Renin-angiotensin system pathway therapeutics associated with improved outcomes in males hospitalized with COVID-19*

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OPEN

Renin-Angiotensin System Pathway Therapeutics Associated With Improved Outcomes in Males Hospitalized With COVID-19*

OBJECTIVES: To determine whether angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors are associated with improved outcomes in hospitalized patients with COVID-19 according to sex and to report sex-related differences in renin-angiotensin system (RAS) components.

DESIGN: Prospective observational cohort study comparing the effects of ARB or ACE inhibitors versus no ARBs or ACE inhibitors in males versus females. Severe acute respiratory syndrome coronavirus 2 downregulates ACE-2, potentially increasing angiotensin II (a pro-inflammatory vasoconstrictor). Sex-based differences in RAS dysregulation may explain sex-based differences in responses to ARBs because the *ACE2* gene is on the X chromosome. We recorded baseline characteristics, comorbidities, prehospital ARBs or ACE inhibitor treatment, use of organ support and mortality, and measured RAS components at admission and days 2, 4, 7, and 14 in a subgroup ($n = 46$), recorded D-dimer ($n = 967$), comparing males with females.

SETTING: ARBs CORONA I is a multicenter Canadian observational cohort of patients hospitalized with acute COVID-19. This analysis includes patients admitted to 10 large urban hospitals across the four most populated provinces.

PATIENTS: One-thousand six-hundred eighty-six patients with polymerase chain reaction-confirmed COVID-19 (February 2020 to March 2021) for acute COVID-19 illness were included.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Males on ARBs before admission had decreased use of ventilation (adjusted odds ratio [aOR] = 0.52; $p = 0.007$) and vasopressors (aOR = 0.55; $p = 0.011$) compared with males not on ARBs or ACE inhibitors. No significant effects were observed in females for these outcomes. The test for interaction was significant for use of ventilation ($p = 0.006$) and vasopressors ($p = 0.044$) indicating significantly different responses to ARBs according to sex. Males had significantly higher plasma ACE-1 at baseline and angiotensin II at day 7 and 14 than females.

CONCLUSIONS: ARBs use was associated with less ventilation and vasopressors in males but not females. Sex-based differences in RAS dysregulation may contribute to sex-based differences in outcomes and responses to ARBs in COVID-19.

KEY WORDS: angiotensin receptor blockers; angiotensin-converting enzyme 2; angiotensin-converting enzyme inhibitors; COVID-19; sex differences

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The renin-angiotensin system (RAS) regulates blood pressure and water balance, as well as important roles in renal function, homeostasis, fibrosis, and inflammation. Angiotensin-converting enzyme (ACE)-2 converts angiotensin II to angiotensin 1–7 (1–3). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein downregulates ACE-2 (4),

decreasing conversion of angiotensin II to angiotensin 1–7 (1–3) that could increase angiotensin II levels, which worsens lung injury in influenza (**Supplemental Fig. S1**, http://links.lww.com/CCM/H133) (5, 6) and SARS models (7). Plasma angiotensin II levels are increased in influenza and are associated with influenza viral load and mortality (8). Angiotensin II levels are increased in some COVID-19 studies but not universally in COVID-19 (9–12).

Angiotensin receptor blockers (ARBs) block angiotensin II receptor 1 (13, 14) countering angiotensin II's effects. ACE inhibitors block conversion of angiotensin I to angiotensin II possibly mitigating angiotensin II in COVID-19. ARBs and ACE inhibitors are commonly used in hypertension (59%) (15), chronic kidney disease (CKD) (16), and diabetes (32%) (17). ARBs and ACE inhibitors target the RAS pathway by different mechanisms and could have different effects in COVID-19.

Trials of ARBs or ACE inhibitors differ: in one trial (18) of patients who were not on ARBs or ACE inhibitors previously who were then randomized to ARBs or not, patients on ARBs had significantly lower mortality. In contrast, trials of continuing or not continuing ARBs in patients already on those drugs found no differences in mortality between groups (19). These trials were all done in mild to moderately ill acute COVID-19 patients.

Males are a higher proportion of hospitalizations (e.g., 54% of cases), ICU admissions (64%), and deaths (57%) in COVID-19 (20–22). However, the biological cause (23, 24) of this differential risk remains unknown. Furthermore, the response to ARBs and ACE inhibitors according to sex has not been reported.

Sex differences in the RAS could explain worse male outcomes with COVID-19. *ACE-2* gene is on the X chromosome, so *ACE-2* X-inactivation in males versus females could cause sex-based differences of COVID-19 outcomes (25). Plasma ACE-2 is higher in males with kidney disease (26), diabetes (27, 28) and are associated with COVID-19 mortality (29).

We hypothesized that ARBs and ACE inhibitors improve outcomes in hospitalized COVID-19 patients according to sex and that sex-related differences in RAS components contribute to sex disparity in outcomes. This was an a priori hypothesis of a Canadian Institutes of Health Research grant in acute COVID-19 (30).

MATERIALS AND METHODS

Patient Population

ARBs CORONA I is a Canadian multisite observational cohort study comparing the effects of ARBs or ACE inhibitor use on outcomes of acute COVID-19 (ClinicalTrials.gov Identifier: NCT04510623). Patients with a positive polymerase chain reaction test admitted to hospital for acute COVID-19 were included. We excluded emergency department visits not requiring admission, those admitted to hospital but not due to acute COVID-19, acute COVID-19 readmissions, those with unknown discharge outcome, and those who remained hospitalized at the time of data censoring (July 10, 2021).

Data Collected

We recorded baseline characteristics, comorbidities (CKD, chronic cardiac disease, diabetes, hypertension), prehospital treatment with ARBs or ACE inhibitors, use of ventilation, vasopressors, and renal replacement therapy (RRT), 28-day and hospital mortality, and ICU and hospital length of stay. Patients were divided into ARBs or ACE inhibitors groups based on chart review and whether current ARBs or ACE inhibitor use was documented at hospital intake. If no ARBs or ACE inhibitor use was recorded, then the patient was classified as a no ARBs or ACE inhibitor control. Discarded clinical EDTA-plasma was collected at baseline (admission = day 0) and days 2, 4, 7, and 14 and stored in at –80°C in a randomly chosen subgroup of patients. For the longitudinal analyses, plasma was collected at days 0, 2, 4, 7, and 14 during hospitalization but no plasma samples were obtained after hospital discharge.

Justification for Use of Clinical Outcomes

Studies of acute COVID-19 report progression to critical care (ICU admission) and mortality, so we strengthened results by evaluating critical care support (i.e., ventilation, vasopressors, and RRT). As in the World Health Organization COVID-19 ordinal outcome scale (31), we assessed ventilation, vasopressors, and RRT (32, 33). We evaluated 28-day mortality because it is the pivotal endpoint for most randomized controlled trials (RCTs) in sepsis (34, 35).

Ethics

This study was approved by Providence Health Care and University of British Columbia Human Research Committee (H20-00600). Anonymized clinical data and use of discarded plasma from clinical blood tests were deemed low risk and informed consent was not required.

Renin-Angiotensin System Components

Plasma RAS components were measured in duplicate by enzyme-linked immunosorbent assays using commercial suppliers (**Supplemental Methods S2**, http://links.lww.com/CCM/H133) as per prior protocols (36, 37).

Statistical Analysis of Clinical Outcomes

We compared males' versus females' outcomes using logistic regression for binary outcomes and Cox regression for time to event. Regression models included sex and prehospital ARBs or ACE inhibitor usage as independent variables, site (to account for site differences in management), and ARBS CORONA I predefined adjustment variables: age, admission systolic blood pressure, chronic cardiac disease, hypertension, CKD, and diabetes. Results were expressed as adjusted odds ratio (aOR) or adjusted hazard ratio (aHR). The adjustment variables are from baseline values defined as the first available data within 24 hours of admission.

Separately analyzed, we added an interaction term between sex and prehospital ARBs or ACE inhibitor use to assess the association of prehospital ARBs or ACE inhibitor use and outcomes by sex and test for homogeneity between males and females. We further adjusted for admission creatinine level because it was different between ARBs or ACE inhibitor users and nonusers within each sex group.

Patients discharged alive prior to day 28 and lost to follow-up were assumed 28-day survivors. For time to hospital discharge, deaths prior to discharge were considered as never discharged and censored at largest observed length of stay. Results were not adjusted for multiple comparisons given the hypothesis-generating nature of the study. Missing data was minimal, so patients with missing data were excluded from the corresponding analysis.

Statistical Analysis of Renin-Angiotensin System Components

Plasma levels of RAS components were not normally distributed, so nonparametric statistics were used. Adjusted analyses based on quantile regression were performed to compare the median plasma RAS component levels at baseline between sexes after adjustment for age, chronic cardiac disease, CKD, diabetes, and hypertension. Due to limited sample size, comparison of plasma RAS component levels on days 2, 4, 7, and 14 were unadjusted for confounders and was based on linear quantile mixed regression with patient-specific random effect (https://www.jstatsoft.org/article/view/v057i13).

RESULTS

Patient Characteristics

Of 2,088 patients in ARBs I admitted between February 28, 2020, and April 14, 2021, we excluded emergency department visits not requiring hospital admission (n = 125), those admitted to hospital not due to acute COVID-19 (n = 220), acute COVID-19 readmissions (n = 37), those with unknown discharge outcome or currently still hospitalized (n = 19), and patient's sex being unspecified (n = 1) (**Table 1**). The final sample size was 1,686 (1,027 males, 658 females); 64% were not taking ARBs or ACE inhibitors at admission (658 males, 428 females), 18% were on ARBs at admission (177 males, 119 females), and 18% were on ACE inhibitors at admission (192 males, 112 females) (**Supplemental Fig. S3**, http://links.lww.com/CCM/H133). Patients on either ARBs or ACE inhibitors had more comorbidities than patients not on ARBs or ACE inhibitors in both males and females (**Supplemental Table S4**, http://links.lww.com/CCM/H133); 53.3% (320/600) continued on ARBs or ACE inhibitors after admission (male: 190/369 [52%], female: 130/231 [56%]).

Comparison of Males to Females

Males had significantly more chronic cardiac disease and a higher serum creatinine at baseline than females (Table 1; and **Supplemental Tables** S4 and **S5**, http://links.lww.com/CCM/H133). Males had significantly greater adjusted odds of inhospital mortality (1.46; 95% CI = 1.11–1.93; p = 0.008), ICU admission (aOR = 1.46; 95% CI = 1.14–1.86; p = 0.003), use of ventilation

TABLE 1.
Baseline Characteristics of Patients Hospitalized for COVID-19

Variable	All (*n* = 1,686)	Sex		*p*
		Male (*n* = 1,027)	Female (*n* = 659)	
Admission date, *n* (%)				0.481
March 2020 to May 2020	475 (28.2)	276 (26.9)	199 (30.2)	
June 2020 to August 2020	58 (3.4)	35 (3.4)	23 (3.5)	
September 2020 to November 2020	356 (21.1)	228 (22.2)	128 (19.4)	
December 2020 to February 2021	565 (33.5)	342 (33.3)	223 (33.8)	
March 2021 to April 2021	232 (13.8)	146 (14.2)	86 (13.1)	
COVID-19 confirmed status, *n* (%)				0.360
Positive–screening test	82 (4.9)	46 (4.5)	36 (5.5)	
Positive–definitive test	1,604 (95.1)	981 (95.5)	623 (94.5)	
Positive for other pathogen, *n* (%)	37 (2.2)	25 (2.4)	12 (1.8)	0.402
Sex, *n* (%)				–
Male	1,027 (60.9)	1,027 (100.0)	0 (0.0)	
Female	659 (39.1)	0 (0.0)	659 (100.0)	
Age				0.158
Mean (SD)	65.6 (16.7)	65.2 (15.9)	66.3 (17.8)	
Median (IQR)	67.0 (55.0–78.0)	66.0 (55.0–77.0)	69.0 (54.0–81.0)	
Range	(19.0–103.0)	(19.0–100.0)	(22.0–103.0)	
Comorbidities, *n* (%)				
Any of the four below	1,131/1,680 (67.3)	691/1,022 (67.6)	440/658 (66.9)	0.751
Chronic cardiac disease	422/1,673 (25.2)	282/1,018 (27.7)	140/655 (21.4)	0.004
Chronic kidney disease	239/1,681 (14.2)	152/1,022 (14.9)	87/659 (13.2)	0.338
Hypertension	890/1,679 (53.0)	548/1,022 (53.6)	342/657 (52.1)	0.530
Diabetes	560/1,679 (33.4)	349/1,021 (34.2)	211/658 (32.1)	0.369
Arterial oxygen saturation (%), mean (SD)	90.4 (9.0)	90.2 (8.9)	90.7 (9.3)	0.241
Missing, *n*	17	11	6	
Creatinine (μmol/L), median (IQR)	86 (69–116)	92 (76–127)	73 (59–99)	<0.001
Missing, *n*	29	17	12	
D-dimer level (ng/mL), median (IQR)	839 (508–1,600)	857 (512–1,590)	815 (503–1,600)	0.937
Missing, *n*	967	601	366	

IQR = interquartile range.

(aOR = 1.54; CI = 1.20–1.99; $p < 0.001$), and use of vasopressors (aOR = 1.58; CI = 1.23–2.03; $p < 0.001$) compared with females (**Fig. 1**; and **Supplemental Table S6**, http://links.lww.com/CCM/H133).

ARBs Versus No ARBs: Within Sex Comparison and Test for Interaction Between Sexes

Males on ARBs had decreased use of ventilation (aOR = 0.52; CI = 0.32–0.83; $p = 0.007$) and decreased use of vasopressors (aOR = 0.55; CI = 0.34–0.87; $p = 0.011$) compared with males not on ARBs or ACE inhibitors, but no significant effects of ARBs were observed in females for these outcomes (**Fig. 2**; and **Supplemental Table S7**, http://links.lww.com/CCM/H133; aOR = 1.33; CI = 0.76–2.30 for ventilation and aOR = 1.08; CI = 0.63–1.87 for use of vasopressors).

Test for interaction between males and females was significant for use of mechanical ventilation

(p = 0.006) and use of vasopressors (p = 0.044) indicating significantly different responses to ARBs between sexes. Time to discharge was also significantly shorter for males on ARBs versus those not on ARBs (aHR = 1.35; CI = 1.08–1.70; p = 0.009; median time to discharge, 17 vs 21 d). The aHR in females was similar to males (aHR = 1.27; CI = 0.97–1.66; p = 0.077; median time to discharge, 15 vs 19 d) and the test for interaction between males and females was not significant (p = 0.706).

ACE Inhibitors Versus No ACE Inhibitors: Within Sex Comparison and Test for Interaction Between Sexes

There were no differences in mortality and other outcomes of males on ACE inhibitors versus males not on ARBs or ACE inhibitors (Fig. 2; and Supplemental Table S7, http://links.lww.com/CCM/H133). There were also no significant effects of ACE inhibitors in females for these outcomes.

ARBs Versus ACE Inhibitors

There was some evidence that the effect of ARBs was different from that of ACE inhibitors in females for use of invasive ventilation (aOR = 1.96; CI = 0.99–3.88; p = 0.054; **Fig. 3**, Supplemental Table S7, http://links.lww.com/CCM/H133). Males on ARBs alone had significantly shorter time to discharge compared with males on ACE inhibitors (aHR = 1.33; CI = 1.02–1.72; p = 0.034; median time to discharge, 17 vs 21 d).

Plasma Levels of RAS Components and D-Dimer

Plasma RAS component levels were measured in a random subgroup of patients (**Fig. 4**; and **Supplemental Table S8**, http://links.lww.com/CCM/H133). Baseline plasma ACE-1 was significantly higher in males (n = 33) than females (n = 13) (estimated difference in median = 78.1 ng/mL; CI = 3.2–153.0; p = 0.042) (Fig. 4*A*). There was no significant difference in ACE-2 levels between males and females. Angiotensin II was significantly higher in males compared with females on day 7 (median: 109.1 vs 66.2; p = 0.047) and 14 (median: 126.4 vs 42.7; p < 0.001) of hospitalization (Fig. 4*B*). Sample size was inadequate to test for differences in RAS components between patients on or not on ARBs or ACE inhibitors.

There were no differences in baseline plasma D-dimer levels between males (median interquartile range [IQR] = 857 [508–1,600]) and females (median [IQR] = 815 [503–1,600]; p = 0.937) (Table 1).

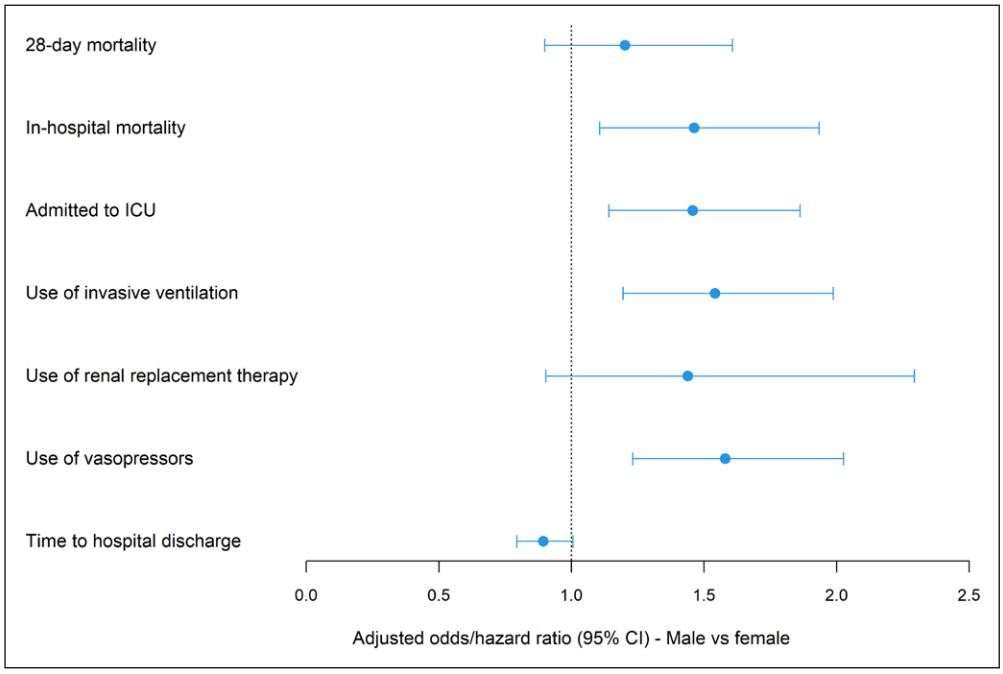

Figure 1. Males experience significantly worse clinical outcomes compared with females overall. *Forest plot* indicating results of separate regression analyses in form of multivariable logistic regression for binary outcomes (adjusted odds ratios) and Cox regression for "time to" outcomes (adjusted hazard ratios), as well as 95% CIs (*x*-axis), comparing males and females overall. *Vertical dashed line* indicates adjusted odds ratio of 1. See *Methods* for list of adjustment variables.

DISCUSSION

Males hospitalized with acute COVID-19 had worse outcomes than females. Our novel, more clinically relevant finding was that males on ARBs had better outcomes than males not on ARBs but females did not. Our finding higher plasma ACE-1 and angiotensin II level in males versus females is also novel, suggesting sex-related RAS dysregulation in acute COVID-19.

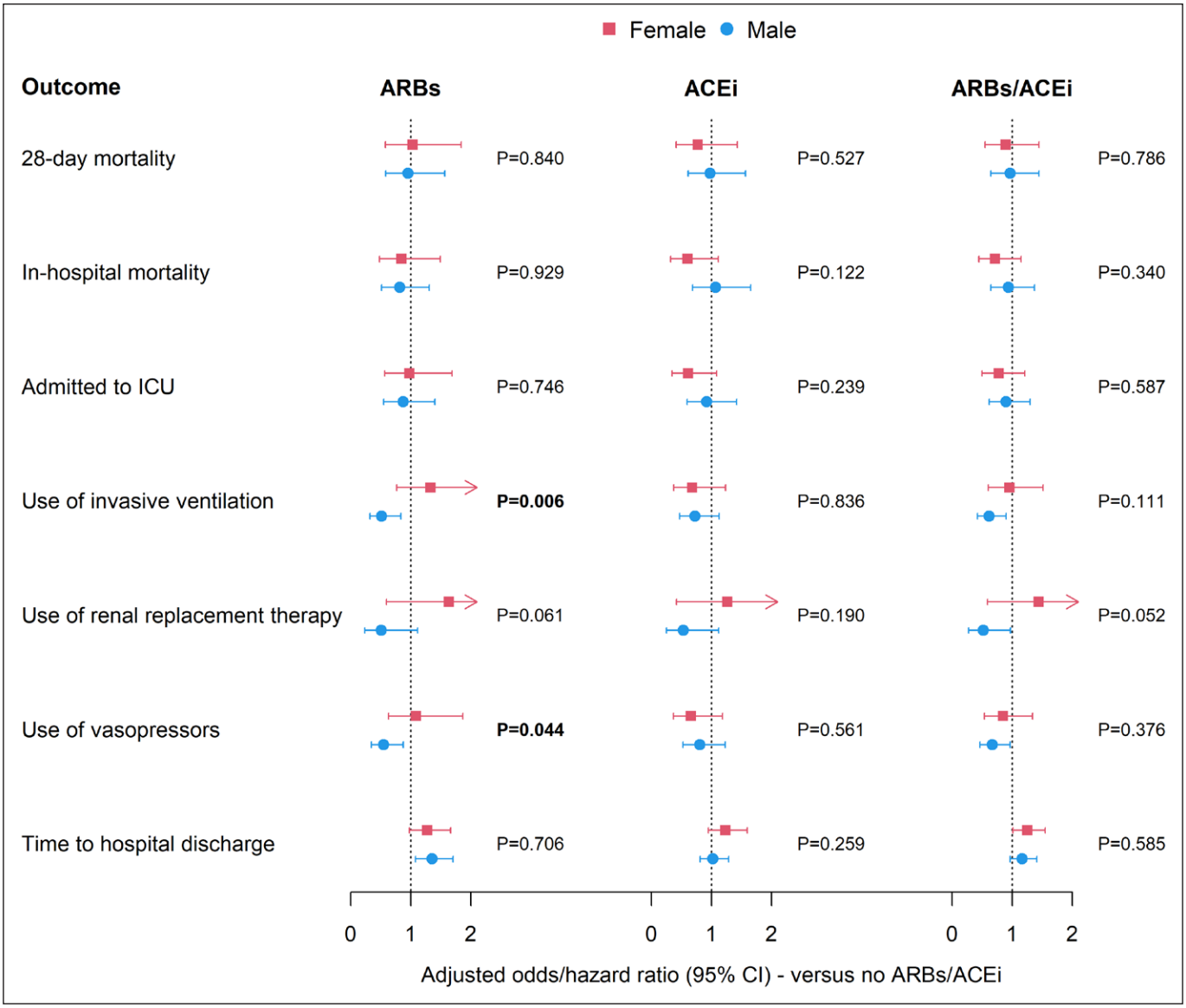

Figure 2. Prehospital angiotensin receptor blockers (ARBs) show protective effects within males: use of ventilation and vasopressors were significantly less than males not on prehospital ARBs or angiotensin-converting enzyme inhibitors (ACEi), and the effect was significantly greater than within females. *Forest plot* showing within sex comparison odds ratios/hazard ratios of clinical outcomes for those on ARBs (*first column*), ACEi (*second column*), or on either ARBs or ACEi (*third column*) versus those not on ARBs or ACEi, respectively. See *Methods* for list of adjustment variables. Test for homogeneity *p* values are included, indicating comparisons where males were significantly different than females.

Males had more frequent acute respiratory distress syndrome (ARDS), RRT use, and greater length of mechanical ventilation and hospital stay and higher hospital mortality than females in another study (38). Globally, males account for a higher proportion of hospitalizations, ICU admissions, and deaths (20).

We proposed a priori and confirmed herein that males on ARBs (but not ACE inhibitors) had lower mortality than males not on ARBs. Meta-analyses (39) report that use of ARBs and ACE inhibitors in COVID-19 is associated with decreased mortality. None have reported associations of ARBs or ACE inhibitors with outcomes of COVID-19 in males versus females.

RCTs of ARBs and ACE inhibitors do not address male versus female responses. Three RCTs compared an ARB to standard of care, two underpowered with nonsignificant findings (40, 41). Telmisartan significantly decreased ICU admission, ventilation and death in one small RCT with a higher proportion of males in the telmisartan versus control group (18). However, there is no direct report of sex-based differences in responses to ARBs or ACE inhibitors.

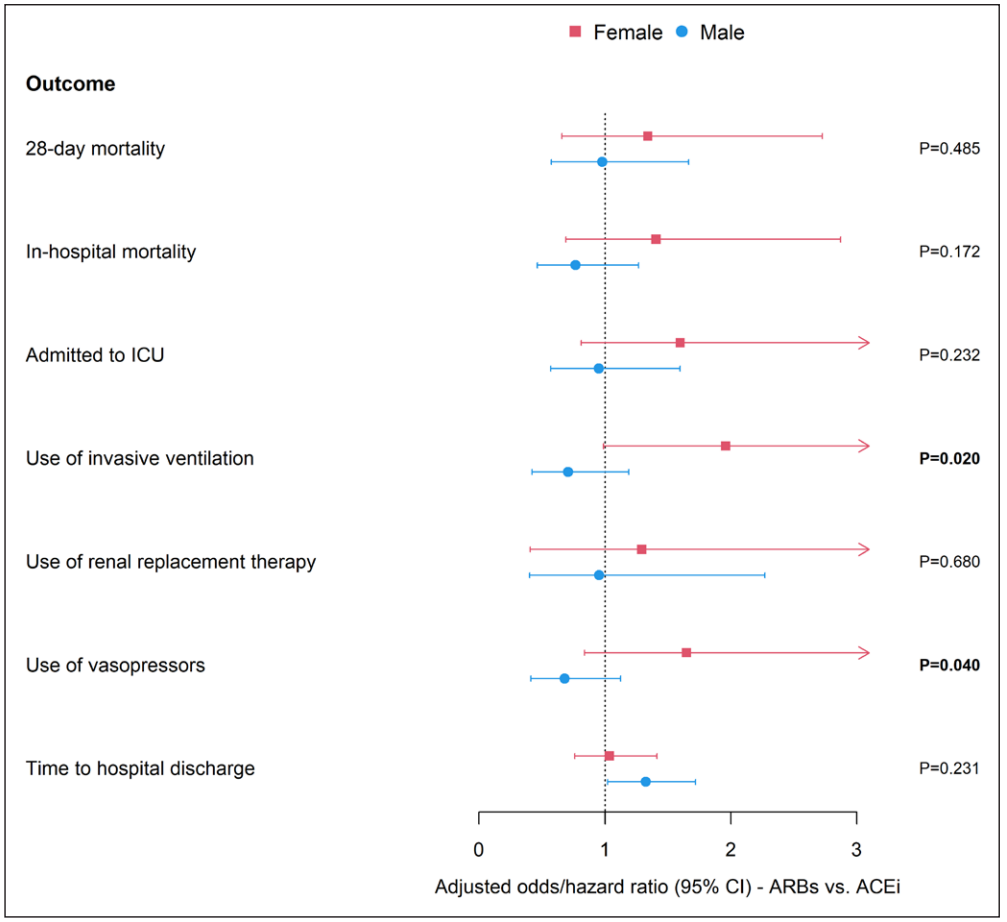

Figure 3. There were varying effects of angiotensin receptor blockers (ARBs) compared with ACE inhibitors (ACEi) within different sexes. Males on ARBs had significantly shorter time to discharge compared with males on ACEi, whereas females on ARBs were significantly more likely to use ventilation than females on ACEi. *Forest plot* showing within sex comparison odds ratios/hazard ratios of clinical outcomes for those on ARBs versus those on ACEi. See *Methods* for list of adjustment variables. Test for homogeneity *p* values are included, indicating the protective effect of ARBs compared with ACEi was significantly greater among males compared with among females, in use of ventilation and use of vasopressor outcomes.

Our analysis is novel and adds to the literature by providing unique insights about why males with acute COVID-19 do worse and the first discovery that males respond better to prior ARBs use than females. Trials of ARBs or ACE inhibitors differ: In one trial (18) of patients who were not on ARBs or ACE inhibitors previously who were then randomized to ARBs or not, patients on ARBs had significantly lower mortality. In contrast, trials of continuing or not continuing ARBs in patients already on those drugs found no differences in mortality between groups (19).

Sex-related differences in ARBs' responses occur in hypertension, and there are improved responses to ARBs in males in hypertension RCTs. In a large meta-analysis, seven of nine trials found ACE inhibitor or ARBs more beneficial in males than females (42).

A fundamental question is whether differences in outcomes between those taking and not taking ARB or ACE inhibitors is related to the patient rather than the drug. Supplemental Table S4 (http://links.lww.com/CCM/H133) shows baseline characteristics stratified by sex (since the final regression models compared within sex also) comparing no ARBs or ACE inhibitor, ACE inhibitor, and ARBs. While there were some differences between patients on ARBs or ACE inhibitor and those not (e.g., males not on ARBs or ACE inhibitor had significantly lower systolic blood pressure than those on ARBs and ACE inhibitor), the adjusted regression model took these patient baseline characteristics into account (Supplemental Tables S6 and S7, http://links.lww.com/CCM/H133). Thus, we suggest that the differences between patients taking versus not taking ARBs and ACE inhibitors is associated with the drugs.

To understand mechanisms for differences in outcomes of males and females, we evaluated RAS components and D-dimers and found higher plasma levels of ACE-1 and angiotensin II in males than females but no differences between sexes in D-dimer levels.

Proposed mechanisms for sex-related differences of COVID-19 include that ACE-2 (the main SARS-CoV-2 receptor) is on the X chromosome and incomplete X chromosome activation could cause sex differences in ACE-2 expression. Transmembrane protease, serine 2 (TMPRSS2) is also required for SARS-CoV-2 cell entry [23, 24]). Androgens regulate TMPRSS2 (43) perhaps

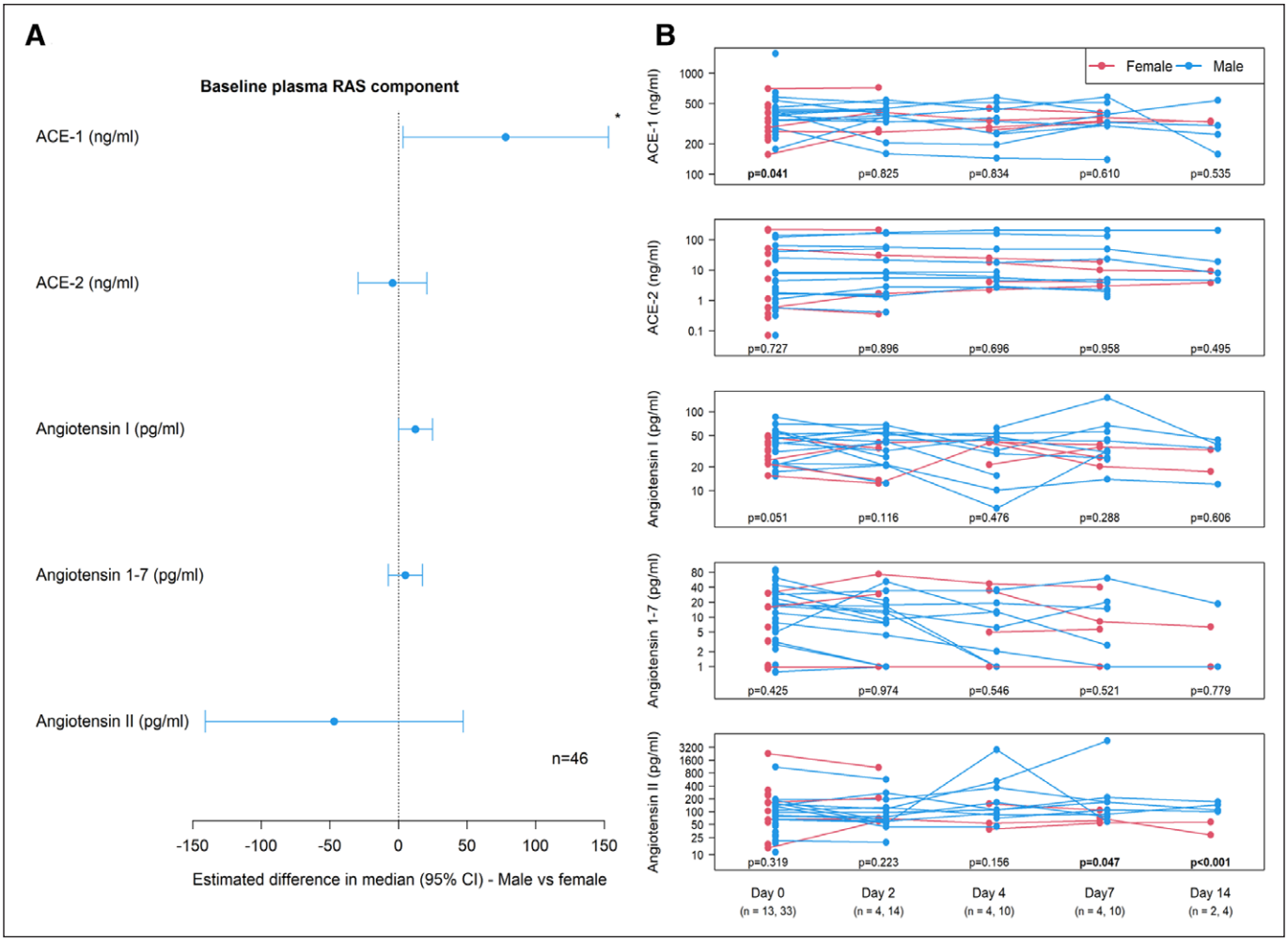

Figure 4. Males' renin-angiotensin system (RAS) component levels compared with those of females hospitalized with COVID-19 at baseline (day 0), day 2, 4, 7, and 14. **A**, Baseline adjusted median difference in RAS component levels males versus females based on quantile regression adjusting for age, chronic cardiac disease, chronic kidney disease, diabetes, and hypertension ($n = 46$). **B**, Comparison of RAS component levels between sexes over time based on adjusted quantile regression (day 0) and linear quantile mixed regression (day 2 and onward; unable to adjust for other variables due to small sample size). ACE = angiotensin-converting enzyme.

altering SARS-CoV-2 uptake in males versus females. We could not assess TMPRSS2 levels in this clinical study.

A recent study (12) found that angiotensin II levels decreased over time in severe COVID-19 suggesting decreased systemic catalytic activity over time following inflammatory ACE-1 shedding from the endothelium. Another recent study (44) found prominent but delayed elevations in renin and ACE-2 among more severely ill patients. Another series (45) reports increases in ACE-2 over time that are not unique to COVID ARDS.

Our findings of higher plasma ACE-1 and angiotensin II in males versus females is novel. No studies of plasma angiotensin II levels in COVID-19 (9–12) compare males to females. High angiotensin II levels are associated with prolonged viral shedding (45), human influenza (8), and worse lung injury (6) possibly explaining why we found that males on ARBs had better outcomes than males not on ARBs; our RAS subgroup sample size was underpowered to evaluate ARBs interaction according to sex.

Females have less frequent thromboembolic complications of COVID-19 compared with males (46). However, we did not find sex-related differences in plasma D-dimer levels.

Strengths of our study are the novel biological sex hypothesis, multicenter design, large sample size, and evaluation of sex-based differences in response to ARBs or ACE inhibitors. Originally the ARBs CORONA I cohort study had a relatively conservative enrollment target based on early estimates

of frequency and prevalence of COVID-19. The COVID-19 pandemic rapidly grew, we secured increased funding and converted our cohort from a closed to an open cohort to increase power and generalizability.

Limitations are that our observational cohort cannot prove causation. Differences based on long-term ARBs and ACE inhibitor use may reflect the underlying cardiorenal vascular disease for which ARBs and ACE inhibitors are prescribed, the degree of chronic disease progression, and adequacy of disease control. Given the multiple indications for treatment (e.g., hypertension, renal protection, myocardial anti-remodeling), it is difficult to adjust for indication severity and/or adequacy of control. Additionally, although hypertension was included in our regression models, other non-ARBs or ACE inhibitor antihypertensive medications were not accounted for and may be confounding factors. Another limitation was the numbers of events on the day of admission were limited; however, there were a sizeable number of patients with events over the course of hospitalization. For example, 62 males on ARBs received vasopressors and 63 males on ARBs received ventilation. We also investigated levels of RAS pathway components over 14 days in hospital and found plasma ACE-1 and angiotensin II were higher in males; however, the sample size and power were limited. Renin, ACE-1, and ACE-2 have high catalytic activity in plasma. Because of this high enzymatic activity, the levels of angiotensinogen metabolites may also be impacted by factors such as time from sample collection, ambient temperature, and plasma pH. Best practice when measuring these metabolites is to limit the amount of time before freezing and/or to add enzymatic inhibitors to stabilize the sample (19). We acknowledge the potentially significant risk of measurement error for angiotensin I, angiotensin II, and angiotensin 1–7. Also, our results were focused on biological sex and not gender and so it was beyond the scope of our study to explore the effects of gender but that may also be an important in COVID-19 and response to ARBs and ACE inhibitors. And finally, chronic RAS blocker therapies may also be in part a proxy for how frequently and how well patients access the healthcare system. This study was done in Canada that has a universal healthcare system, and while this does not remove all barriers, it does address some disparities. We do recognize that the longitudinal management of chronic disease may also drive our finding associations according to sex with better outcomes.

There was considerable controversy around early versus conservative intubation in acute COVID-19. Unfortunately, we do not know local practices regarding intubation, which is an additional limitation that may have impacted the event rate for invasive ventilation.

CONCLUSIONS

Males hospitalized with COVID-19 had worse clinical outcomes than females. Prehospital ARBs use—but not ACE inhibitor use—was associated with significantly better clinical outcomes in males but not in females. While the main insights of our study are the clinical outcomes according to sex and use of ARBs or ACE inhibitors, the RAS pathway component analyses suggest but do not prove a possible mechanism of the clinical findings.

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