based on inclusion and exclusion criteria.

Eligibility criteria

Due to the novelty of COVID-19 infection, randomised case-controlled trial data are currently lacking. As a result, studies collated for the meta-analysis were retrospective observational cohort studies. Primary outcome focused on mortality during any length of study period with secondary outcome comparing severity or ICU. Studies were included if mortality or severity of illness were recorded specifically for COVID-19 positive hypertensive patients with and without RAAS inhibitor treatment. Patients were excluded if they <18 years or pregnant. Mortality and illness severity were at times calculated form supplementary data provided by studies, separate from the published articles as online data uploads. RAAS inhibitors was classified as the use of ACE-is or ARB before hospital admission, previously prescribed by a clinician or general practitioner (Negreira-Caamaño et al., 2020). Patients needed to have a confirmed diagnosis by one of three methods: (i) real-time fluorescent reverse transcription - PCR (RT-PCR), positive for nucleic acid; (ii) viral gene sequence homologous to previously known corona-viruses; or (iii) SARS-Cov-2 specific IgM or IgG detection.

The definition of severity of cases differed among studies, however, for the analysis this was assorted into three categories ranging from mild to mortality (Table 1; Gao et al., 2020; Yang et al., 2020). For this analysis cases analysed were severe to critical and in hospital mortality. Patients were considered hypertensive if they were on anti-hypertensive medication before infection with SARS-Cov-2, along with a confirmed diagnosis from the patient's physician in medical records. Total number of patients on anti-hypertensive medication either prior or during the hospital stay was also extracted where possible. Despite any additional use of other anti-hypertensive medication, cases were included in the RAAS Positive cohort if one inhibitor (ACE-i/ARB) was being used at all (Huang et al., 2020). Other antihypertensive medication was not considered a relevant cofounder as the pharmacology is different and ultimately would not affect the RAAS pathway.

Table 1. Patient categories used to classify severity within the analysis, based on current best understanding (Gao et al., 2020; Yang et al., 2020).

Patient severity category	Clinical symptoms
Mild to Moderate	Signs of fever, respiratory tract symptoms and evidence of pneumonia
Severe to Critical	Respiratory distress, hypoxia, respiratory failure including requiring mechanical ventilation, septic shock, multiple organ failure or admission to intensive care unit (ICU)
Mortality	In hospital mortality

Statistical analysis

Review Manager 5.4, software produced by the Cochrane collaboration, was used to conduct the meta-analysis (RevMan5). Data were analysed using the Generic-Inverse variance formula and reported by log[Odds Ratios] and Standard Errors. Odds ratios were calculated through RAAS positive events/total divided by RAAS negative events/total. Standard errors were calculated as a summary of all events based on Cochrane review methods (Deeks et al., 2021; Higgins et al., 2021). Where mortality recorded in a cohort was 0, odds ratios were calculated after study results were adjusted using the Haldane-Anscome Correction (Weber et al., 2020).

Due to the nature of the COVID-19 virus disproportionately affecting the older demographic, the majority of severe clinical cases are 65 years of age and over resulting in a smaller population study demographic. Therefore, median age, sex and existing comorbidities of reviewed studies were taken into consideration.

The pooled analysis for both mortality and survival used random effect models regardless of heterogeneity, to factor possible uncertainty between study variances. Results were considered significant when $p<0.05$, with 95% confidence intervals (95% CI) and reported using a Chi – Squared statistic, degrees of freedom (df), and I^2 index for heterogeneity. Interstudy heterogeneity was evaluated using Cochrane guide of heterogeneity and I^2 values, where significant heterogeneity was considered to be $I^2 > 50\%$ and $p <0.01$ (Deeks et al., 2021; Higgins et al., 2021). To further investigate heterogeneity, funnel plots were reported to assess potential publication bias by displaying a distribution of weight and odds ratios of each study. To assess the impact, effect and influence of key assumptions a sensitivity analysis was undertaken removing the three largest and three smallest studies of each form each pooled analysis (Thabane et al., 2013). This was done to review both small and large study effects on the overall significance of each analysis.

Results

Selection Criteria

For this analysis 2,890 studies were identified through database searching (Figure 1). Following the removal of duplicates and any papers where titles did not have any relevance to the outcome of interest, 196 papers were left to be screened. Of these, 47 were deemed eligible for full text review subsequent to analysis of abstracts. Removal was largely due to studies not reviewing hypertensive patients or outcome was based on alternate medication in conjunction with COVID-19. After, completing a full text review, a total of 22 studies were left for qualitative

synthesis and subsequently included in the metanalysis, with 20 and 15 studies eligible for mortality and severity
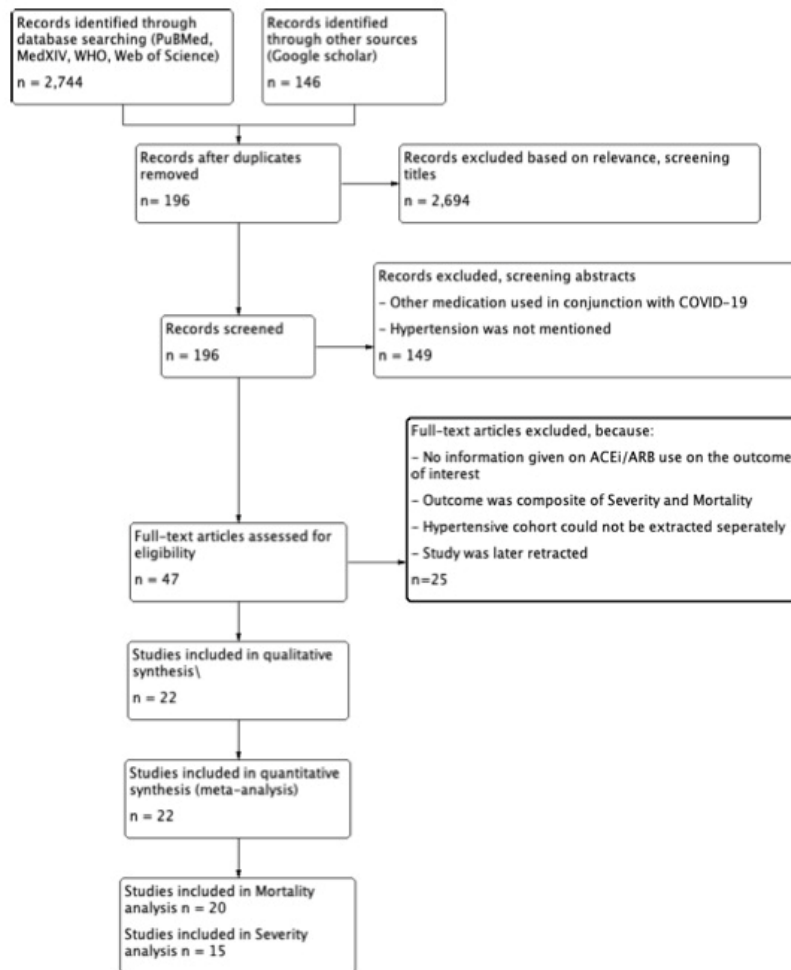
respectively (Figure 1).

Figure 1: PRISMA flow diagram to determine inclusion criteria for this study.

Of the 22 studies collected, median age of patients was 67 years old, ranging from 55-82 years of age (Table 2), percentage (%) of males in each study ranged from 44.4 %-76.3%, with a mean of 54.5 % (8,523 patients) for the pooled analysis. Twelve studies (3,101 total patients) were from hospitals within Wuhan, People's Republic of China (China) and the surrounding province of Hubei, China. The remaining studies were conducted in Europe (1,596 total patients), Asia (581 total patients) and America (10,506 total patients) where the majority of patients are a nationwide US study (Khera et al., 2021). In total 15,784 hypertensive COVID-19 patients were documented in the meta-analysis, with 8,035 taking ACEIs/ARBs treatment in comparison to 7,024 without (Table 2). Occasionally studies included propensity matched cohorts, these cohorts were not used in the study as they were not explicitly classified as hypertensive.

Table 2. Characteristics of study demographics

Author	Date of Study	Location	Total Hypertensive Patients	RAAS	Non-RAAS	Mean Age (IQR)	Sex (% male)

Bravi *et al.*	02/05/2020 - 24/05/2020	University Hospital of Ferrara/ Pescara Hospital	543	450	93	58	47.3
Chen et al.	10/01/2020 - 30/03/2020	Tongji Hospital, Wuhan, China	1,182	355	827	68	49.1
Cheng et al.	11/01/2020 - 20/02/2020	Hospitals from Hubei and Chongqing	70	23	47	68.5	54.3
Conversano et al.	27/02/2020 - 17/03/2020	San Raffaele Hospital, Milan	96	68	28	70.6 ± 11.8	76.3
Covino et al.	01/03/2021 - 31/03/2020	Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy	166	111	55	74(65-82)	66
Felice *et.al*	09/03/2020 - 31/03/2020	Italy	133	82	51	72.7	65.5
Feng et al.	17/01/2020 - 28/02/2020	University of South China in Hunan province	82	16	49	60	54.7
Gao *et al*	05/02/2020 - 05/03/2020	Huo Shen Shan Hospital- Wuhan China	850	183	527	64.24	52.1
Huang *et.al.*	07/02/2020 - 03/03/2020	Renmin Hospital of Wuhan University	50	20	30	60.21	54
Jung et al.	00/00/0000 -18/4/2020	Nationwide Korean Population	542	348	194	63.3	51
Khera et al.	05/01/2020 - 10/05/2020	Nationwide US study	7933	4587	3346	77	45.4
Li *et.al.*	15/01/2020 - 15/03/2020	Central Hospital of Wuhan	362	115	247	66(59-73)	52.2
Matsuzawa et al.	01/02/2020 - 20/05/2020	Six Hospitals in Kanagawa Prefecture, Japan	39	21	18	71 ± 12	69.2
Meng *et.al.*	11/01/2020 - 23/02/2020	Shenzhen Third People's Hospital	42	17	25	64.5 (55.8-69)	57.1

Negreira-Caamaño et al	03/03/2020 - 30/04/2020	University General Hospital of Ciudad Real, Spain	545	392	153	76.5	50
Reynolds et al.	01/03/2020 - 15/04/2020	New York University (NYU) Langone Health	2,573	1019	986	64(54-75)	50.8
Selcuk et l	N/A	Sultan Abdu¨lhamid Han Training and Research Hospital, Turkey	113	74	39	62.5 RAAS 67 Non-RAAS 58	47.8
Tan et al.	28/01/2020 - 08/04/2020	Sun Yat-sen University Hospital/Wuhan Union Hospital	100	31	69	67	49
Yang et.al	05/01/2020 - 03/03/2020	HPHTCM: Hubei Provincial Hospital of Traditional Chinese Medicine	126	43	83	66(61-73)	49.2
Zeng et al	05/01/2020 - 08/03/2020	Hankou Hospital, Wuhan China	75	28	47	67	55
Zhong et al.	17/01/2020 - 08/03/2020	Public Health Treatment Centre of Changsha and Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology	126	37	89	66.3	44.4
Zhou et al.	23/01/2020 - 10/02/2020	Wuhan Fourth Hospital, China	36	15	21	64.8	52.8

Mortality

In total, 20 studies contained data on mortality of COVID-19 patients with and without RAAS inhibitors. Of the studies, only three studies reported an association between RAAS inhibitor use and increased mortality from COVID-19 (8,212 out of 12,466 patients). Kera et al. (2020) reported the majority of these patients (7,933 patients) from a nationwide US study (OR 1.05 [0.92, 1.19]). Despite this, only one study (Selcuk et al., 2020) reported that this association was statistically significant (OR 6.31 [2.03, 19.58]). Of the studies reporting a decrease in COVID-19 mortality in RAAS inhibitor patients; 17 out of 20 studies (4,254 out of 12,466 patients); three papers indicated a statistically significant reduction (Chen et al., 2020; Felice et al., 2020; Negreira-Caamaño et al., 2020). Only one study did not specify date of study, and had a proportionately older cohort for RAAS inhibitors (67 years), to Non- RAAS (58yrs; Selçuk et al., 2020).

The meta-analysis of the 20 identified studies showed a statistically significant difference in mortality favouring RAAS inhibition in a random effect model (OR 0.68 [0.51, 0.90], p = 0.008 (Figure 2). The I^2 value for

this analysis was 62%, p =0.0008. This indicates heterogeneity between studies suggesting a possible uncertainty within the dataset. Removal of possible outliers within the study such as Selcuk et al. (2020) and Chen et al. (2020) did reduce heterogeneity within the study form significant to mild (62% to 27%), however, this did not affect the significance of the analysis (OR 0.73 [0.59, 0.89], p=0.003; *c.f.* Higgins et al., 2021).
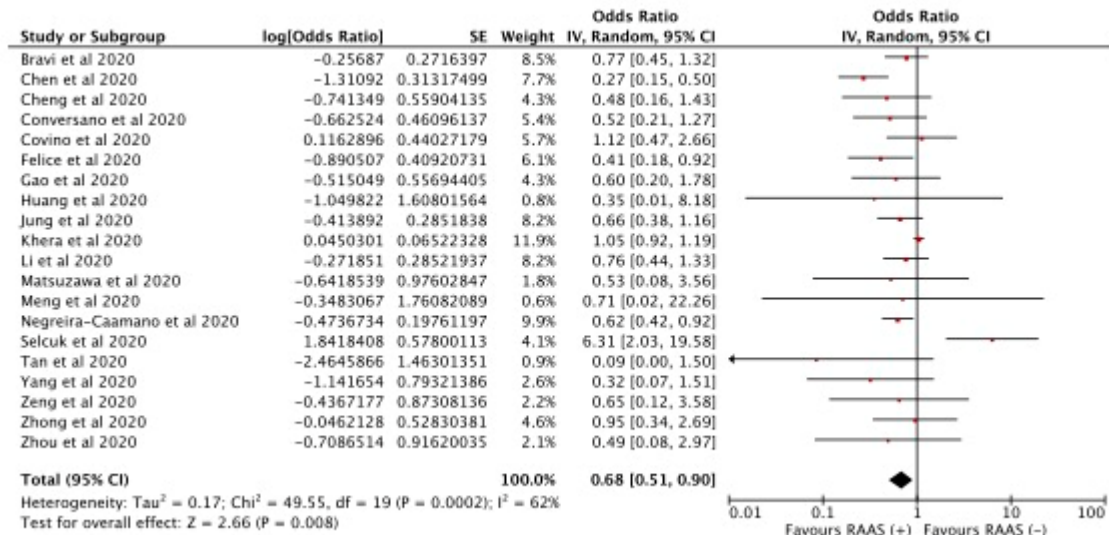

Figure 2: The pooled analysis of studies of interest, comparing the association between RAAS inhibitor use and mortality displayed as a Forest plot.

Following a sensitivity analysis for uncertainty (Adalsteinsson & Toumi, 2013), removing the three largest weighted studies (Bravi et al., 2020; Negreira-Caamaño et al., 2020; Khera et al., 2021), and the three smallest weighted studies (Huang et al., 2020; Meng et al., 2020; Tan et al., 2020) showed consistency in the results with no substantial variation (Table 3). Removal of these three largest and three smallest did not change the significance of the results, mortality was significantly decreased in the RAAS inhibitor cohort.

Table 3: Sensitivity analysis of overall study effect with revised Odds Ratios removing the three largest studies, and three smallest studies for Mortality of hypertensive COVID-19 patients.

Study Removal	Revised Odds Ratios	Confidence intervals (95% CI)
3 largest weighted studies	0.63	[0.44, 0.91]
3 smallest weighted studies	0.7	[0.52, 0.93]

Funnel plot analysis displayed an asymmetrical outline for mortality with a disproportionate number of studies reporting fewer deaths in RAAS inhibitor patients. The X-axis represents Odds Ratios, with the Y- axis illustrating sample size and index of precision of studies. As a result, outlying studies previously mentioned which altered the significance could indicate possible publication bias (Figure 3).
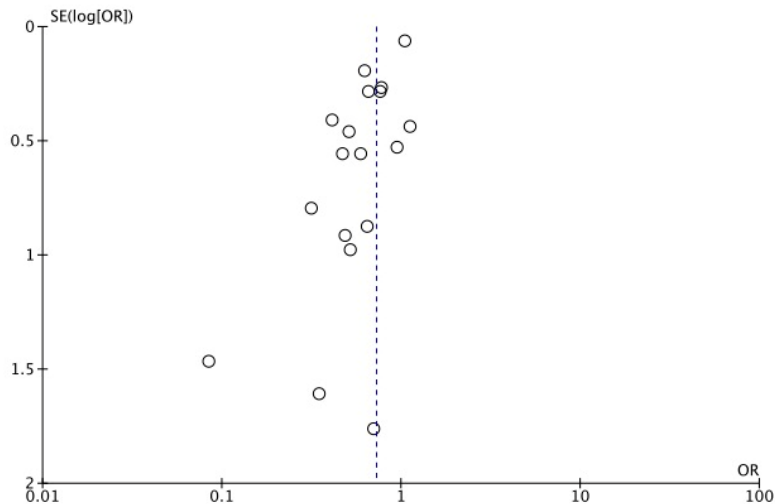
Figure 3: Funnel plot analysis of Mortality studies, displaying publication bias and symmetry of the selected sources for meta-analysis

Severity of symptoms

In total, 15 studies contained data on Severity of COVID-19 patients with and without RAAS inhibitors. Of the studies, seven studies reported an association between RAAS inhibitor use and increased severity of COVID-19 (4,607 out of 5,762 patients). Reynolds et al. (2020), reported the majority of these patients (2, 573 patients) from a New York health study (0.97 [0.77, 1.23]). Despite this, no studies reported that this association was statistically significant. Of the studies reporting a decrease in COVID-19 severity in RAAS inhibitor patients; 8 out of 15 studies (1,155 out of 5,762 patients); two studies indicated a statistically significant reduction (Cheng et al., 2020; Felice et al., 2020).

Pooled analysis in a random effect model of severity indicated no statistically significant difference in severity between RAAS vs Non-RAAS (OR 0.91 [0.63, 1.31], p = 0.62, I^2= 77% (Figure 4). Removal of possible outliers Negreira-Cammano et al. (2020), Zhou et al. (2020) & Covino et al. (2020) did not affect the outcome of the study, however, removal did reduce both significance and heterogeneity of the study. Wide confidence intervals across both mortality and severity suggest small study effect, due to possible sample size and variability in the population. Due to significant heterogeneity a random affects model was compiled to reduce study affects, however, analysis was also considered with a fixed effect model. A sensitivity analysis for uncertainty of overall study effect for severity (Adalsteinsson & Toumi, 2013), resulted in minor changed in Odds ratios, and a lower study effect following removal of the three larger studies (Gao et al., 2020; Li et al., 2020; Reynolds et al., 2020) (Table 4). Despite this, revised Odds ratios excluding the three largest studies (OR 0.79 [042, 1.49]), did not change the study outcome indicating a significant difference in severity of the RAAS cohort to the Non-RAAS cohort. The three largest weighted studies accounted for over 30% of the overall study. Removal of the three smallest studies did not significantly impact the Odds ratios or CI, maintaining consistency with the results (Feng et al., 2020; Negreira-Caamano et al., 2020; Tan et al., 2020 (Table 4).

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Bravi et al 2020	-0.25685729	0.2716397	3.9%	0.77 [0.45, 1.32]
Chen et al 2020	-1.31092017	0.31327499	3.0%	0.27 [0.15, 0.50]
Cheng et al 2020	-0.74134928	0.55904135	0.9%	0.48 [0.16, 1.43]
Conversano et al 2020	-0.6625243	0.46096137	1.4%	0.52 [0.21, 1.27]
Covino et al 2020	0.11628959	0.44027179	1.5%	1.12 [0.47, 2.66]
Felice et al 2020	-0.8905066	0.40920731	1.7%	0.41 [0.18, 0.92]
Gao et al 2020	-0.515049	0.55694405	0.9%	0.60 [0.20, 1.78]
Huang et al 2020	-1.0498221	1.60801564	0.1%	0.35 [0.01, 8.18]
Jung et al 2020	-0.4138917	0.2851838	3.6%	0.66 [0.38, 1.16]
Khera et al 2020	0.04503014	0.06522328	68.3%	1.05 [0.92, 1.19]
Li et al 2020	-0.2718506	0.28521937	3.6%	0.76 [0.44, 1.33]
Matsuzawa al 2020	-0.6418539	0.97602847	0.3%	0.53 [0.08, 3.56]
Meng et al 2020	-0.3483067	1.76082089	0.1%	0.71 [0.02, 22.26]
Negreira–Caamano et al 2020	-0.4736734	0.19761197	7.4%	0.62 [0.42, 0.92]
Selcuk et al 2020	1.84184079	0.57800113	0.9%	6.31 [2.03, 19.58]
Tan et al 2020	-2.4645866	1.46301351	0.1%	0.09 [0.00, 1.50]
Yang et al 2020	-1.141654	0.79321386	0.5%	0.32 [0.07, 1.51]
Zeng et al 2020	-0.4367177	0.87308136	0.4%	0.65 [0.12, 3.58]
Zhong et al 2020	-0.0462128	0.52830381	1.0%	0.95 [0.34, 2.69]
Zhou et al 2020	-0.7086514	0.91620035	0.3%	0.49 [0.08, 2.97]
Total (95% CI)			**100.0%**	**0.89 [0.80, 0.99]**

Heterogeneity: Chi^2 = 49.55, df = 19 (P = 0.0002); I^2 = 62%
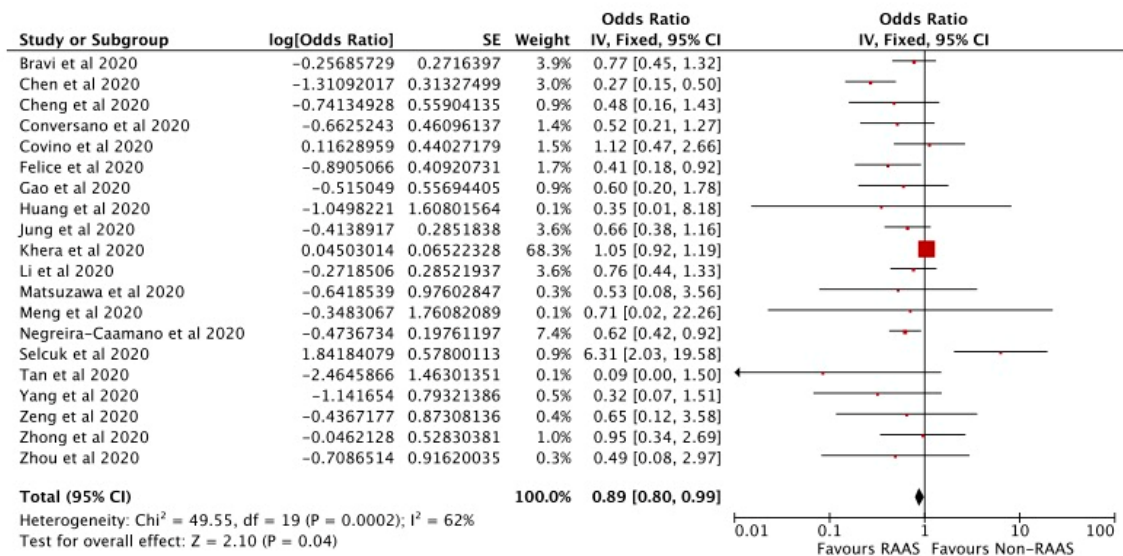Test for overall effect: Z = 2.10 (P = 0.04)

Figure 4: Pooled analysis using a random effects model for severity, the association between RAAS inhibitor use and hypertensive COVID-19 patient severity.

Table 4: Sensitivity analysis of overall study effect with revised Odds Ratios removing the three largest studies, and three smallest studies for severity of hypertensive COVID-19 patients.

Study Removal	Revised Odds Ratios	Confidence intervals (95% CI)
3 largest weighted studies	0.79	[0.42,1.49]
3 smallest weighted studies	0.95	[0.66, 1.37]

Severity funnel plot analysis was quantitively symmetrical with a moderately even distribution of weighting and Odds ratio amongst the papers (Figure 5). This quantitative symmetry would suggest that any inconsistencies during the sensitivity analysis (Table 4) was not affected by publication bias within the meta-analysis.
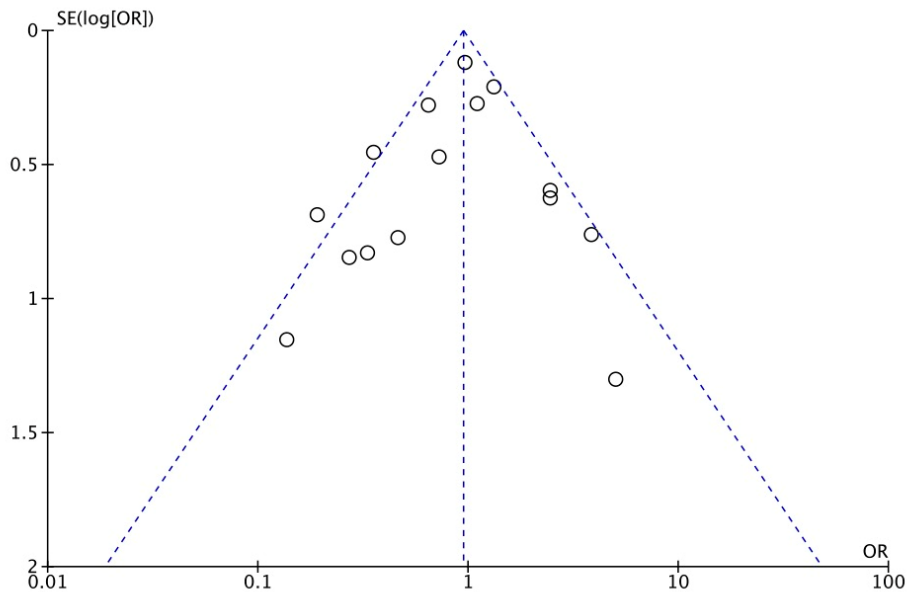
Figure 5: Funnel plot analysis of severity studies, displaying symmetry of the selected sources for meta-analysis.

Discussion

The use of RAAS inhibitors was associated with decreased mortality in hypertensive COVID-19 patients. Pooled analysis of the studies showed a statistically significant reduction in mortality (Figure2). In contrast, the meta-analysis found no statistically significant difference in the severity of hypertensive COVID-19 patients when using RAAS inhibitors in random effect models (Figure 4).

Removal of outliers Chen et al. (2020) and Selcuk et al. (2020) in the sensitivity analysis, did relatively reduce heterogeneity within mortality from substantial to mild (56% to 8%) indicating removal of inconsistencies that were not due to chance (Higgins et al., 2021). This variation in Selcuk et al. (2020) is likely due to discrepancies in age within Non-RAAS and RAAS cohort (58yrs vs 67yrs) (Table 2), moreover, only reviewing moderate to severe COVID-19 pneumonia patients, therefore, it is doubtful that study findings could be applied to all COVID-19 patients. Chen et al. (2020) suggests disparity in BMIs of the study population in comparison to other study cohorts with increased obesity, diabetes, chronic kidney disease and chronic heart disease (Reynolds et al., 2020). Funnel plots supported publication bias within the study, with reported asymmetry within mortality due to a bias towards favourable studies; however, there was no visible bias within severity (Sedgwick, 2013). Furthermore, outliers within severity analysis, Negreira-Cammano et al. (2020), could be due to the association of geographical mortality and common practice of anti-hypertensive use in Europe.

Previous systematic reviews have shown no trend or an increasing trend in mortality for RAAS hypertensive COVID-19 cases, however, these have not been shown to be statistically significant (Pranata et al., 2020; Richardson et al., 2020). As data availability increases, numerous studies have reported no association between RAAS inhibitors and adverse COVID-19, or an improvement of outcomes in hypertensive RAAS patients (Guo et al., 2020; Salah et al., 2020).

Randomised clinical trials (RCTs) have commenced to evaluate whether RAAS inhibitors should be discontinued in COVID-19 hypertensive patients. Out of the 10 trials currently registered, five are based in Europe whereas, four are based in the USA (Cohen et al., 2021). To date, both REPLACE-COVID and BRACE CORONA studies from the USA have reported no association between adverse effects of COVID-19 and RAAS inhibitor patients (Gault et al., 2021). Despite this, due to the need for high enrolment within the studies, REPLACE-COVID could not further identify any variation between ACE-is and ARBs with outcome, due to lack of participants (Cohen et al., 2021). The BRACE CORONA trial enrolled 500 participants from 34 regions of Brazil,

determining that discontinuation of RAAS inhibitors do not increase days alive and out of hospital. These trails are randomised, controlled and blinded reducing the limitations within observational studies. Rigid selection criteria, such as exclusion of patients with recent decompensated heart failure and use of more than three antihypertensives, will likely produce more precise and accurate results (Lopes et al., 2020).

Under normal hypertensive treatment practice, inhibition of the RAAS pathway aids in maintaining stable blood pressure. Both ACE and ACE2 perform vasodilator and vasoconstrictor functions, the activities of both enable the transformation of proteins providing vasodilatory, anti-inflammatory and an endothelial protective effect (Zhong et al., 2020). Due to the mechanisms of this pathway, it was speculated that inhibition through ACEi's and ARBs could upregulate ACE2 in the lungs (Liu et al., 2020).

Similar to SARS-CoV, SARS-CoV-2 needs the entry activators ACE2 receptor and the protease TMPRSS2, to assist its cell entry mechanisms (Kuster et al., 2020; Shang et al., 2020). In spite of these similarities, SARS-CoV-2 has 10-20-fold higher binding affinity to the ACE2 receptor (Busse et al., 2020). Considering this, upregulation of cellular ACE2 could facilitate an increase of SARS-CoV-2 infiltration, in turn, increasing severity and mortality of patients (Khashkhusha et al., 2020). Evidence supports that the use of ACE-is and ARB to inhibit the RAAS pathway in hypertensive patients upregulates ACE2r, therefore, potentially increasing binding sites for SARS-CoV-2 (Furuhashi et al., 2015). The docking site and cell entry of SARS-CoV-2 is a vital mechanism to understand the association between hypertensive patients and adverse clinical outcomes of COVID-19.

Genomic population data speculates that, further to this, ACE2 gene polymorphisms and variants could impact viral entry into the cell contributing to pulmonary and systemic injury, thereby affecting clinical outcome (Calcagnile et al., 2021). Despite this, there is no current evidence that supports that this upregulation as a result of SARS-CoV-2 viral entry is associated with increased susceptibility and risk of adverse effects in RAAS inhibitor patients. In addition, sudden removal of longstanding blood pressure medication could cause increased adverse risks, leading to unstable blood pressure and deterioration of cardiac function (Turnbull, et al., 2007; Zhang et al.,2020). This is particularly critical amongst the African American population, whose RAAS system has lower plasma renin activity, this is reflected in in-hospital blood pressure treatment given by clinicians (Doumas et al., 2020). As a result, RAAS inhibitors are used less frequently amongst Black patients, however, more Black patients are admitted to ICU or die with COVID-19. Its speculated, that this disparity could exceed social and economic imbalance, in place of the potential interconnection between ACE2 polymorphisms and the African American cohort (Doumas et al., 2020).

This meta-analysis supports more recent evidence, that inhibition of the RAAS system could be beneficial in downregulation of overexpressed Angiotensin II in hypertensive COVID-19 Patients (Meng et al., 2020). Within the RAAS system ACE is a generator of Angiotensin II, in comparison to ACE2 which negatively regulates the system reducing the levels of Angiotensin II (Crackower et al., 2002). Severe COVID-19 patients have been found to have abnormal Angiotensin II levels, related to hypertension, heart failure and both lung and renal dysfunction (Liu et al., 2020). Angiotensin II enhances regulation of inflammatory cytokines; this overexpression and upregulation is likely more damaging for COVID-19 patients. Overexpression of ACE2, upregulates production of angiotensin 1-7 through disintegration of angiotensin II. In turn, this promotes anti-inflammatory properties of 1-7 whilst downregulating the inflammatory properties of angiotensin II (Schiffrin et al., 2020). Therefore, use of ACE-is and ARBs inhibiting the RAAS pathway and reducing levels of IL-6 is potentially beneficial to the clinical outcome of hypertensive COVID-19 patients.

Furthermore, blockade of RAAS, boots inflammatory response though increased levels of CD3 and CD8 T cells in the peripheral blood weakening peak viral load (Meng et al., 2020). Viral load has been strongly associated with disease severity, in particular the development of lung failure and acute respiratory distress syndrome (ARDS); during many cases this progression led to ICU admission and mechanical ventilation (Liu et al., 2020). A lower peak viral load through inhibition of RAAS could reduce the most adverse outcomes during hospitalisation. Subsequently, SARS-CoV-2 was shown to downregulate the expression of ACE2, increasing levels of Angiotensin II; therefore, reduction of ACE generating angiotensin II through inhibition could perhaps explain the survival benefit to hypertensive COVID-19 cases (Salah et al., 2020).

In addition, angiotensin II has been proposed to reduce overall viral entry of SARS-CoV-2. Initially, via competition for binding sites on ACE2, reducing the available viral entry for SARS-CoV-2 (Busse et al., 2020; Schiffrin et al., 2020). Secondly, in both animal and human models in vitro exogenous Angiotensin II is thought to bind to

the membrane bound AT-1 receptor which is suspected to internally downregulate ACE2. Following this, the angiotensin II AT-1 receptor binding is proposed to cause receptor dependent destruction of ACE2 into lysosomal degradation (Busse et al., 2020). Ultimately, these disruptions could result in reduced viral entry, improving outcomes for hypertensive patients inhibiting RAAS.

Following this analysis, there is no significant association between RAAS inhibitors and increased likelihood of adverse outcomes in hypertensive COVID-19 patients. This supports guidance by medical councils and the world health organisation to continue the medications in hospital treatment (WHO, 2020). In addition, the possibility of increased adverse risks form the sudden removal of longstanding blood pressure medication could lead to unstable blood pressure and deterioration of cardiac function (Turnbull, et al., 2007; Zhang et al.,2020).

Intensive care physicians have observed that blood pressure physiology in COVID is different to other critically unwell patients with severe inflammation. It is rare for patients to require ICU admission for blood pressure maintenance unless the disease is complicated by bacterial infection or thrombus. Some patients have required the resumption of their normal anti-hypertensive medications while being ventilated. This is a very unusual practice in intensive care, due to the mechanical ventilation and sedatives used to facilitate this cause hypotension (Hanidziar & Bittner, 2020). More research is needed to determine if the RAAS system could play a role in this unusual maintenance of normal blood pressure despite widespread inflammation.

As research progresses, there is a possibility of these effects changing with the ever moving, fast paced COVID-19 pandemic. New variants of COVID-19 could affect the binding and viral entry of the virus. Bosso et al. (2020), suggests that gene variants withing the ACE2 receptor could impact susceptibility, reducing the effectiveness of the ACE2 receptor and decreasing the infectivity. Human genetic variation has previously been associated with disease progression such as the variation in CCR5, affecting the outcome of HIV advancing to AIDS (Gibson et al., 2020). Frequent variants of ACE genes, including ACE insertion and deletion are among the most notable human polymorphisms. Individuals with a deletion-deletion genotype, are found to have higher ACE blood levels with increased likelihood of ARDS and pneumonia in COVID-19 patients (Gómez et al., 2020). Additional research is needed to further understand the association between both genetic and viral variants in the hypertensive cohort along with all COVID-19 patients.

The ethnicity, race and geographical distribution of populations is a likely factor in the variation amongst study results. Negreira-Caamaño et al. (2020) hightlights the variation in use of antihypertensives between geographical study populations, in Europe use of ACE-i/ARB are the most common medication, as opposed to China where calcium channel blockers (CCB) are more frequently used (Wang et al., 2018). Chen et al. (2020) suggests an association between antihypertensive medication used in conjunction with CCBs, could alter likelihood of ICU admission and mortality. As a result, countries that favour use of CCB as standard medical practice as opposed to ACE-is could cause inconsistencies within the pooled analysis (Wang et al., 2011; Jarari et al., 2015). Both American studies were the only studies that reported race as a considerable factor within study characteristics. Reynolds et al., (2020) reported 35% (1,537/4,357 patients) of the population Black or Hispanic and Khera et al., (2020) reporting 22% (505/2,263) of the cohort African American, Native American or Hispanic. In consideration of the higher proportion of Black patients reviewed, the potential association of lower plasma renin activity in Black populations could impact the significance of both study outcomes (Doumas et al., 2020). Despite this, no other studies reported a race as a factor, therefore causing clinical variation within the selection of patients studied. Different study cohorts also had variation in levels of infection per person, populations with higher prevalence of infection and use of anti-hypertensive are likely to have increased adverse results (Negreira-Caamaño et al., 2020).

Despite the pooled analysis showing a reduced risk of mortality when using RAAS hypertensive COVID-19 patients and no statistically significant association between severity of cases, limitations and bias within the studies must be considered. Overall, more studies reported beneficial outcomes of RAAS inhibitors creating bias within the clinical advice given. All studies were retrospective observational studies conducted under unregulated and pressurised time frames due to the urgency of the pandemic, as a result they have not been adapted for cofounders (such as sex, age, background) (Cohen et al., 2021). Consequently, the nature of observational trials removes the possibility of quality assessing all data recorded.

The majority of patients had other comorbidities that could impact severity and outcome of the virus. Hypertension, diabetes and ischaemic heart disease are significantly over represented among COVID-19 cases all

of which are regularly treated with RAAS inhibitors (de Abajo et al., 2020). Due to the majority of clinical cases affected being over the age of 65, age is likely to play a modulating factor affecting clinical outcome, disproportionately skewing the distribution of cases. Recognising this, adjustments to any cofounders could result in varying conclusions. Despite all cases included in the study having confirmed COVID-19 test through PCR, there is chance of sampling errors such as, false negative tests recorded within any of the studies (Richardson et al., 2020; López-Otero et al., 2021). Ultimately, this could impact the number of cases infected which haven't been considered in results.

In account of the biologically comparable mechanisms of both ACE-i and ARB inhibitors, a subgroup analysis of each inhibitor association was not assessed for this thesis. Subsequent to further quality assessed results becoming available, studies could review subgroup analyses, such as co-morbidity and overall significance of ACE-is and ARBs separately. This could also be reviewed in subgroups according to risk factor such as Age, sex, and race to consider increased affect across varying cofounders (de Abajo et al., 2020; Williams & Zhang, 2020).

As of the 3rd of May 2021, there have been 152,933,322 cases of COVID-19, this meta-analysis reviews data form less than 20,000 patients (< 0.01%) of global cases. It is vital to acknowledge that major geographical regions were not considered in this analysis, as data was taken form 4 out of 10 of the most affected countries (China, USA, Italy and Spain). In view of the small sample size and geographical constraints, it is questionable that these results could be generalised globally for regions such as India (2nd) and Eastern Europe (Russia 6th), which have different population genetics and existing hypertension practices (Dong et al., 2021). These results support, that using RAAS inhibitors can decrease mortality, if not severity of disease, in hypertensive COVID-19 patient. Following these results there would not be sufficient evidence to remove longstanding RAAS inhibitor anti-hypertensive medication in COVID-19 patients, as this suggests no association between increased adverse outcomes in patients using ACE-i/ARBs (Turnbull, et al., 2007; Zhang et al.,2020). Despite this, the majority of patients assessed had other comorbidities such as, diabetes and heart disease which are regularly treated with RAAS inhibitors (de Abajo et al., 2020). Both observational and randomised control studies are needed to assess association between other specific comorbidities, the genomic variation within ACE2 and RAAS inhibition. Ultimately, this represents a short-term assessment of clinical outcomes from the impact of anti-hypertensive treatments, long-term prospective studies investigating the effects of these treatments are still needed. Fundamentally, with current research RAAS inhibitors cannot be associated as either a friend or foe of all patients with the COVID-19 infection, in fact inhibitors could truly be one man's friend and another's enemy. Nonetheless, this pathway must be recognised as a considerable factor in the viral entry of SARS-CoV-2 and subsequently in hospital treatment.

Acknowledgments

References

Adalsteinsson, E., & M. Toumi, 2013. Benefits of probabilistic sensitivity analysis – a review of NICE decisions. Journal of Market Access & Health Policy 1: 21240.

Bosso, M., T. A. Thanaraj, M. Abu-Farha, M. Alanbaei, J. Abubaker, & F. Al-Mulla, 2020. The two faces of ACE2: The role of ACE2 receptor and its polymorphisms in hypertension and COVID-19. Molecular Therapy: Methods & Clinical Development 18: 321–327.

Bravi, F., M. E. Flacco, T. Carradori, C. A. Volta, G. Cosenza, A. De Togni, C. A. Martellucci, G. Parruti, L. Mantovani, & L. Manzoli, 2020. 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 15: 1-10.

Busse, L. W., J. H. Chow, M. T. McCurdy, & A. K. Khanna, 2020. COVID-19 and the RAAS - A potential role for angiotensin II?. Critical Care 24: 1–4.

Calcagnile, M., P. Forgez, A. Iannelli, C. Bucci, M. Alifano, & P. Alifano, 2021. Molecular docking simulation reveals ACE2 polymorphisms that may increase the affinity of ACE2 with the SARS-CoV-2 spike protein. Biochimie 180: 143–148.

Chen, C., F. Wang, P. Chen, J. Jiang, G. Cui, N. Zhou, F. Moroni, J. J. Moslehi, E. Ammirati, & D. W. Wang, 2020. Mortality and pre-hospitalization use of renin-angiotensin system inhibitors in hypertensive COVID-19 Patients. Journal of the American Heart Association 9: e017736.

Cheng, X., G. Cai, X. Wen, L. Gao, D. Jiang, M. Sun, S. Qin, J. Zhou, & D. Zhang, 2020. Clinical characteristics and fatal outcomes of hypertension in patients with severe COVID-19. Aging 12: 23436–23449.

Cohen, J. B., A. M. South, H. A. Shaltout, M. R. Sinclair, & M. A. Sparks, 2021. Renin–angiotensin system blockade in the COVID-19 pandemic. Clinical Kidney Journal 14: i48–i59.

Crackower, M. A., R. Sarao, A. J. Oliveira-dos-Santos, J. Da Costa, & L. Zhang, 2002. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 417: 822–828.

de Abajo, F. J., S. Rodríguez-Martín, V. Lerma, G. Mejía-Abril, M. Aguilar, A. García-Luque, L. Laredo, O. Laosa, G. A. Centeno-Soto, M. Ángeles Gálvez, M. Puerro, E. González-Rojano, L. Pedraza, I. de Pablo, F. Abad-Santos, L. Rodríguez-Mañas, M. Gil, A. Tobías, A. Rodríguez-Miguel, D. Rodríguez-Puyol, D. Barreira-Hernandez, P. Zubiaur, E. Santos-Molina, E. Pintos-Sánchez, M. Navares-Gómez, R. M. Aparicio, V. García-Rosado, C. Gutiérrez-Ortega, C. Pérez, A. Ascaso, & C. Elvira, 2020. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. The Lancet 395: 1705–1714.

Deeks JJ, J.P.T. Higgins, D.G. Altman (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021 [www.training.cochrane.org/handbook]. Accessed from 24 Feb 2021

Dong E., H. Du, L. Gardner, 2021. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infectious Diseases 20: 533-534.

Doumas, M., D. Patoulias, A. Katsimardou, K. Stavropoulos, K. Imprialos, & A. Karagiannis, 2020. COVID19 and increased mortality in African Americans: socioeconomic differences or does the renin angiotensin system also contribute?. Journal of Human Hypertension 34: 764–767.

Felice, C., C. Nardin, G. L. Di Tanna, U. Grossi, E. Bernardi, L. Scaldaferri, M. Romagnoli, L. Tonon, P. Cavasin, S. Novello, R. Scarpa, A. Farnia, E. De Menis, R. Rigoli, F. Cinetto, P. Pauletto, C. Agostini, & M. Rattazzi, 2020. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: Results from an Italian cohort of 133 hypertensives. American Journal of Hypertension 33: 944–948.

Feng, Z., J. Li, S. Yao, Q. Yu, W. Zhou, X. Mao, H. Li, W. Kang, X. Ouyang, J. Mei, Q. Zeng, J. Liu, ; Xiaoqian Ma, P. Rong, W. Wang, 2020. The Use of Adjuvant Therapy in Preventing Progression to Severe Pneumonia in Patients with Coronavirus Disease 2019: A Multicenter Data Analysis. MedRxiv.

Fletcher, J., 2007. What is Heterogenity and why is it important. British Medical Journal 334: 94–96.

Furuhashi, M., N. Moniwa, T. Mita, T. Fuseya, S. Ishimura, K. Ohno, S. Shibata, M. Tanaka, Y. Watanabe, H. Akasaka, H. Ohnishi, H. Yoshida, H. Takizawa, S. Saitoh, N. Ura, K. Shimamoto, & T. Miura, 2015. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. American Journal of Hypertension 28: 15–21.

Gao, C., Y. Cai, K. Zhang, L. Zhou, Y. Zhang, X. Zhang, Q. Li, W. Li, S. Yang, X. Zhao, Y. Zhao, H. Wang, Y. Liu, Z. Yin, R. Zhang, R. Wang, M. Yang, C. Hui, W. Wijns, J. W. McEvoy, O. Soliman, Y. Onuma, P. W. Serruys, L. Tao, & F. Li, 2020. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. European Heart Journal 41: 2058–2066.

Gault, N., M. Esposito-Farese, M. Revest, J. Inamo, A. Cabie, É. Polard, J.-S. Hulot, J. Ghosn, C. Chirouze, L. Deconinck, J.-L. Diehl, J. Poissy, O. Epaulard, B. Lefèvre, L. Piroth, E. de Montmollin, E. Oziol, M. Etienne, C. Laouenan, P. Rossignol, D. Costagliola, E. Vidal-Petiot, & French-Covid cohort investigators and study group, 2021. Chronic use of Renin-Angiotensin-Aldosterone-System blockers and mortality in COVID-19: a multicenter prospective cohort and literature review. Fundamental & Clinical Pharmacology.

Gibson, W. T., D. M. Evans, J. An, & S. J. Jones, 2020. ACE 2 coding variants: A potential X-linked risk factor for COVID-19 disease. bioRxiv.

Gómez, J., G. M. Albaiceta, M. García-Clemente, C. López-Larrea, L. Amado-Rodríguez, I. Lopez-Alonso, T. Hermida, A. I. Enriquez, P. Herrero, S. Melón, M. E. Alvarez-Argüelles, J. A. Boga, S. Rojo-Alba, E. Cuesta-Llavona, V. Alvarez, R. Lorca, & E. Coto, 2020. Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. Gene 762: 145102.

Guo, X., Y. Zhu, & Y. Hong, 2020. Decreased Mortality of COVID-19 with Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients with Hypertension: A Meta-Analysis. Hypertension. 76: E13–E14.

Hanidziar, D., & E. A. Bittner, 2020. Hypotension, Systemic Inflammatory Response Syndrome, and Coronavirus Disease 2019: A Clinical Conundrum. Anesthesia and Analgesia.

Higgins JPT, J. Thomas, J. Chandler, M. Cumpston , T. Li , MJ. Page, VA. Welch (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021 [www.training.cochrane.org/handbook]. Accessed 24 Feb 2021.

Huang, Z., J. Cao, Y. Yao, X. Jin, Z. Luo, Y. Xue, C. Zhu, Y. Song, Y. Wang, Y. Zou, J. Qian, K. Yu, H. Gong, & J. Ge, 2020. The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension. Annals of Translational Medicine 8: 430–440.

Jarari, N., N. Rao, J. R. Peela, K. A. Ellafi, S. Shakila, A. R. Said, N. K. Nelapalli, Y. Min, K. D. Tun, S. I. Jamallulail, A. K. Rawal, R. Ramanujam, R. N. Yedla, D. K. Kandregula, A. Argi, & L. T. Peela, 2015. A review on prescribing patterns of antihypertensive drugs. Clinical Hypertension 22: 1–8.

Khashkhusha, T. R., J. S. K. Chan, & A. Harky, 2020. ACE inhibitors and COVID-19: We don't know yet. Journal of Cardiac Surgery 35: 1172–1173.

Khera, R., C. Clark, Y. Lu, Y. Guo, S. Ren, B. Truax, E. S. Spatz, K. Murugiah, Z. Lin, S. B. Omer, D. Vojta, & H. M. Krumholz, 2020. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19. MedRxiv.

Kuster, G. M., O. Pfister, T. Burkard, Q. Zhou, R. Twerenbold, P. Haaf, A. F. Widmer, & S. Osswald, 2020. SARS-CoV2: Should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19?. European Heart Journal 41: 1801–1803.

Li, G., R. Hu, & X. Zhang, 2020. Antihypertensive treatment with ACEI/ARB of patients with COVID-19 complicated by hypertension. Hypertension Research 43: 588–590.

Liu, Y., Y. Yang, C. Zhang, F. Huang, F. Wang, J. Yuan, Z. Wang, J. Li, J. Li, C. Feng, Z. Zhang, L. Wang, L. Peng, L. Chen, Y. Qin, D. Zhao, S. Tan, L. Yin, J. Xu, C. Zhou, C. Jiang, & L. Liu, 2020. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Science China Life Sciences 63: 364–374.

Lopes, R. D., A. V. S. Macedo, P. G. M. de Barros e Silva, R. J. Moll-Bernardes, A. Feldman, G. D'Andréa Saba Arruda, A. S. de Souza, D. C. de Albuquerque, L. Mazza, M. F. Santos, N. Z. Salvador, C. M. Gibson, C. B. Granger, J. H. Alexander, & O. F. de Souza, 2020. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–The BRACE CORONA Trial. American Heart Journal 226: 49–59.

López-Otero, D., J. López-Pais, C. E. Cacho-Antonio, P. J. Antúnez-Muiños, T. González-Ferrero, M. Pérez-Poza, Ó. Otero-García, B. Díaz-Fernández, M. Bastos-Fernández, N. Bouzas-Cruz, X. C. Sanmartín-Pena, A. Varela-Román, M. Portela-Romero, L. Valdés-Cuadrado, A. Pose-Reino, & J. R. González-Juanatey, 2021. Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. CARDIOVID registry. Revista Espanola de Cardiologia (English Edition) 74: 175–182.

Meng, J., G. Xiao, J. Zhang, X. He, M. Ou, J. Bi, R. Yang, W. Di, Z. Wang, Z. Li, H. Gao, L. Liu, & G. Zhang, 2020. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerging Microbes and Infections 9: 757–760.

Negreira-Caamaño, M., J. Piqueras-Flores, J. Martínez-DelRio, P. Nieto-Sandoval-Martin-DeLaSierra, D. Aguila-Gordo, C. Mateo-Gomez, D. Salas-Bravo, M. Rodriguez-Martinez, & M. Negreira-Caamaño, 2020. Impact of Treatment with Renin–Angiotensin System Inhibitors on Clinical Outcomes in Hypertensive Patients Hospitalized with COVID-19. High Blood Pressure and Cardiovascular Prevention 27: 561–568.

Pranata, R., H. Permana, I. Huang, M. A. Lim, N. N. M. Soetedjo, R. Supriyadi, A. Y. Soeroto, A. A. Alkatiri, D. Firman, & A. A. Lukito, 2020. The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14: 983–990.

Reynolds, H. R., S. Adhikari, C. Pulgarin, A. B. Troxel, E. Iturrate, S. B. Johnson, A. Hausvater, J. D. Newman, J. S. Berger, S. Bangalore, S. D. Katz, G. I. Fishman, D. Kunichoff, Y. Chen, G. Ogedegbe, & J. S. Hochman, 2020. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. New England Journal of Medicine 382: 2441–2448.

Richardson, S., J. S. Hirsch, M. Narasimhan, J. M. Crawford, T. McGinn, K. W. Davidson, D. P. Barnaby, L. B. Becker, J. D. Chelico, S. L. Cohen, J. Cookingham, K. Coppa, M. A. Diefenbach, A. J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T. G. Harvin, D. A. Hirschwerk, E. J. Kim, Z. M. Kozel, L. M. Marrast, J. N. Mogavero, G. A. Osorio, M. Qiu, & T. P. Zanos, 2020. Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City

Area. JAMA 323: 2052–2059.

Salah, H. M., G. Calcaterra, & J. L. Mehta, 2020. Renin-Angiotensin System Blockade and Mortality in Patients With Hypertension and COVID-19 Infection. Journal of Cardiovascular Pharmacology and Therapeutics 25: 503–507.

Schiffrin, E. L., J. M. Flack, S. Ito, P. Muntner, & R. C. Webb, 2020. Hypertension and COVID-19. American Journal of Hypertension 33: 373–374.

Sedgwick, P., 2013. Meta-analyses: How to read a funnel plot. BMJ 346: fi342.

Selçuk, M., T. Çınar, M. Keskin, V. Çiçek, Ş. Kılıç, B. Kenan, S. Doğan, S. Asal, N. Günay, E. Yıldırım, Ü. Keskin, & A. L. Orhan, 2020. Is the use of ACE/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients?. Clinical and Experimental Hypertension 42: 738–742.

Shang, J., Y. Wan, C. Luo, G. Ye, Q. Geng, A. Auerbach, & F. Li, 2020. Cell entry mechanisms of SARS-CoV-2. Proceedings of the National Academy of Sciences 117: 11727–11734.

Tan, N.-D., Y. Qui, X.-Bi. Xing, S. Ghosh, M.-H. Chen, & R. Mao, 2020b. Associations between Angiotensin-Converting enzyme inhibitors and Angiotensin II Receptor Blocker use, gastrointestinal symptoms, and mortality among patients With COVID-19. Gastroenterology 159: 1170–1172.

Thabane, L., L. Mbuagbaw, S. Zhang, Z. Samaan, M. Marcucci, C. Ye, M. Thabane, L. Giangregorio, B. Dennis, D. Kosa, V. B. Debono, R. Dillenburg, V. Fruci, M. Bawor, J. Lee, G. Wells, & C. H. Goldsmith, 2013. A tutorial on sensitivity analyses in clinical trials: The what, why, when and how. BMC medical research methodology 13: 1–12.

Turnbull, F., B. Neal, & M. Pfeffer, 2007. Blood pressure-dependent and independent effects of agents that inhibit the renin–angiotensin system. Journal of Hypertension 25: 952–958.

Wang, J. G., K. Kario, T. Lau, Y. Q. Wei, C. G. Park, C. H. Kim, J. Huang, W. Zhang, Y. Li, P. Yan, & D. Hu, 2011. Use of dihydropyridine calcium channel blockers in the management of hypertension in Eastern Asians: A scientific statement from the Asian Pacific Heart Association. Hypertension Research. 34: 423–430.

Wang, Z., Z. Chen, L. Zhang, X. Wang, G. Hao, Z. Zhang, L. Shao, Y. Tian, Y. Dong, C. Zheng, J. Wang, M. Zhu, W. S. Weintraub, & R. Gao, 2018. Status of hypertension in China: Results from the China hypertension survey, 2012-2015. Circulation 137: 2344–2356.

Weber, F., G. Knapp, K. Ickstadt, G. Kundt, & Ä. Glass, 2020. Zero-cell corrections in random-effects meta-analyses. Research Synthesis Methods 11: 913–919.

Williams, B., & Y. Zhang, 2020. Hypertension, renin–angiotensin–aldosterone system inhibition, and COVID-19. The Lancet 395: 1671–1673.

Yang, G., Z. Tan, L. Zhou, M. YAng, L. Peng, J. Liu, J. Cai, R. Yang, J. HAn, Y. Huang, & S. He, 2020. Angiotensin II Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors Usage is Associated with Improved Inflammatory Status and Clinical Outcomes in COVID-19 Patients With Hypertension. MedRxiv.

Zhang, J., M. Wang, W. Ding, & J. Wan, 2020. The interaction of RAAS inhibitors with COVID-19: Current

progress, perspective and future. Life Sciences 257: 118142.

Zhong, Y., L. Zhao, G. Wu, C. Hu, C. Wu, M. Xu, H. Dong, Q. Zhang, G. Wang, B. Yu, J. Lv, C. Wu, S. Zhang, C. Cao, L. Shu, Y. Pan, X. Liu, & F. Wu, 2020. Impact of renin–angiotensin system inhibitors use on mortality in severe COVID-19 patients with hypertension: a retrospective observational study. Journal of International Medical Research 48: 1–11.

Zhou, X., J. Zhu, & T. Xu, 2020. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin–angiotensin system inhibitors. Clinical and Experimental Hypertension 42: 656–660.