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CV & COVID-19 Journal Club

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Outline

- **Journal 1:** Renin–Angiotensin–Aldosterone System Blockers and the Risk of COVID-19
- **Journal 2:** Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment
- **Take Home Message**

COVID19 Journal Reading Part 1

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

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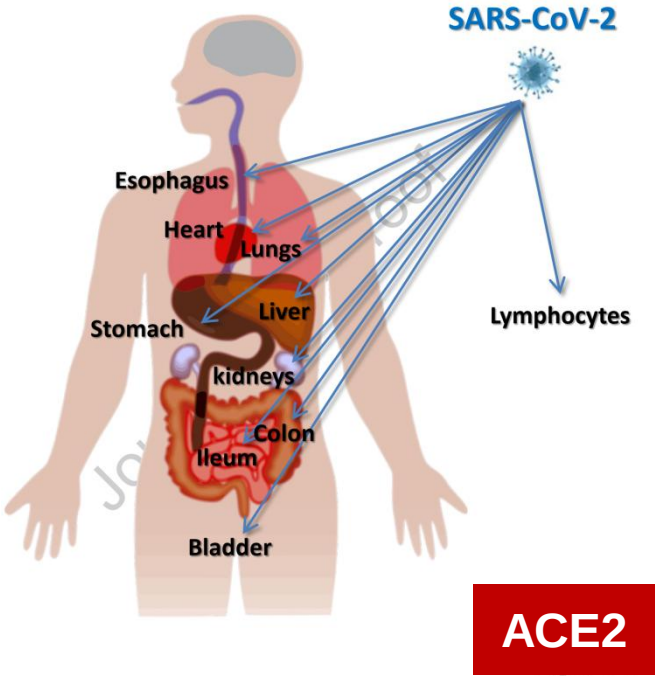
Background & Aim

- **Background**
  - Angiotensin-converting enzyme 2 (ACE2) is abundantly expressed in the lung, the heart and other tissue
  - SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor binding domain for its spike protein
  - Angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors increase the expression of ACE2
- **Aim**
  - To study potential associations between the use of angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (COVID-19)

ACE2 Distribution & Renin-Angiotensin-Aldosterone System(RAAS)

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor binding domain for its spike protein

- **ACE2 distribution**



ACE2

- **RAAS Pathways**

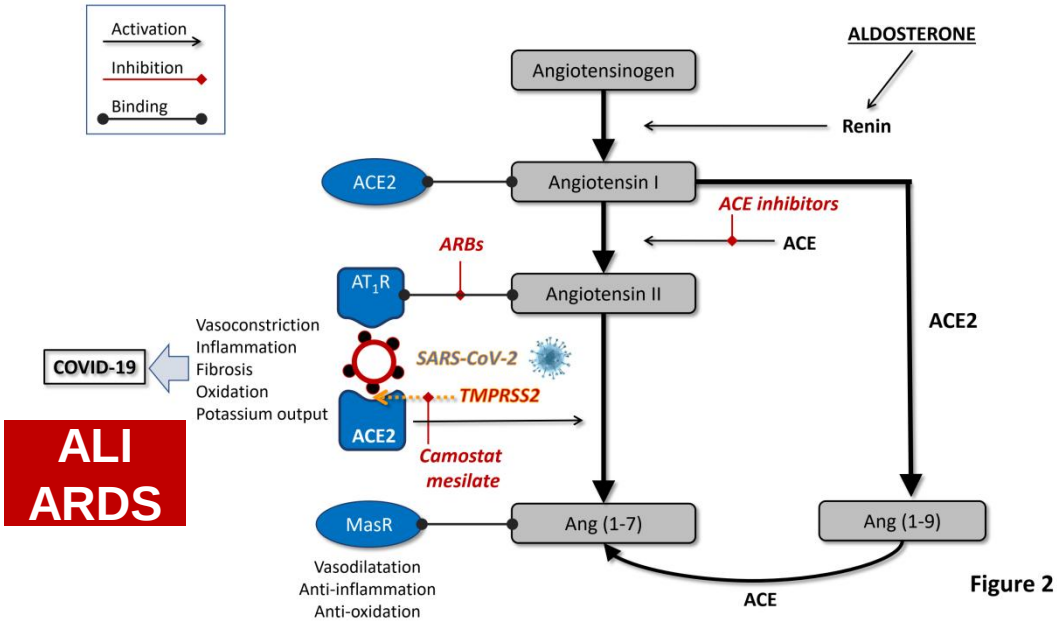


Figure 2

Angiotensin-Converting Enzyme 2 and Anti-Hypertensives (Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors) in Coronavirus Disease 2019 (COVID-19) *DOI: https://doi.org/10.1016/j.mayocp.2020.03.026*

Current Guideline Recommendation

All guidelines recommend continuing ACEIs/ARBs in pts with COVID-19

Table. Recommendations on the Use of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in Patients With Coronavirus Disease 2019 (COVID-19)

Professional society; source	Date of release	Key statements
HFSA, ACC, and AHA; https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19	March 17, 2020	"The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease. In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation. Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice."
ESC Council on Hypertension; https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang	March 13, 2020	"The Council on Hypertension strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection."
ESH; https://www.eshonline.org/spotlights/esh-stabtement-on-covid-19/	March 12, 2020	• "In stable patients with COVID-19 infections or at risk for COVID-19 infections, treatment with ACEIs and ARBs should be executed according to the recommendations in the 2018 ESC/ESH guidelines." • "The currently available data on COVID-19 infections do not a support a differential use of RAS blockers (ACEI or ARBs) in COVID-19 patients."
Hypertension Canada; https://hypertension.ca/wp-content/uploads/2020/03/2020-30-15-Hypertension-Canada-Statement-on-COVID-19-ACEi-ARB.pdf	March 13, 2020	• "However, there is no evidence that patients with hypertension or those treated with ARB or ACE inhibitor antihypertensive therapy are at higher risk of adverse outcomes from COVID-19 infection." • "We endorse patients with hypertension to continue with their current blood pressure treatment."
The Canadian Cardiovascular Society and the Canadian Heart Failure Society; https://www.ccs.ca/images/Images_2020/CCS_CHFS_statement_regarding_COVID_EN.pdf	March 15, 2020	"The Canadian Cardiovascular Society and the Canadian Heart Failure Society strongly discourage the discontinuation of guideline directed medical therapy (GDMT) involving Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARB) or Angiotensin Receptor Neprilysin Inhibitors (ARNi) in hypertensive or heart failure patients as a result of the COVID-19 pandemic."
International Society of Hypertension; https://ish-world.com/news/a/A-statement-from-the-International-Society-of-Hypertension-on-COVID-19/	March 16, 2020	"[T]here is no good evidence to change the use of ACE-inhibitors or ARBs for the management of raised blood pressure in the context of avoiding or treating COVID-19 infection."
BCS and BSH; https://www.britishcardiovascularsociety.org/news/ACEi-or-ARB-and-COVID-19	March 19, 2020	"[T]he BCS and the BSH…share the view of the European Society of Hypertension and the Renal Association that patients should continue treatment with ACEi and ARB unless specifically advised to stop by their medical team."

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BCS, British Cardiovascular Society; BSH, British Society for Heart Failure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HFSA, Heart Failure Society of America; RAAS, renin angiotensin aldosterone system.

Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers
doi:10.1001/jamacardio.2020.1282

Methods

- **Population-based case–control study in the Lombardy region of Italy**
  - A total of 6272 case patients, residents in Lombardy, 40 years of age or older, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  - COVID-19 Dx was confirmed by nasopharyngeal swab PCR
  - Odds ratios and 95% confidence intervals for associations between drugs and infection, with adjustment for confounders, were estimated by means of logistic regression

Results

Case patients: 6272 **Controls: 30759**

Table 1. Demographic and Clinical Characteristics of Patients with Covid-19 (Case Patients) and Matched Controls.*

Characteristic	Case Patients (N=6272)	Controls (N=30,759)	Relative Difference
			%
Age — yr	68±13	68±13	MV
Female sex — no. (%)	2303 (36.7)	11,357 (36.9)	MV
Drugs — no. (%)†			
Antihypertensive drugs overall	3632 (57.9)	15,319 (49.8)	14.0
ACE inhibitors	1502 (23.9)	6,569 (21.4)	10.5
ARBs	1394 (22.2)	5,910 (19.2)	13.3
Calcium-channel blockers	1446 (23.1)	5,926 (19.3)	13.1
Beta-blockers	1826 (29.1)	7,123 (23.2)	20.5
Diuretics	1902 (30.3)	7,420 (24.1)	20.5
Thiazide or thiazide-like diuretics	1104 (17.6)	5,074 (16.5)	6.4
Loop diuretics	871 (13.9)	2,411 (7.8)	43.6
Mineralocorticoid-receptor antagonists	239 (3.8)	738 (2.4)	37.1
Monotherapy	1067 (17.0)	4,903 (15.9)	6.4
Combination therapy	2565 (40.9)	10,416 (33.9)	17.3
Oral antidiabetic drugs overall	861 (13.7)	3,158 (10.3)	25.0
Metformin	628 (10.0)	2,331 (7.6)	24.4
Sulfonylureas	214 (3.4)	781 (2.5)	25.6
DPP-4 inhibitors	89 (1.4)	313 (1.0)	28.4
GLP-1–receptor agonists	65 (1.0)	195 (0.6)	38.9
SGLT2 inhibitors	47 (0.7)	109 (0.4)	52.8
Thiazolidinediones	35 (0.6)	95 (0.3)	44.7
Other oral antidiabetic agents	219 (3.5)	825 (2.7)	23.3
Insulin	338 (5.4)	863 (2.8)	47.8
Lipid-lowering drugs	1928 (30.7)	7,833 (25.5)	16.9
Antiplatelet drugs	1363 (21.7)	4,868 (15.8)	26.9
Oral anticoagulant agents	643 (10.3)	2,173 (7.1)	30.9
Digitalis	66 (1.1)	170 (0.6)	47.3
Nitrates	201 (3.2)	624 (2.0)	36.5
Drugs for respiratory disease overall	943 (15.0)	3,170 (10.3)	31.3
Long-acting β-agonists	508 (8.1)	1,527 (5.0)	38.5
Short-acting β-agonists	268 (4.3)	880 (2.9)	32.8
Inhaled glucocorticoids	499 (8.0)	1,658 (5.4)	32.0
Other drugs for respiratory disease	258 (4.1)	614 (2.0)	51.3
Immunosuppressive agents	802 (12.8)	2,711 (8.8)	30.9
Nonsteroidal antiinflammatory drugs	1036 (16.5)	4,579 (14.9)	10.0
Nonselective COX inhibitors	864 (13.8)	3,914 (12.7)	7.7
Selective COX2 inhibitors	252 (4.0)	1,039 (3.4)	16.0

Table 1. (Continued)

Characteristic	Case Patients (N=6272)	Controls (N=30,759)	Relative Difference
			%
Coexisting conditions and associated procedures — no. (%)			
Cardiovascular disease	1891 (30.1)	6,679 (21.7)	28.0
Coronary artery disease	473 (7.5)	1,519 (4.9)	34.6
Percutaneous coronary intervention	244 (3.9)	823 (2.7)	31.3
Heart failure	323 (5.1)	759 (2.5)	52.1
Respiratory disease	651 (10.4)	1,716 (5.6)	46.3
Chronic obstructive pulmonary disease	188 (3.0)	433 (1.4)	53.1
Asthma	18 (0.3)	35 (0.1)	60.4
Kidney disease	311 (5.0)	818 (2.7)	26.8
Chronic kidney disease	181 (2.9)	393 (1.3)	55.8
Dialysis	49 (0.8)	54 (0.2)	77.6
Cancer	1091 (17.4)	4,639 (15.1)	13.3
Chronic Related Score — no. (%)‡			
0	2116 (33.7)	13,051 (42.4)	−25.8
1	1450 (23.1)	7,625 (24.8)	−7.2
2	1117 (17.8)	4,856 (15.8)	11.4
3	676 (10.8)	2,458 (8.0)	25.9
4	913 (14.6)	2,769 (9.0)	38.2

* Plus–minus values are means ±SD. Cases of coronavirus disease 2019 (Covid-19) were diagnosed between February 21 and March 11, 2020. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, COX cyclooxygenase, COX-2 cyclooxygenase 2, DPP-4 dipeptidyl peptidase 4, GLP-1 glucagon-like peptide 1, MV matching variable, and SGLT2 sodium–glucose cotransporter 2.

† Data are for patients who received at least one prescription during 2019. Only 10 patients (1 case patient and 9 controls) received renin inhibitors, and 87 patients (28 case patients and 59 controls) received sacubitril–valsartan.

‡ The Chronic Related Score is a new index of patients' clinical profile that is derived from inpatient and outpatient services provided by the Regional Health Service and is validated for outcome prediction.[28] Five categories of progressively worsening clinical profile are considered.

The use of ACE inhibitors and ARBs was more common among case patients than among controls

Results

Table 2. Odds Ratios for Covid-19 Associated with Use of RAAS Blockers, Other Blood-Pressure–Lowering Drugs, Drugs for Other Disease, and Other Features.*

Variable	Odds Ratio for Covid-19 (95% CI)†	
	Unadjusted	Adjusted
Drugs‡		
Antihypertensive drugs overall	1.53 (1.43–1.63)	
ACE inhibitors	1.16 (1.08–1.24)	0.96 (0.87–1.07)
ARBs	1.20 (1.12–1.29)	0.95 (0.86–1.05)
Calcium-channel blockers	1.28 (1.18–1.38)	1.03 (0.95–1.12)
Beta-blockers	1.42 (1.33–1.51)	0.99 (0.91–1.08)
Diuretics as a whole	1.69 (1.57–1.83)	
Thiazide or thiazide-like diuretics	1.09 (1.01–1.17)	1.03 (0.86–1.23)
Loop diuretics	2.01 (1.83–2.20)	1.46 (1.23–1.73)
Mineralocorticoid-receptor antagonists	1.59 (1.37–1.85)	0.90 (0.75–1.07)
Oral antidiabetic drugs overall	1.40 (1.28–1.52)	1.07 (0.97–1.17)
Insulin	1.98 (1.74–2.25)	1.37 (1.19–1.58)
Lipid-lowering drugs	1.33 (1.24–1.41)	1.02 (0.94–1.10)
Antiplatelet drugs	1.52 (1.41–1.63)	1.19 (1.09–1.30)
Oral anticoagulant agents	1.51 (1.37–1.66)	1.16 (1.04–1.30)
Digitalis	1.94 (1.45–2.59)	1.24 (0.91–1.69)
Nitrates	1.55 (1.31–1.83)	1.04 (0.87–1.24)
Drugs for respiratory disease overall	1.54 (1.43–1.67)	1.25 (1.15–1.36)
Immunosuppressant agents	1.50 (1.38–1.63)	1.30 (1.20–1.42)
Nonsteroidal antiinflammatory drugs	1.13 (1.05–1.22)	1.06 (0.98–1.15)
Coexisting conditions		
Cardiovascular disease	1.66 (1.55–1.78)	1.01 (0.91–1.10)
Respiratory diseases	1.19 (1.10–1.28)	1.37 (1.23–1.54)
Kidney disease	1.97 (1.79–2.17)	1.13 (0.94–1.36)
Cancer	1.93 (1.68–2.21)	1.04 (0.94–1.16)
Chronic Related Score		
0	1.00 (reference)	1.00 (reference)
1	1.33 (1.23–1.43)	1.19 (1.09–1.31)
2	1.70 (1.56–1.86)	1.38 (1.23–1.54)
3	2.12 (1.91–2.36)	1.55 (1.34–1.78)
4	2.63 (2.37–2.91)	1.57 (1.34–1.84)

* CI denotes confidence interval, and RAAS renin–angiotensin–aldosterone system.
† Shown are odds ratios for Covid-19 associated with exposure to treatments and coexisting conditions. Absence of exposure was considered as the reference, unless otherwise indicated. Estimates were obtained by fitting conditional logistic-regression models. Both unadjusted estimates and estimates that were fully adjusted for drugs and coexisting conditions are shown. Fully adjusted estimates were obtained from a unique multivariate analysis.
‡ Data are for patients who received at least one prescription during 2019.

- Use of ARBs or ACE inhibitors did not show any association with COVID-19 among case patients overall or among patients who had a severe or fatal course of the disease

- The multivariable adjusted risk of COVID-19 was increased in patients with previous hospitalizations for cardiovascular or non-cardiovascular diseases.

Results

- Neither monotherapy nor combination therapy showed a significant association with the risk of COVID-19.

Table 3. Odds Ratios for Covid-19 Associated with Use of Antihypertensive Drugs Dispensed as Monotherapy or Combination Therapy.

Variable	Odds Ratio for Covid-19 (95% CI)*	
	Unadjusted	Adjusted
No use during 2019	1.00 (reference)	1.00 (reference)
Use only as monotherapy	1.39 (1.28–1.51)	1.03 (0.90–1.18)
Use as combination therapy	1.60 (1.50–1.72)	0.99 (0.90–1.09)

* Shown are odds ratios for Covid-19 associated with drug use. Nonuse was considered as the reference. Estimates were obtained by fitting conditional logistic-regression models. Both unadjusted estimates and estimates that were fully adjusted for drugs and coexisting conditions are shown.

Results

- Data on the risk of COVID-19 infection associated with the use of RAAS blockers and other drugs were similar in men and in women.

Table 4. Adjusted Odds Ratios for Covid-19 Associated with Use of RAAS Blockers and Other Antihypertensive Drugs.

Variable	Odds Ratio for Covid-19 (95% CI)*				
	ACE Inhibitors	ARBs	Calcium-Channel Blockers	Diuretics	Beta-Blockers
Severity of clinical manifestations†					
Mild to moderate	0.97 (0.88–1.07)	0.96 (0.87–1.07)	1.01 (0.92–1.10)	1.07 (0.97–1.19)	0.98 (0.89–1.07)
Critical or fatal	0.91 (0.69–1.21)	0.83 (0.63–1.10)	1.15 (0.91–1.44)	0.96 (0.74–1.26)	1.07 (0.84–1.37)
Sex‡					
Female	0.95 (0.81–1.12)	0.89 (0.76–1.05)	1.06 (0.92–1.23)	1.12 (0.94–1.34)	1.04 (0.91–1.20)
Male	0.98 (0.87–1.11)	0.98 (0.86–1.11)	1.00 (0.90–1.11)	1.02 (0.91–1.15)	0.97 (0.87–1.08)
Age at diagnosis§					
<60 Yr	0.94 (0.71–1.25)	0.89 (0.67–1.18)	1.13 (0.88–1.46)	0.99 (0.75–1.31)	1.00 (0.78–1.29)
≥60 Yr	0.97 (0.87–1.08)	0.95 (0.85–1.06)	1.01 (0.93–1.11)	1.07 (0.97–1.19)	0.99 (0.90–1.08)

* Shown are odds ratios for Covid-19 associated with exposure to antihypertensive drugs (at least one prescription during 2019). Absence of exposure was considered as the reference. Estimates were obtained by fitting conditional logistic-regression models. Estimates were fully adjusted for drugs and coexisting conditions.

† Data are for 5655 case patients with mild-to-moderate disease and 27,790 matched controls and for 617 case patients with critical or fatal disease and 2969 matched controls.

‡ Data are for 13,660 women (2303 case patients and 11,357 controls) and 23,371 men (3969 case patients and 19,402 controls).

§ Data are for 11,547 patients (1932 case patients and 9615 controls) younger than 60 years of age and 25,484 patients (4340 case patients and 21,144 controls) 60 years of age or older.

Discussion

- Patients with COVID-19 had a higher baseline prevalence of cardiovascular conditions and diseases (hypertension, coronary heart disease, heart failure, and chronic kidney disease)

- No evidence that RAAS blockers alter the evolution of the disease

- RAAS blockers do not modify susceptibility to COVID-19 applies to both sexes as well as to younger and older persons.

Conclusion

- There was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.

COVID19 Journal Reading Part 2

Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment

Circulation
An American Heart Association Journal

DOI: 10.1161/CIRCULATIONAHA.120.047521

Circulation April, 2020

Background

- **Hydroxychloroquine**
  - Act on the entry and post-entry stages of SARS-CoV and SARS-CoV-2 infection
- **Azithromycin**
  - Prolong QT and may provoke non-pause-dependent VT and Torsade de pointes

Risk Factor of QTc Prolongation

- Hypokalemia
- Hypomagnesemia
- Fever
- Inflammatory status

Management of QTc Prolongation

- Withhold the drugs in patients with baseline QT prolongation (eg, **QTc ≥500 msec**) or with known congenital long QT syndrome
- Monitor cardiac rhythm and QT interval; withdrawal of the drugs if **QTc > 500msec**
- Correction of hypokalemia and hypomagnesemia
  - Keep **K > 4 mEq/L** and **Mg>2mg/dL**
- Avoid other QT prolonging agents

Potential Adverse Events Associated with Possible COVID-19 Repurposed Drug

Table. Torsade de pointes potential and post-marketing adverse events associated with possible COVID-19 repurposed pharmacotherapies.

Possible COVID-19 Treatment	CredibleMeds Classification	VT/VF/TdP/LQTS in FAERS	Cardiac Arrest in FAERS
Repurposed antimalarial agents			
Chloroquine	Known risk	72	54
Hydroxychloroquine	Known risk	222	105
Repurposed antiviral agents			
Lopinavir/ritonavir	Possible risk	27	48
Adjunct agents			
Azithromycin	Known risk	396	251

COVID-19 indicates coronavirus disease 2019; FAERS, US Food and Drug Administration Adverse Event Reporting System; LQTS, long QT syndrome; and TdP, torsade de pointes.

Take Home Message

- There was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19
- All guidelines recommend **continuing ACEIs/ARBs** in pts with COVID-19
- Withhold the drugs in patients with baseline QT prolongation (eg, **QTc ≥500 msec**) or with known congenital long QT syndrome
  - Monitor cardiac rhythm and QT interval → withdrawal of drug if **QTc > 500msec**
  - Keep **K > 4 mEq/L** and **Mg>2mg/dL**


Thanks for
Your Attentions
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