Among patients with hypertension with or without other vascular comorbidities, is the use of RAAS antagonists associated with severe COVID disease or COVID-related deaths?

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Date of Review: [11-APRIL-2020 (version 1)]
Last Updated: [1-MAY-2020 (version 2)]

KEY FINDINGS

Among patients with confirmed COVID-19 infection and hypertension with or without other vascular comorbidities, there is insufficient evidence that RAS antagonists are associated with mortality or severe COVID-19 disease.

- There is uncertainty with regard to continued use of renin-angiotensin system (RAS) antagonists for COVID-19 patients with hypertension and other comorbidities because of two possible contradictory mechanisms 1) upregulation of ACE2 receptors that may facilitate the virus entry into the lung.[1] and 2) control of unabated angiotensin II levels reducing acute lung injury.[2]
- Among patients with hypertension with or without other vascular comorbidities and taking RAS antagonists, there is a trend towards less severe COVID-19 compared to those on other antihypertensive drugs (pooled results from 9 observational studies). There is also a trend towards reduced mortality among these patients (pooled results of six observational studies).
- There are 36 ongoing studies (21 RCTs, 1 single-arm trial, 4 prospective cohorts, 4 retrospective cohorts, 4 case-control, and 2 cross-sectional) on this topic.
- The European Society of Cardiology (ESC) Council on Hypertension, the International Society of Hypertension (ISH) and the joint statement by the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) all caution against discontinuing RAS-related treatments in patients with hypertension because of COVID-19 infection.[3,4]

RESULTS

Results of Search

We found 13 retrospective cohort studies in this review; 5 of them were preprints (Appendix 1). [5–9]. We pooled the results of 9 studies; 1 study could not be pooled since the comparator group consisted of patients who were not on any antihypertensive drug (Richardson 2020),[10] and another 3 studies did not provide raw data (Rubin 2020; Zhang 2020a; Zhang 2020b).[7,9,11]

Risk of Bias Assessment

We assessed the risk of bias in the included studies using appraisal criteria for studies on harm (Painless Evidence-Based Medicine 2nd ed.). [12] (Summary of appraisal in Appendix 2). The appraisal of the five retrospective cohort studies included in the meta-analyses showed high or unclear risk for bias mainly due to the following methodologic limitations 1) not all important prognostic factors considered, 2) inadequate follow-up period, and 3) exclusion of participants with incomplete data in 4 studies (Feng 2020a; Guo 2020; Ip 2020; Zhang 2020a). In addition, not the whole target population of patients with COVID-19 were recruited in most of the studies that were conducted in the hospital setting.

Effects of Use of RAS antagonists

Severe COVID-19 Among Patients with Hypertension on RAS Antagonists

Among patients with confirmed COVID-19, hypertension, with or without other vascular comorbidities, on RAS antagonists, there was a trend towards ~~reduced odds of~~ less severe COVID-19 disease compared to those on other antihypertensive drugs. However, this was not statistically significant (9 pooled studies, N=2016; OR, 0.69 [0.44, 1.07]) (Figure 1). There was significant heterogeneity (I^2=63%) probably due to differences in definition of severity outcomes.

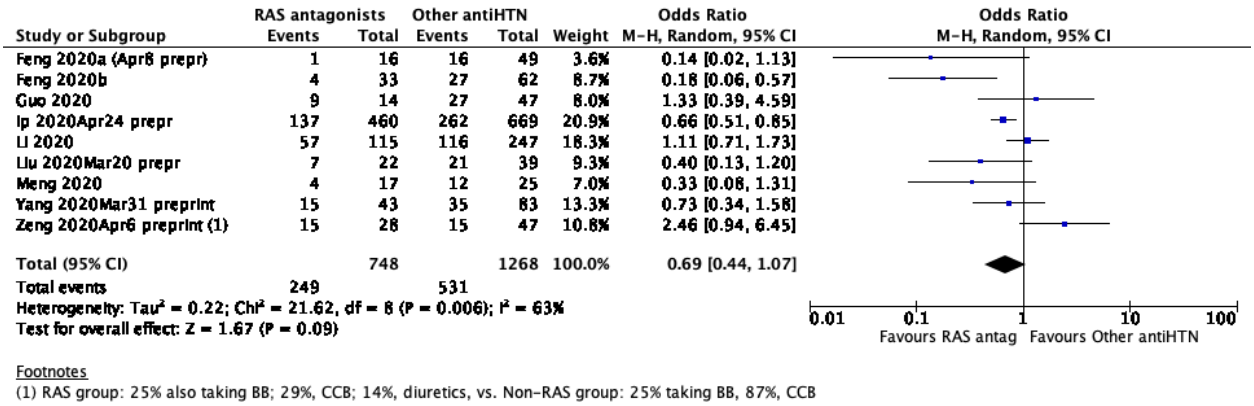

Figure 1. RAS antagonists vs other antihypertensive drugs: Severe COVID disease among patients with hypertension with or without other vascular comorbidities

Mortality Among Patients with Hypertension with or without other vascular comorbidities and on RAS Antagonists

We pooled five studies to determine the association between COVID-19-related mortality and the use of RAS antagonists among patients with hypertension. There was a trend towards lower odds of dying among those on RAS antagonists compared to those on other antihypertensive drugs (5 studies, N=666; OR, 0.69, 95% CI 0.43, 1.09; I^2=0%) (Figure 2).

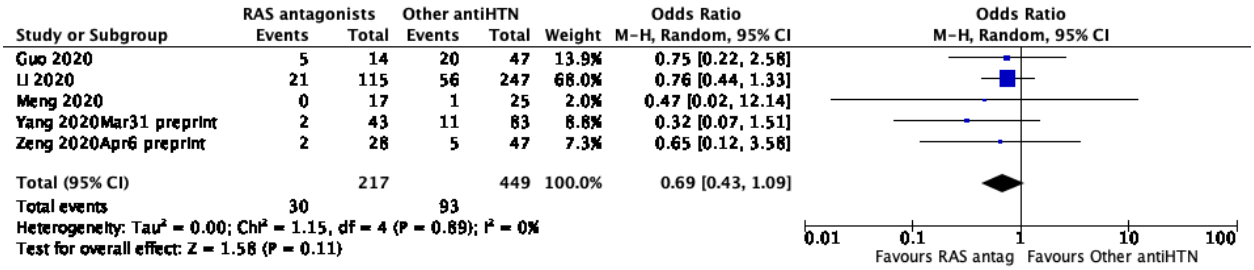

Figure 2. RAS antagonists vs other antihypertensive drugs: COVID-associated deaths among patients with hypertension

One large retrospective cohort study (N=1366) in the US compared the outcome between RAS antagonist users and non-users (including patients not on any antihypertensive drug). This showed increased odds for invasive mechanical ventilation (OR 1.54, 95% 1.14, 2.07) and a trend towards higher mortality (OR 1.26, 95% CI 0.98, 1.63) among those on RAS antagonists compared to those on other antihypertensive drugs or no drug. (Richardson 2020)[10]

A small retrospective cohort study reported results of univariate and multivariate analysis for prognostic factors and showed no correlation between disease progression and the use of ACEI or ARBs (Table 1) (Rubin 2020).[7]

Table 1. Correlation of severe disease outcomes with use of RAS antagonists (N=54)

Outcome	Univariate analysis (P-value)	Multivariate analysis (P-value)
Admission to ICU		
Use of ACEI	1.000	0.995
Use of ARB	0.459	0.433
Progression to ARDS		
Use of ACEI	1.000	0.997
Use of ARB	0.330	0.467

One large retrospective cohort study (N=1128) reported increased survival among patients who had inpatient use of RAS antagonists compared to use of other antihypertensive drugs (propensity score-matched hazard ratio of 0.37, 95% CI 0.15-0.89). (Zhang 2020b)[[13]]

One other small retrospective cohort (N=90) reported a lower case fatality rate with use of other antihypertensive drugs (including ACEI, ARBs and diuretics) compared to calcium channel blockers or no treatment (HR 0.47, 95% CI, 0.06, 3.83), but this was not statistically significant (Zhang 2020a).[9]

Table 1. Summary of results

Outcome	Source of data	Intervention group (RAS antagonist), n	Control (Other antiHTN), n	OR (95% CI)	Heterogeneity (I^2) (%)	Result
Severe disease	Pooled data from 9 studies (Figure 1)	748	1268	0.69 [0.44, 1.07]	63	Trend favoring RAS antagonist
Mortality	Pooled data from 5 studies (Figure 2)	217	449	0.69 [0.43, 1.09]	0	Trend favoring RAS antagonist
	Zhang 2020b[13]	188	940	HR 0.37, [0.15-0.89]	NA	Reduced mortality with RAS antagonist
	Zhang	ACEI/ARB	No drug	HR 0.47, 95%	NA	Uncertain

	2020a[9]	grouped with diuretics 17	73	CI, 0.06, 3.83		effect
Mortality or mechanical ventilation	Richardson 2020[10]	413	Other antiHTN or no drug 953	OR 1.54, 95% 1.14, 2.07	NA	Mortality- Trend against RAS antagonist Mechanical ventilation- Higher risk with RAS antagonist
ICU Admission Disease progression	Rubin 2020[7] (Table 1)	9	Other antiHTN or no drug 5	NA	NA	No correlation with use of RAS antagonist

Recommendations of Organizations and Medical Groups

The European Society of Cardiology (ESC) Council on Hypertension, the International Society of Hypertension (ISH) and the joint statement by the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) all caution against discontinuing RAS-related treatments in patients with hypertension who become infected with COVID-19.[3,4]

CONCLUSION

Based on low quality of evidence, among patients with hypertension with or without other vascular comorbidities, there is a trend towards less severe COVID-19 and reduced mortality among those taking RAS antagonists compared to those taking other anti-hypertensive medications.

There are still several ongoing clinical trials and prospective cohort studies that may give us more conclusive results.

Declaration of Conflict of Interest

No conflict of interest

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Appendix 1. Characteristics of included studies

No.	Study ID/Title	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Clinical Outcomes	Key Findings
RAS antagonists vs other antihypertensive drugs								
1	Feng 2020a[14] (preprint) The Use of Adjuvant Therapy in Preventing Progression to Severe Pneumonia in Patients with Coronavirus Disease 2019: A Multicenter Data Analysis	Retrospective cohort	China, 9 hospitals in 7 cities January 17 to February 28, 2020 (final date of follow-up: March 15, 2020)	65 adult patients with confirmed COVID-19 and hypertension on antihypertensive drugs (17 were excluded due to lack of data and were given amlodipine or nitrendipine as needed) Of 564 consecutively hospitalized patients: Median age = 47 years (IQR, 36-58; range, 19-84 years) (50.4%) were men. 132 (23.4%) patients had comorbidities, (including hypertension: n = 82 [14.5%]; DM 8%; CVD 3.9%)	ACEI/ARB (n=16/65)	Other antihypertension drugs (calcium blockers, beta-blockers, diuretics) (n=49/65)	Severe COVID Discharge Deaths (not reported)	Fewer hypertensive patients on ACEI/ARB therapy developed severe pneumonia in contrast with those on non-ACEI/ARB antihypertensive therapy (1 of 16 [6.3%] patients and 16 of 49 [32.7%] patients, respectively [difference, 26.4%; 95% CI, 1.5% to 41.3%])
2	Feng 2020b[15] COVID-19 with Different Severity: A Multi-center Study of Clinical Features	Retrospective cohort	China Admitted to 3 hospitals in Wuhan, Shanghai and Anhui Jan 1 to Feb 15, 2020 (End of data collection: February 15)	95 patients w/ HTN and on antiHTN drugs 476 patients with COVID-19; 113 w/ HTN; 205 patients (43.1%) w/ comorbidities; median age, 53 years [IQR, 40-64]; male, 56.9%)	ACEI/ARB (n=33/95)	Other antiHTN drugs (n=62/95)	Disease severity (Moderate, severe, critical) (5th version of the guidelines issued by the National Health Commission of China on Diagnosis and Treatment of COVID-19)	Compared with severe and critical groups, there were more patients taking ACEI/ARB in moderate group. There was a significant difference in angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers usage among patients with different severities.
3	Guo 2020[16] Cardiovascular Implications of Fatal Outcomes of Patients With	Retrospective cohort	China (Wuhan) Hospitalized at designated COVID hospital; January 23 to February 23, 2020	61 COVID-19 treated patients with **hypertension (**out of 187); Mean age (SD) = 58.5 yrs. (14.66)	ACEI/ARB (n=14/61)	Other antihypertension drugs (n=47/61)	COVID-19-associated death Acute respiratory distress syndrome	"The mortality rates of patients with and without use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was 36.8% (7 of

	Coronavirus Disease 2019 (COVID-19)			Either **discharged or died during hospitalization** (NOT includes those still admitted); Excluded 67 patients who were not yet discharged or died)			(not reported) Malignant arrhythmia (not reported) Acute myocardial injury	19) and 25.6% (43 of 168)."
4	Ip 2020[17] Hypertension and Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19	Retrospective cohort	US (NJ) Admitted to Hackensack Meridian Health network Convenience sampling Discharged or deceased cohort with known outcomes	1129 w/ HTN and known outcomes 1584 w/ HTN (52.5% of 3017 hospitalized COVID-19 patients)	ACEI/ARB (n=460/1129)	Other antiHTN drugs (n=669/1129)	Discharged or died	The mortality rates were lower for hypertensive patients prescribed ACE1 (27%, p=0.001) or ARBs (33%, p=0.12) compared to other anti-hypertensive agents (39%) in the unadjusted analyses. RAAS inhibitor therapy appeared protective compared to other anti-hypertensive agents (p=0.001).
5	Li 2020[18] 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	Retrospective cohort	China (Hubei) Admitted to Central Hospital of Wuhan January 15 to March 15, 2020 (End of study not stated)	362 patients with HTN and COVID-19 52.2% men 259 (71.5%)were older than 60 years	ACEIs/ARBs (n=115/362)	Other antiHTN drugs (n=247/362)	Severe disease (diagnosis and treatment scheme for COVID-19 of Chinese (5th edition) Deaths	The current findings did not identify an association between treatment with ACEIs/ARBs and either severity or clinical outcomes of COVID-19 hospitalizations in patients with hypertension.
6	Liu 2020a (preprint) [6] Antihypertensive Angiotensin II receptor blockers associated to mitigation of	Retrospective cohort	China (Shenzhen) admitted to 3 hospitals Jan 11 to Feb 5, 2020; Wuhan, Jan 12 to Feb 9, 2020;	78 adult patients with COVID-19 and **hypertension**; Average age = 65.2 yrs. (10.7)	ACE inhibitors or ARB (n=22/78)	Other antiHTN drugs (CCB or Thiazide or BB) (n=39/78) No drug (n=17/78)	Mild versus Severe COVID (New Coronavirus Pneumonia Prevention and Control Program published by the National Health Commission of	"No statistical difference in disease severity between any of the 5 different types of anti-hypertensive drugs (CCB, ARB, ACEI, Thiazide or BB) compared to no drugs taken by all COVID-19 patients with hypertension comorbidity in the study."

	disease severity in elderly COVID-19 patients		Beijing, Dec 27, 2019 to Feb 29, 2020)				China)	
7	Meng 2020[19] Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension.	Retrospective cohort	China (Shenzhen) Hospitalized January 11 to February 23 2020	42 patients with COVID-19 **with hypertension AND on anti-hypertensives;** Median age = 64.5 yrs. (range, 55.8-69.0）out of 51 with HTN but 9 not on antiHTN drugs) (out of 417 admitted patients)	ACE inhibitors or ARB, diff doses (n=17/42)	Other anti-HTN drugs (e.g., amlodipine, L-amlodipine, felodipine, laxidipine, , metoprolol, bisoprolol, spironolactone) (n=25/42)	Deaths	"We observed that patients receiving ACEI or ARB therapy had a lower rate of severe diseases… This evidence supports the benefit of using ACEIs or ARBs to potentially contribute to the improvement of clinical outcomes of COVID-19 patients with hypertension."
8	Yang 2020a (preprint) [8] 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	Retrospective cohort	China (Hubei) January 5 to February 22, 2020 Final follow-up March 3, 2020	126 COVID-19 patients with preexisting **hypertension** were retrospectively allocated into two subgroups, ARBs/ACEIs and non-ARBs/ACEIs group, according to their usage of antihypertensive drugs. Median age, 66 (IQR, 61-73)	ARBs/ACEIs (n=43/126)	Other antiHTN drugs (n=83/126)	1. Severe COVID (5th Trial Version of the Chinese National Health Commission) 2.Deaths	"Furthermore, much lower proportion of critical patients (9.3% *vs* 22.9%; p=0.061), and a lower death rate (4.7% *vs* 13.3%; p=0.216) were observed in ARBs/ACEIs group than non-ARBs/ACEIs group, although these differences failed to reach statistical significance. Our findings thus support the use of ARBs/ACEIs in COVID-19 patients with preexisting hypertension."
9	Zeng 2020[20] Hypertension in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study	Retrospective cohort	China (Wuhan) Admitted to Hankou Hospital January 5 and March 8, 2020 (Minimum 14 days follow-up, even after discharge)	75 with hypertension Mean age (SD), 67(11); 55% M) (out of 274 patients with clinically confirmed COVID-19; mean age 60 [SD 15]; 55% M)	ACEI/ARB (n=28/75) On B-blockers (n= 7/28, 25%) On CCB (n= 8/28, 29%) On diuretics (n = 4/28, 14%)	Non-ACEI/ARB drugs (n=47/75) On B-blockers (n=12/47, 25%) On CCB (n=41/47, 87%) On diuretics (n=0)	28-day mortality Severity of pneumonia Length of hospital stay Discharge rate from hospital Hospitalization	Patients with hypertension who had previously taken ACEI/ARB drugs for antihypertensive treatment have an increased tendency to develop severe pneumonia after infection with SARS-COV-2 (P = 0.064).

10	Zhang 2020a (Apr 8 preprint)[14] Calcium channel blocker amlodipine besylate is associated 1 with reduced case 2 fatality rate of COVID-19 patients with hypertension	Retrospective cohort In vitro anti-viral testing	China Admitted to 2 hospitals: Tongji Hospital from January 17 to February 14, 2020 Union Hospital from January 10 to March 30, 2020	90 patients, who only had hypertension as the comorbidity and were either discharged from the hospital or deceased (out of 487 adult COVID-19 patients with Hypertension) Median 67(59.5–72); 63% M (amlodipine group) to 65 (57–74) 40.9% M (non-amlodipine group)	AntiHTN drugs (including ARBs, ACEIs, β-blockers, and thiazide) (n=17/90)	Amlodipine besylate (n=44/90) Nifedipine (n=16/90), Other CCBs (n=4/90) No antiHTN drug (n=9/90)	Deaths (not reported for ACEI/ARBs alone)	Calcium channel blockers (CCB) can significantly inhibit the post-entry replication events of SARS-CoV-2 in vitro. Comparison with two other major types of anti-hypertension drugs, the angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), showed that only CCBs display significant anti-SARS-CoV-2 efficacy.
11	Zhang 2020b[21] Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19	Retrospective cohort	China (Hubei province) Admitted to 9 hospitals December 31, 2019 to February 20, 2020 Final date of ff-up: March 7, 2020	1128 adult patients with hypertension diagnosed with COVID-19	ACEI/ARB group (n=188/1128) Median age 64 [IQR 55-68] years; 53.2% men)	Other antiHTN drugs (n=940/1128) Median age 64 [IQR 57-69]; 53.5% men)	All-cause mortality Septic shock DIC Only reported HR, not raw data	Among hospitalized COVID-19 patients with hypertension, inpatient use of ACEI/ARB was associated with lower risk of all-cause mortality compared with ACEI/ARB non-users. While study interpretation needs to consider the potential for residual confounders, it is unlikely that in-hospital use of ACEI/ARB was associated with an increased mortality risk.
RAS antagonists vs other antihypertensive drugs or no drugs								
12	Richardson 2020[10] Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area	Retrospective cohort	USA (NY) Admitted to 12 hospitals in New York City, Long Island, and Westchester County, New York, within the Northwell Health system. March 1 and April 4, 2020 Most patients in this study were still	1366 patients with HTN (out of 2411 with home medication information out of 2634 who were discharged or died; out of 5700 sequentially hospitalized patients with COVID-19) Median age, 63 years [IQR, 52-75; range, 0-107 years]; 60.3% male) HTN (56.6%), obesity (41.7%), and diabetes	ACEI/ARB (n=413/1366)	Not on ACEI/ARB (n =953/1366) *unspecified how many were on other antiHTN or no drugs	Invasive mechanical ventilation, kidney replacement therapy, and death.	Mortality rates for patients with hypertension not taking an ACEi or ARB, taking an ACEi, and taking an ARB were 26.7%, 32.7%, and 30.6%, respectively. (...results are unadjusted for known confounders, including age, sex, race, ethnicity, socio- economic status indicators, and comorbidities such as diabetes, chronic kidney disease, and heart failure).

			in hospital at the study end point (3066, 53.8%).	(33.8%) Median no. of medications, 3 (IQR 0–7)				
13	Rubin 2020 (preprint[7] Clinical characteristics associated with COVID-19 severity in California	Retrospective cohort	USA (California) Stanford Hospital (OPD & inpatient) by March 16, 2020	14 w/ HTN (out of 54 COVID-19 patients who and w/ past medical history documentation; 18 inpatients, 36 outpatients) Median 53.5 yrs. [IQR, 32.75; range, 20–91]); 50% M	ACE-I or ARB (n=9/14)	Non-ACE/ARB drugs or no drug use (?) (n=5/14)	Progression to severe disease 1. Recommendation for further hospital care, 2. Admission to ICU 3. Diagnosis of pneumonia 4. Progression to ARDS No raw data; Reported only as p-values using univariate and multivariate analysis	"In our study, history of ACE-I or ARB use did not affect diagnosis rate or predispose patients to worse disease outcomes. However, our study is underpowered to draw definitive conclusions from such negative data."

Appendix 2. Summary of Risk of Bias Appraisal for Studies on Harm

	Study ID	1. Did the exposure in question precede the undesirable outcome?	2. Were important prognostic factors balanced at the time of exposure? If not, were statistical adjustments made for these factors?	3. Were unbiased criteria used to determine exposure in all patients?	4. Were unbiased criteria used to detect the outcome in all patients?	5. Was the follow-up rate adequate?
1	Feng 2020Apr8 preprint	Y	Y	Y	Y	N
2	Feng 2020Apr10	Y	N	Y	Y	N
3	Guo 2020	Y	N	Y	Y	N
4	Ip 2020Apr24 preprint	UC	N	Y	Y	N
5	Li 2020	Y	Y	UC	Y	UC
6	Liu 2020Mar20 preprint	Y	UC	Y	Y	N
7	Meng 2020	Y	Y	Y	Y	N
8	Richardson 2020	Y	N	Y	Y	N
9	Rubin 2020Mar 27 preprint	Y	Y	Y	N	N
10	Yang 2020Mar31 preprint	Y	UC	Y	Y	N
11	Zeng 2020Apr6 preprint	Y	N	Y	Y	Y
12	Zhang 2020	Y	Y	Y	Y	Y
13	Zhang 2020Apr8 preprint	Y	Y	N	Y	Y

Y, Yes; N, No; U, Unclear