

Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study

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Aims

It remains unknown whether the treatment of hypertension influences the mortality of patients diagnosed with coronavirus disease 2019 (COVID-19).

Methods and results

This is a retrospective observational study of all patients admitted with COVID-19 to Huo Shen Shan Hospital. The hospital was dedicated solely to the treatment of COVID-19 in Wuhan, China. Hypertension and the treatments were stratified according to the medical history or medications administered prior to the infection. Among 2877 hospitalized patients, 29.5% (850/2877) had a history of hypertension. After adjustment for confounders, patients with hypertension had a two-fold increase in the relative risk of mortality as compared with patients without hypertension [4.0% vs. 1.1%, adjusted hazard ratio (HR) 2.12, 95% confidence interval (CI) 1.17–3.82, $P = 0.013$]. Patients with a history of hypertension but without antihypertensive treatment ($n = 140$) were associated with a significantly higher risk of mortality compared with those with antihypertensive treatments ($n = 730$) (7.9% vs. 3.2%, adjusted HR 2.17, 95% CI 1.03–4.57, $P = 0.041$). The mortality rates were similar between the renin–angiotensin–aldosterone system (RAAS) inhibitor (4/183) and non-RAAS inhibitor (19/527) cohorts (2.2% vs. 3.6%, adjusted HR 0.85, 95% CI 0.28–2.58, $P = 0.774$). However, in a study-level meta-analysis of four studies, the result showed that patients with RAAS inhibitor use tend to have a lower risk of mortality (relative risk 0.65, 95% CI 0.45–0.94, $P = 0.02$).

Conclusion

While hypertension and the discontinuation of antihypertensive treatment are suspected to be related to increased risk of mortality, in this retrospective observational analysis, we did not detect any harm of RAAS inhibitors in patients infected with COVID-19. However, the results should be considered as exploratory and interpreted cautiously.

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Keywords

COVID-19 • Angiotensin-converting enzyme inhibitors (ACEIs) • Angiotensin receptor blockers (ARBs)
• Antihypertensive regimen

Introduction

Coronavirus disease 2019 (COVID-19) is a current pandemic disease caused by the positive-sense RNA virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Along with the highly infectious capacity of the virus, the mortality rates have been reported to range from 1% to >5%.¹ It has been reported that patients with COVID-19 and hypertension may have an increased risk for adverse outcomes in unadjusted epidemiological studies summarizing the characteristics of the COVID-19 epidemic in China. Despite limited sample sizes, previous studies have reported that hypertension had a hazard ratio (HR) of 1.70 [95% confidence interval (CI) 0.92–3.14] to 3.05 (95% CI 1.57–5.92) for mortality, respectively.^{2,3} However, neither of these previous studies has adjusted for confounding factors, for example, age, which is emerging as the strongest predictor of COVID-19-related death.^{3,4}

Angiotensin-converting enzyme 2 (ACE2) is required for viral entry of SARS-CoV-2.⁵ ACE2 is widely expressed in the human body, with expression found in the gastrointestinal tract, heart, and kidney, and alveolar cells in the lungs.^{6,7} Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the two types of renin–angiotensin–aldosterone system (RAAS) inhibitors widely used for treating hypertension, and heart and renal failure. There are reports in animal models⁸ and humans⁹ suggesting that the expression of ACE2 may be increased after treatment with an ACEI or ARB (some reports incriminated only ARBs¹⁰), which might augment patients' susceptibility to viral host cell entry and propagation.¹¹ Although the effects of ACEIs or ARBs on ACE2 in humans are still inconclusive, previous findings have led to a growing concern that ACEIs or ARBs may increase (or decrease) mortality in patients with COVID-19.^{12,13} Therefore, evidence of the impact of these medications in patients with COVID-19 is urgently needed.

Here, we investigated 2877 consecutive patients admitted to Huo Shen Shan Hospital, which is a hospital dedicated solely to the treatment of COVID-19, in Wuhan, China. We tested the hypothesis that treatment of hypertension, especially with RAAS inhibitors, might impact on the mortality of patients with COVID-19.

Methods

Study design and participants

This is a retrospective observational study comparing the association of both hypertensive status and antihypertensive treatment class with mortality among hospitalized patients with COVID-19. All patients admitted to Huo Shen Shan Hospital, Wuhan, China, from 5 February to 15 March 2020, with confirmed COVID-19 were included in this study. Huo Shen Shan Hospital was opened by the government on 5 February 2020, and assigned to treat exclusively COVID-19 patients. Patients with COVID-19 included in this study were diagnosed according to World Health

Organization interim guidance and Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia from the the National Health Commission of China.^{14,15} In brief, clinical manifestations of COVID-19 are defined as the development of fever and/or respiratory symptoms; computed tomography (CT) imaging showing characteristics consistent with COVID-19; or normal or decreased white blood cell (WBC) count, and normal or decreased lymphocyte count in the early stage of the disease. Patients with a suspicious epidemiological history (i.e. contact with novel coronavirus-infected people or patients from Wuhan who have fever or respiratory symptoms) plus any two clinical manifestations or no clear epidemiological history but with all three clinical manifestations were considered as possible COVID-19 case. Patients who were considered as possible COVID-19 cases, with or without laboratory confirmation of SARS-Cov-2 infection, were admitted to the Huo Shen Shan Hospital.

The confirmation of SARS-Cov-2 infection was defined as suspect cases with one of the following serological findings: (i) real-time fluorescent reverse transcription–PCR (RT–PCR) positive for new coronavirus nucleic acid; (ii) viral gene sequence highly homologous to known new coronaviruses; and (iii) SARS-Cov-2-specific IgM or IgG are detected in serum, or SARS-Cov-2-specific IgG is detectable or reaches a titration of at least a four-fold increase during convalescence compared with the acute phase.

This study was approved by the National Health Commission of China and the institutional review board at Huo Shen Shan Hospital (Wuhan, China). Written informed consent was waived by the ethics committee of the designated hospital for patients with emerging infectious diseases.

Data collection

Patients' demographic characteristics and clinical data (symptoms, comorbidities, laboratory findings, and outcomes) during hospitalization were collected from electronic medical records by two investigators (R.Z. and Y.C.). All data were independently reviewed and entered into the computer database by two analysts (C.G. and Y.C.).

Clinical endpoints

The primary endpoint was all-cause mortality during hospitalization. Other endpoints included the time elapsed between onset of symptoms and discharge, the rates of use of invasive mechanical ventilation, and the severity of COVID-19. The severity of COVID-19 was categorized as mild, severe, or critical. Mild included non-pneumonia and mild pneumonia cases. Severe was characterized by dyspnoea, respiratory frequency ≥ 30 /min, blood oxygen saturation $\leq 93\%$, PaO₂/FiO₂ ratio < 300 , and/or lung infiltrates $> 50\%$ within 24–48 h. Critical cases were defined as respiratory failure requiring mechanic ventilation, septic shock, and/or multiple organ dysfunction/failure.^{1,16} The final date of follow-up was 1 April 2020 and the median duration of follow-up (hospitalization) was 21 (12–32) days.

The diagnosis of hypertension was given by the patient's physician prior to the infection with SARS-CoV-2. These data were collected from patients' documented medical files (e.g. the diagnosed patients with antihypertensive drugs and blood pressure $< 140/90$ mmHg upon admission were still identified as 'with a history of hypertension'). There was no

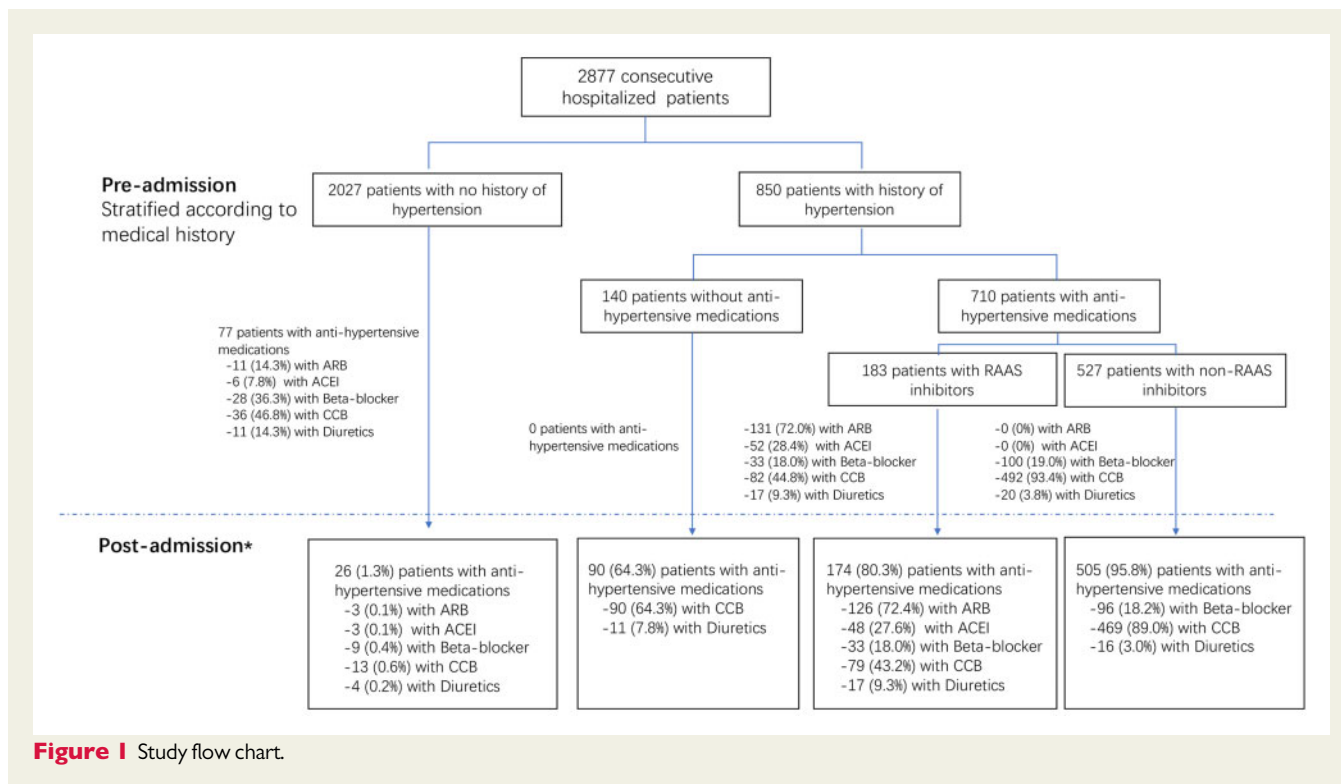


Figure 1 Study flow chart.

formal committee to adjudicate the status of hypertension; however, these diagnoses were rechecked by two individual investigators (R.Z. and Y.C.) during data collection, using office systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure values ≥ 90 mmHg¹⁷ as the criteria.

Figure 1 shows the flow chart of the study. The antihypertensive regimens were in principle unchanged during hospitalization whenever the patients had previous prescriptions before admission. Discontinuation or alteration of the antihypertensive treatment during hospitalization was at the physician's discretion. Those who required antihypertensive medication during hospitalization with no prior prescription, or those who had discontinued the medications prior to admission, were treated with calcium channel blockers (CCBs) or diuretics. The cohorts of 'without antihypertensive' and 'with antihypertensive treatments', as well as the cohorts of 'RAAS inhibitors' (ACEI/ARBs) and 'non-RAAS inhibitors' (beta-blockers, CCBs, or diuretics), were stratified at the time of their admission and according to their pre-admission medications. There were 15 patients (no death events) taking spiro lactone but were categorized in the 'non-RAAS inhibitors' group in the analysis. Patients were included in the RAAS inhibitor cohort whenever at least one RAAS inhibitor (an ACEI or ARB) was prescribed, disregarding whether or not they were treated with a beta-blocker, CCB, or diuretics. Nevertheless, a sensitivity analysis was performed by including patients who were treated solely with one medication (Supplementary material online, Table S3).

Statistical analysis

Continuous variables with normal distribution are expressed as mean \pm standard deviation (SD), and those with skewed distribution are expressed as median \pm interquartile range (IQR). Categorical variables are presented as counts and percentages. Means of two continuous variables were compared by independent Student's *t*-test or Mann–

Whitney *U*-test when appropriate. The frequencies of categorical variables were compared using Fisher's exact test. Survival was estimated by the Kaplan–Meier method (Figure 2). The variances in outcomes between exposure cohorts were assessed by the multivariable Cox proportional hazards model. The covariates in the multivariable model included age (as a continuous variable), sex, medical history of diabetes, insulin-treated diabetes, myocardial infarction, treatment by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), renal failure, chronic heart failure, asthma, chronic obstructive pulmonary disease (COPD), and stroke (as binary variables). Cox proportionality assumptions were checked by using the Schoenfeld residuals against the transformed time, and the assumptions were met in all models. There was no formal correction for multiple testing, taking into account the observational nature of the analysis.¹⁸

The details of statistical approaches for the meta-analysis are provided in Supplementary material online, Methods. Analyses were performed using the R-project (R Foundation, Vienna, Austria). A two-sided *P*-value < 0.05 was considered as statistically significant.

Results

Participants

In total, 2877 consecutive hospitalized patients with confirmed COVID-19 were enrolled in the study. The median time from symptom onset to discharge (last follow-up) was 39 (30–50) days. Baseline characteristics are presented in Table 1. The results of the laboratory tests are presented in the Supplementary material online, Tables S6–S8. Among these patients, 29.5% (850/2877) had a medical history of hypertension. When compared with patients without hypertension, those with hypertension were older, more often had a prior history

Table 1 Baseline characteristics

	Hypertension (-) (n = 2027)	Hypertension (+) (n = 850)	P-value	Antihypertension (-) (n = 140)	Antihypertension (+) (n = 710)	P-value	RAAS inhibitor (-) (n = 527)	RAAS inhibitor (+) (n = 183)	P-value
Age, years	55.38 (14.86)	64.24 (11.2)	<0.001	64.08 (11.3)	64.27 (11.17)	0.433	64.84 (11.19)	62.64 (11)	0.919
Male sex	1027 (50.7%)	443 (52.1%)	0.487	73 (52.1%)	370 (52.1%)	1	266 (50.5%)	104 (56.8%)	0.145
Symptoms at admission									
Fever	1492 (73.6%)	611 (71.9%)	0.357	97 (69.3%)	514 (72.4%)	0.472	385 (73.1%)	129 (70.5%)	0.503
Cough	1405 (69.3%)	585 (68.8%)	0.791	103 (73.6%)	482 (67.9%)	0.196	356 (67.6%)	126 (68.9%)	0.783
Fatigue	1090 (53.8%)	471 (55.4%)	0.436	73 (52.1%)	398 (56.1%)	0.404	300 (56.9%)	98 (53.6%)	0.438
Muscle ache	667 (32.9%)	248 (29.2%)	0.054	45 (32.1%)	203 (28.6%)	0.416	160 (30.4%)	43 (23.5%)	0.087
Headache	40 (2.0%)	18 (2.1%)	0.773	2 (1.4%)	16 (2.3%)	0.752	12 (2.3%)	4 (2.2%)	1
Haemoptysis	11 (0.54%)	2 (0.2%)	0.368	0 (0%)	2 (0.3%)	1	2 (0.4%)	0 (0%)	1
Shortness of breath	904 (44.6%)	399 (46.9%)	0.251	66 (47.1%)	333 (46.9%)	1	248 (47.1%)	85 (46.5%)	0.932
Chest pain	36 (1.8%)	21 (2.5%)	0.241	4 (2.9%)	17 (2.4%)	0.765	15 (2.9%)	2 (1.1%)	0.263
Diarrhoea	94 (4.6%)	44 (5.2%)	0.566	11 (7.9%)	33 (4.7%)	0.141	23 (4.4%)	10 (5.5%)	0.544
Shivering	31 (1.5%)	20 (2.4%)	0.162	6 (4.3%)	14 (2%)	0.121	14 (2.7%)	0 (0%)	0.026
Blood pressure at admission (mmHg)									
Systolic	126 (18, 135)	136 (125, 150)	<0.001	137 (125–152)	136 (125–150)	0.902	136 (125–150)	136 (125–152)	0.934
Diastolic	80 (73, 87)	83.5 (76, 91)	<0.001	84.5 (77–92)	83 (76–91)	0.644	83 (76–91)	84 (76–92)	0.894
Heart rate (b.p.m.)	86.76 (13.4)	86.77 (13.3)	0.988	85.72 (13.32)	86.97 (13.23)	0.872	87.19 (13.17)	86.35 (13.4)	0.896
Respiratory rate (per/min)	20.25 (2.5)	20.45 (2.8)	0.057	20.32 (2.63)	20.48 (2.8)	0.667	20.54 (2.85)	20.3 (2.64)	0.815
Medical history									
Diabetes	159 (7.8%)	228 (26.8%)	<0.001	33 (23.6%)	195 (27.5%)	0.404	140 (26.6%)	55 (30.1%)	0.387
Myocardial angina	83 (4.1%)	138 (16.2%)	<0.001	26 (18.6%)	112 (15.8%)	0.452	80 (15.2%)	32 (17.5%)	0.481
Myocardial infarction	8 (0.4%)	4 (0.5%)	0.757	1 (0.7%)	3 (0.4%)	0.514	3 (0.6%)	0 (0%)	0.573
PCI/CABG	21 (1.0%)	41 (4.8%)	<0.001	4 (2.9%)	37 (5.2%)	0.286	28 (5.3%)	9 (4.9%)	1.000
Peripheral vascular disease	0 (0%)	2 (0.2%)	0.087	0 (0%)	2 (0.3%)	1.000	1 (0.2%)	1 (0.6%)	0.449
Chronic heart failure	13 (0.6%)	10 (1.2%)	0.215	1 (0.7%)	9 (1.3%)	0.900	8 (1.5%)	1 (0.5%)	0.530
Stroke	20 (1.0%)	32 (3.8%)	<0.001	6 (4.3%)	26 (3.7%)	0.634	20 (3.8%)	6 (3.3%)	1.000
Renal failure	11 (0.5%)	18 (2.1%)	<0.001	6 (4.3%)	12 (1.7%)	0.098	10 (1.9%)	2 (1.1%)	0.740
Chronic obstructive pulmonary disease	20 (1.0%)	11 (1.3%)	0.437	2 (1.4%)	9 (1.3%)	0.700	8 (1.5%)	1 (0.6%)	0.460
Pneumonia	23 (1.1%)	13 (1.5%)	0.365	3 (2.1%)	10 (1.4%)	0.459	8 (1.5%)	2 (1.1%)	1.000
Obstructive sleep apnoea	2 (0.1%)	0 (0.0%)	0.888	0 (0.0%)	0 (0.0%)	NA	0 (0%)	0 (0%)	NA
Asthma	17 (0.8%)	5 (0.6%)	0.639	1 (0.7%)	4 (0.6%)	1.000	3 (0.6%)	1 (0.5%)	1.000
Cancer	34 (1.7%)	15 (1.8%)	0.875	1 (0.7%)	14 (2%)	0.487	9 (1.7%)	5 (2.7%)	0.368
Alcoholism	91 (4.5%)	33 (3.9%)	0.546	4 (2.9%)	29 (4.1%)	0.635	20 (3.8%)	9 (4.9%)	0.518
Smoking	133 (6.6%)	57 (6.7%)	0.870	10 (7.1%)	47 (6.6%)	0.853	33 (6.3%)	14 (7.7%)	0.494

Table 2 Comparison of mortality between cohorts

Hypertension	No history of hypertension		HR (95% CI)	P-value
34/850 (4.0%)	22/2027 (1.1%)	Unadjusted	3.75 (2.19–6.41)	<0.001
		Adjusted	2.06 (1.10–3.83)	0.023
		Propensity score adjusted	3.45 (1.39–8.55)	0.008
No antihypertensive treatment	Antihypertensive treatment		HR (95% CI)	P-value
11/140 (7.9%)	23/710 (3.2%)	Unadjusted	2.52 (1.23–5.17)	0.012
		Adjusted	2.24 (1.05–4.76)	0.037
		Propensity score adjusted	2.43 (1.01–5.38)	0.028
RAAS inhibitors	Non-RAAS inhibitors		HR (95% CI)	P-value
4/183 (2.2%)	19/527 (3.6%)	Unadjusted	0.60 (0.20–1.76)	0.354
		Adjusted	0.85 (0.28–2.58)	0.774
		Propensity score adjusted	0.93 (0.31–2.84)	0.901

Adjusted for age, sex, medical history of diabetes, insulin-treated diabetes, myocardial infarction, underwent PCI/CABG, renal failure, stroke, heart failure, and COPD.

Table 3 Comparison of clinical outcomes between cohorts

	Time from symptom onset to discharge [median (IQR), days]				Severity of COVID-19				Invasive mechanical ventilation	
	Overall cases	P-value	Severe/critical cases	P-value	Mild	Severe	Critical	P for trend	No. of ventilations (%)	P-value
No history of hypertension	39 (30–50)	0.263	41 (30–52)	0.003	1578 (77.8%)	431 (21.3%)	18 (0.9%)	<0.001	26 (1.3%)	<0.001
Hypertension	40 (30–49)		44 (34–56)		555 (65.3%)	270 (31.8%)	25 (2.9%)		39 (4.6%)	
No antihypertensive treatment	39 (30–46)	0.538	42 (31–52)	0.014	98 (70%)	37 (26.4%)	5 (3.6%)	0.331	9 (6.4%)	0.268
Antihypertensive treatment	40 (31–50)		35 (21–48)		457 (64.4%)	233 (32.8%)	20 (2.8%)		30 (4.2%)	
Non-RAAS inhibitors	40 (31–49)	0.372	46 (36–56)	0.004	348 (66.0%)	161 (30.6%)	18 (3.4%)	0.372	25 (4.7%)	0.292
RAAS inhibitors	42 (33–51)		40 (30–50)		109 (59.6%)	72 (39.3%)	2 (1.1%)		5 (2.7%)	

of diabetes, angina, stroke, renal failure, or previous revascularization (PCI or CABG), and were receiving more medication for diabetes and hypertension. The spectrum of symptoms of COVID-19 at admission between the two cohorts did not differ significantly.

There were 710/850 (83.5%) patients with hypertension taking antihypertensive medications. The medical history, symptoms onset, and blood pressure at admission did not differ significantly between patients with no antihypertensive medications and those with medications, except that patients with antihypertensive medications were treated more often with oral medication for diabetes. There were 183 (25.7%) patients treated with RAAS inhibitors and 527 (74.2%) treated with beta-blockers, CCBs, or diuretics (non-RAAS inhibitors) (Supplementary material online, Table S1). The medical history and blood pressure at admission did not differ significantly between the RAAS inhibitor-treated [RAASi (+)] and non-RAAS inhibitor-treated patients [RAASi (-)]. There were 14 patients who reported shivering at admission in the RAASi (-) cohort, compared with none in the RAASi (+) cohort (Table 1).

Outcomes of the patients

A total of 34/850 (4.0%) patients died in the hypertension cohort and 22/2027 (1.1%) died in the no hypertension cohort (crude HR 3.75,

95% CI 2.19–6.41, $P < 0.001$; Figure 1A). After adjustment for confounders, hypertension was still associated with a two-fold increase in the risk of mortality as compared with no hypertension (adjusted HR 2.12, 95% CI 1.17–3.82, $P = 0.013$; Table 2). The time from symptom onset to discharge was comparable between the two cohorts; however, patients with hypertension had the propensity to develop more severe/critical COVID-19 disease (P for trend < 0.001) and were more likely to receive invasive mechanical ventilation ($P < 0.001$) (Table 3).

For the patients with hypertension, those without antihypertensive treatment (11/140) had a significantly higher rate of mortality compared with those with antihypertensive (23/710) treatments (7.9% vs. 3.2%, HR 2.52, 95% CI 1.23–5.17, $P = 0.012$; Figure 1B; Table 2). After adjustment, the risk of mortality was still higher in patients without antihypertensive treatment (HR 2.17, 95% CI 1.03–4.57, $P = 0.041$).

There were 183 (25.7%) patients treated with RAAS inhibitors and 527 (74.2%) with beta-blockers, CCBs, or diuretics (non-RAAS inhibitors). The numerical difference in rates of mortality between the RAAS inhibitor and non-RAAS inhibitor cohorts were non-significant before or after adjustment (2.2% vs. 3.6%, adjusted HR 0.85, 95% CI 0.28–2.58, $P = 0.774$). The time from symptom onset to

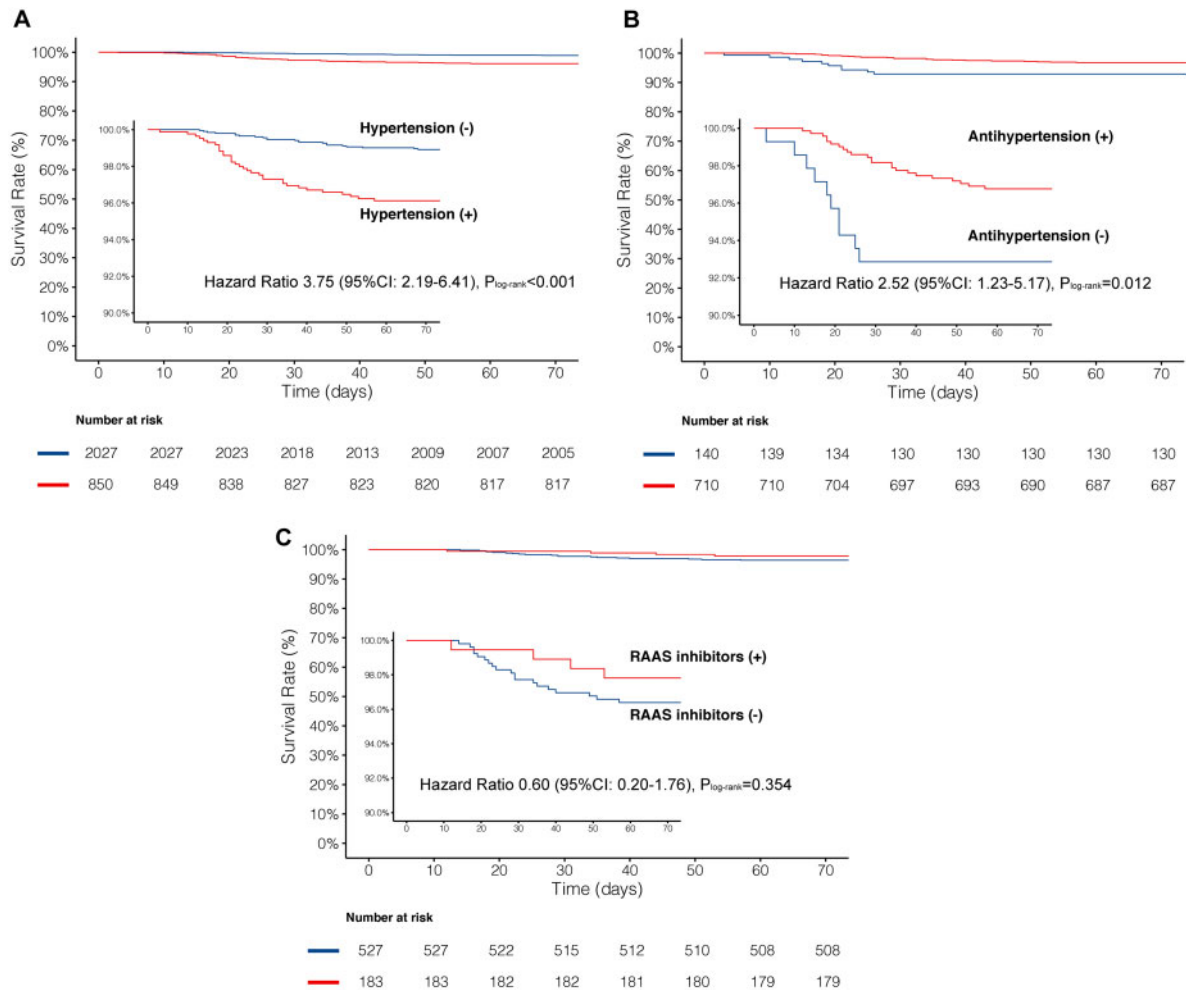


Figure 2 Kaplan–Meier survival curves for mortality from the time of symptom onset. (A) Patients with or without hypertension, (B) patients with or without antihypertensive treatment, (C) patients with ACEI/ARBs (RAAS inhibitors), or beta-blocker, CCB, or diuretics (non-RAAS inhibitors),

discharge, the severity of the COVID-19, and percentage of ventilation were all similar between the two cohorts.

To understand whether ACEIs and ARBs had distinct effects on outcomes, we have also compared the influence of ACEIs and ARBs with those of non-RAAS inhibitors. Compared with non-RAAS inhibitors, the risks of mortality in patients with ARBs or ACEIs were both numerically lower. Since the sample size was small in both groups, any results could be largely due to play of chance; however, these results did not show an obvious propensity that ARBs and ACEIs had an adverse HR (>1) as far as the mortality is concerned (Supplementary material online, Table S2).

Comparison of characteristics between patients who survived and those who died

To further explore the potential risk factors for mortality, we performed a multivariable Cox regression analysis with backwards-stepwise selection to identify the predictors of mortality. A total of seven variables were identified, namely fatigue, age, hypertension,

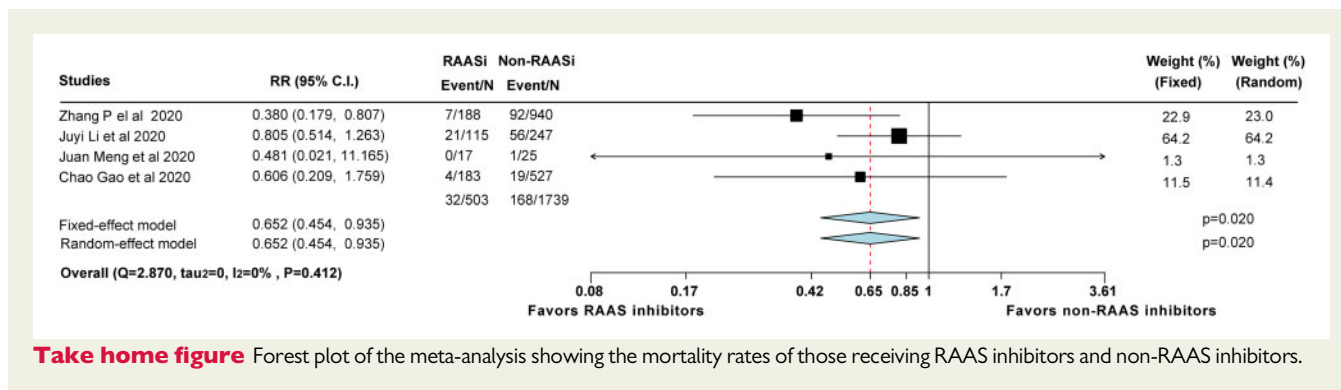
myocardial infarction, renal failure, respiratory rate, and chronic heart failure. These results are shown in the Supplementary material online, Tables S4 and S5; Figure S1.

Meta-analysis

Most recently, there are three other groups in China who have reported their data regarding the influence of RAAS inhibitors in COVID-19 patients. We have summarized all the available data in a meta-analysis.^{19–21} Together with our current data, we found that compared with non-RAAS inhibitors, RAAS inhibitors were associated with a lower risk of mortality (relative risk 0.65; 95% CI, 0.45–0.94, $P = 0.02$), regardless of the model used.

Discussion

The main findings of this analysis can be summarized as follows: (i) after adjustment for confounders and compared with the non-hypertensive patients, the hypertensive patients continued to



demonstrate a two-fold relative increase in the risk of COVID-19 mortality; (ii) the patients with a history of hypertension but without antihypertensive treatment were associated with a significantly higher risk of mortality compared with those with antihypertensive treatments; and (iii) the relative rates of mortality, the severity of COVID-19, and percentages of ventilation were not statistically different between the patients treated with RAAS inhibitors and non-RAAS inhibitors. However, in the meta-analysis, RAAS inhibitors tend to be associated with a lower risk of mortality.

Patients with COVID-19 and hypertension have been reported to have an increased risk of adverse outcomes. Chen *et al.* suggested that chronic hypertension was more frequent among patients who died compared with recovered patients.²² In line with this finding, Wu *et al.* found that hypertension has an HR of 1.70 for death in 201 patients with COVID-19,² and Zhou *et al.* found hypertension had an HR of 3.05 for in-hospital mortality in 191 patients with COVID-19.³ Meanwhile, there was also a study which enrolled 416 patients which suggested that after the adjustment for confounders, hypertension was no longer an independent risk factor for COVID-19.²³ In the current study, we found that after adjustment for confounders, patients with hypertension still had a significantly two-fold higher risk of mortality when compared with patients with no hypertension.

So far, there is limited clinical evidence demonstrating that antihypertensive treatments could influence the prognosis of COVID-19. Despite the lack of evidence, the Council on Hypertension of the European Society of Cardiology (ESC) recommends that physicians and patients should continue treatment with their usual antihypertensive therapy.²⁴ Our analysis showed that patients with antihypertensive treatments pre-admission had a lower rate of mortality compared with those without treatment of hypertension. These data support ESC's recommendation stating that patients should not discontinue or change their antihypertensive treatment, unless instructed by a physician.

Recently ACE2 has been identified to be necessary for viral entry for SARS-CoV-2. As ACE generates angiotensin II from angiotensin I, ACE2 degrades angiotensin II to angiotensin (1-7), which, after binding to the Mas receptor, shifts the balance from vasoconstriction with angiotensin II to vasodilation. Under normal circumstances, the circulating levels of soluble ACE2 are low and the functional role of ACE2 in the lungs appears to be relatively limited,²⁵ but may be up-regulated with certain medications or clinical states. This has led to a two-fold concern whereby ACEIs and ARBs might affect the severity

and mortality of COVID-19.^{12,13} One is that ACEIs could directly inhibit ACE2. However, despite substantial structural homology between ACE and ACE2, their enzyme active sites are distinct. As a result, ACEIs in clinical use do not directly affect ACE2 functions.²⁶

In addition, there is the concern that the use of ACEIs and ARBs will increase the expression of ACE2⁸ and therefore increase patient susceptibility to viral host cell entry and propagation. Conflicting and limited evidence stemming from laboratory or clinical studies has shown changes in serum or pulmonary ACE2 levels in response to ACEIs or ARBs.¹² However, even if an ACEI or ARB could actually modify ACE2 levels or activity (or both) in target tissue beds, evidence is still lacking to indicate whether this would facilitate greater involvement of spike protein and cell entry of SARS-CoV-2.

Given the uncertainty due to lack of clinical data, there are both advocates and objectors toward the use of RAAS inhibitors during the COVID-19 pandemic. In our study, we found that the risks of mortality after adjustment were not significantly different between RAAS inhibitors and non-RAAS inhibitors. Furthermore, after pooling with previously published data^{19–21} in a study-level meta-analysis, we found that patients with RAAS inhibitor use were possibly associated with a lower risk of mortality (*Take home figure*).

The underlying mechanism of why patients could eventually benefit from RAAS inhibitors during COVID-19 is putative. However, results from laboratory studies reported that after the initial engagement of SARS-CoV-1 spike protein, ACE2 abundance was down-regulated on cell surfaces.²⁷ The down-regulation of ACE2 and the dysregulation of its activity in the lungs may facilitate the initial neutrophil infiltration in response to bacterial endotoxin and may result in unopposed angiotensin II accumulation and local RAAS activation.²⁸ An animal study has also shown that in mouse models, exposure to SARS-CoV-1 spike protein induced acute lung injury, which is limited by RAAS blockade.²⁷ Therefore, some researchers have hypothesized that high ACE2 expression could be deleterious during the contamination phase, whereas the high ACE2 expression could, in contrast, be beneficial during the inflammation phase²⁷ and may possibly prevent organ injury in COVID-19.^{29,30} To further verify our results, as well as this hypothesis, we have also designed a randomized controlled trial, which is ongoing, investigating this issue (NCT04330300).

As described above, these data showed that untreated hypertensive patients are at the highest risk. There are remaining questions: (i) which kind of medication should be given to those patients (CCBs or

RAAS inhibitors); (ii) could such medications mitigate the risk of these patients; and (iii) will the use of RAAS inhibitors affect the risk of infection when equally exposed to the virus?

Limitations

- i. The multivariable-adjusted Cox proportional hazard models were performed in an attempt to estimate the true treatment effects of antihypertensive medications. However, the usual deficiency of observational studies exists, such as the inability to include all relevant confounders, especially those unmeasured, causing bias that cannot be adjusted.
- ii. Although the current study enrolled 2877 patients, to our knowledge so far one of the largest cohorts reported, only 183 patients with RAAS inhibitors and 527 patients with non-RAAS inhibitors were compared. Statistically underpowered, our findings should be interpreted cautiously.
- iii. As a retrospective study, some data such as electrocardiogram and echocardiography were not recorded in detail in the study owing to the limitations imposed in the isolation ward and the urgency of containing the COVID-19 epidemic.
- iv. The data in this study permit a short-term assessment of the clinical outcomes of the impact of antihypertensive treatments. Long-term prospective studies investigating the effects of these treatments are still needed.

Conclusion

While hypertension is independently associated with mortality from COVID-19, the discontinuation of the antihypertensive treatment is suspected to be associated with an increased risk of mortality. Patients with RAAS inhibitors were not exposed to a higher risk of mortality in our study and, after pooling previously published data in a study-level meta-analysis, the use of RAAS inhibitors was shown to be possibly associated with lower risk of mortality. Nevertheless, due to the observational nature of the study, the results should be interpreted cautiously and considered as no obvious additional risk to continue RAAS inhibitors in patients with COVID-19 infection.

Supplementary material

Supplementary material is available online at *European Heart Journal*.

Conflict of interest: none declared.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**:1239–1242.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;doi: 10.1001/jamainternmed.2020.0994.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–1062.
4. Wu JT, Leung K, Bushman M, Kishore N, Niehus R, de Salazar PM, Cowling BJ, Lipsitch M, Leung GM. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nat Med* 2020;**26**:506–510.
5. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;**181**:271–280.
6. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;**203**:631–637.
7. Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombar L, John D, Schmitto JD, Heineke J, Emrich F, Arsalan M, Holubec T, Walther T, Zeiher AM, Dimmeler S. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur Heart J* 2020;doi: 10.1093/eurheartj/ehaa311.
8. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005;**111**:2605–2610.
9. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, Sasse T, Kummer E, Jando J, Hamie QM, Meier CF, Hunziker S, Forras-Kaufmann Z, Kuyumcu S, Fox M, Schwizer W, Fried M, Lindenmeyer M, Gotze O, Verrey F. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids* 2015;**47**:693–705.
10. Deshotels MR, Xia H, Sriramula S, Lazartigues E, Filipeanu CM. Angiotensin II mediates angiotensin converting enzyme type 2 internalization and degradation through an angiotensin II type 1 receptor-dependent mechanism. *Hypertension* 2014;**64**:1368–1375.
11. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;**367**:1260–1263.
12. Vaduganathan M, Vardeny O, Michel T, McMurray JVV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;**382**:1653–1659.
13. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA* 2020;doi: 10.1001/jama.2020.4812.
14. World Health Organization. *Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (nCoV) Infection is Suspected*. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
15. China National Health Commission. *Diagnosis and Treatment Protocol for COVID-19*. [https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf](https://www.chinadaily.com.cn/pdf/2020/1/Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf).
16. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. *Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) -China, 2020*. <http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51>.
17. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
18. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, Devereaux PJ, Thabane L. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol* 2017;**46**:746–755.
19. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, Yang R, Di W, Wang Z, Li Z, Gao H, Liu L, Zhang A. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020;**9**:757–760.
20. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang XJ, Wang X, Touyz RM, Xia J, Zhang BH, Huang X, Yuan Y, Rohit L, Liu PP, Li H. 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; doi: 10.1161/CIRCRESAHA.120.317134.
21. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.1624.
22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;**368**:m1091.

23. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.0950.
24. Hypertension ECo. *Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers*. [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang).
25. Serfozo P, Wysocki J, Gulua G, Schulze A, Ye M, Liu P, Jin J, Bader M, Myohanen T, Garcia-Horsman JA, Battle D. Ang II (angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (prolyloligopeptidase)-dependent and ACE2 (angiotensin-converting enzyme 2)-independent. *Hypertension* 2020; **75**:173–182.
26. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J* 2004;**383**:45–51.
27. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;**11**:875–879.
28. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, McCray PB Jr, Chappell M, Hackam DJ, Jia H. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg(9) bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *Am J Physiol Lung Cell Mol Physiol* 2018;**314**:L17–L31.
29. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;**63**:364–374.
30. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020;doi: 10.1002/ddr.21656.