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Association of outpatient use of renin–angiotensin–aldosterone system blockers on outcomes of acute respiratory illness during the COVID-19 pandemic: a cohort study

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ABSTRACT

Objectives Evaluate the associations between patients taking ACE inhibitors and angiotensin receptor blockers (ARBs) and their clinical outcomes after an acute viral respiratory illness (AVRI) due to COVID-19.

Design Retrospective cohort.

Setting The USA; 2017–2018 influenza season, 2018–2019 influenza season, and 2019–2020 influenza/COVID-19 season.

Participants People with hypertension (HTN) taking an ACEi, ARB or other HTN medications, and experiencing AVRI.

Main outcome measures Change in hospital admission, intensive care unit (ICU) or coronary care unit (CCU), acute respiratory distress (ARD), ARD syndrome (ARDS) and all-cause mortality, comparing COVID-19 to pre-COVID-19 influenza seasons.

Results The cohort included 1 059 474 episodes of AVRI (653 797 filled an ACEi or ARB, and 405 677 other HTN medications). 58.6% were women and 72.9% with age ≥65. The ACEi/ARB cohort saw a larger increase in risk in the COVID-19 influenza season than the other HTN medication cohort for four out of five outcomes, with an additional 1.5 percentage point (pp) increase in risk of an inpatient stay (95% CI 1.2 to 1.9 pp) and of ICU/CCU use (95% CI 0.3 to 2.7 pp) as well as a 0.7 pp (0.1 to 1.2 pp) additional increase in risk of ARD and 0.9 pp (0.4 to 1.3 pp) additional increase in risk of ARDS. There was no statistically significant difference in the absolute risk of death (−0.2 pp, 95% CI −0.4 to 0.1 pp). However, the relative risk of death in 2019/2020 versus 2017/2018 for the ACEi/ARB group was larger (1.40 (1.36 to 1.44)) than for the other HTN medication cohort (1.24 (1.21 to 1.28)).

Conclusions People with AVRI using ACEi/ARBs for HTN had a greater increase in poor outcomes during the COVID-19 pandemic than those using other medications to treat HTN. The small absolute magnitude of the differences likely does not support changes in clinical practice.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ It uses an approach of difference-in-differences that mitigates some of the limitations of observational studies.
⇒ The cohort includes a diverse sample of US residents, including people with commercial insurance and Medicare Advantage.
⇒ The cohort is not representative of people without insurance or people with Medicaid or other insurance types.
⇒ Given the observational design, it is not possible to make causal claims.

INTRODUCTION

The renin–angiotensin–aldosterone system (RAAS) is a hormone system responsible for several physiologic functions including vascular resistance, electrolyte homeostasis and fluid balance. Medications such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) interrupt different steps in this system and are commonly used in clinical practice for outpatient blood pressure or heart failure management. Early in the COVID-19 pandemic, preclinical studies raised concerns about the association between use of ACEi or ARBs and severe illness in hypertensive patients with COVID-19.[1] Angiotensin-converting enzyme 2 (ACE-2) is the binding site for respiratory viruses including the SARS-CoV-2, and two opposing theories on the potential effects of these medications have been debated: one postulating an increased susceptibility to SARS-CoV-2 through upregulation of ACE-2 receptors, and one postulating a protection against severe disease through suppression of angiotensin II and subsequent prevention of virus-mediated acute lung injury.[1]

Since the hypothesis that the prior use of RAAS inhibitors could be associated with worse clinical outcomes in hypertensive patients diagnosed with COVID-19 was raised,

several clinical studies were published.[2] In the latest update of a living systematic review addressing this question by Mackey and colleagues, the authors reported high confidence based on 78 studies (77 observational studies, 1 randomised controlled trial (RCTs)) in the finding that ACEi/ARB use is not associated with COVID-19 severity.[2] Another 21 systematic reviews and/or meta-analyses have been consistent with this conclusion as well.[3–23] Furthermore, two recently published RCTs do not support the discontinuation of these drugs in hypertensive patients admitted to the hospital with COVID-19.[24 25]

Most existing studies, however, are of relatively small sample size with low methodological quality. The RCTs addressing discontinuation of ACEi/ARBs in people hospitalised with COVID-19, while reassuring for clinicians and patients, do not directly address the question of whether the risk of hospitalisation may be increased in this population. In this study, we aimed to evaluate the associations between prescription fills for ACE inhibitors (ACEis) and ARBs and clinical outcomes with an acute viral respiratory illness (AVRI) due to COVID-19. We use a difference-in-differences approach comparing the COVID-19 period to prior AVRI seasons and comparing users of ACEis or ARBs versus other hypertension (HTN) medications in order to control for otherwise unobserved differences in underlying health and healthcare-seeking behaviour between the medication cohorts. We assessed severity of illness and mortality in AVRI across cohorts of patients with HTN using ACEis, ARBs and other HTN medications, and we compared the differential effects of these medications on outcomes of AVRI in the 2017/2018 and 2018/2019 influenza seasons to those in the 2019/2020 influenza/COVID-19 season in the USA.

METHODS

We adhered to the REporting of studies Conducted using Observational Routinely collected health Data statement.[26]

Data source and study setting

We used deidentified administrative claims data from the OptumLabs Data Warehouse (OLDW) to identify episodes of AVRI in people with Medicare Advantage or commercial health insurance in the USA. The OLDW includes medical and pharmacy claims, laboratory results and enrolment records for commercial and Medicare Advantage enrollees.[27] The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities, and geographical regions across the United States. This study was deemed exempt by the Institutional Review Board.

Study design and participants

We created a cohort of patients with one or more episodes of AVRI with an initial date of service (index date) between 1 October 2017, and 30 November 2020. AVRI was defined using ICD-10 diagnosis codes for viral causes of respiratory illness: bronchitis, pneumonia, influenza, influenza-like illness and lower respiratory infections. (online supplemental material S1). Each episode of AVRI started on the first date on which the patient had a claim with an AVRI diagnosis code and continued until the patient experienced a 30-day span with no AVRI diagnoses.

We required 180 days of continuous insurance enrolment before the index date of the AVRI episode. Insurance claims during this period were used to identify HTN diagnoses as well as other comorbidities that could be associated with COVID-19 morbidity and mortality risk or with the choice of medications to treat HTN, as explained below.

Variables and measurements

Patient age, sex, residence state and insurance enrolments dates and coverage type (commercial vs Medicare Advantage) were taken from insurance enrolment data.

HTN and comorbidities

HTN and most comorbidities were defined based on the Quan-enhanced Elixhauser comorbidity ICD-10 codes[28]; codes used to define comorbidities not included in the Elixhauser index (coronary artery disease, stroke, deep vein thrombosis and pulmonary embolism) are available in online supplemental material S1. HTN and diabetes were coded hierarchically such that people with both complicated and uncomplicated disease were coded as complicated. All comorbidities required at least one inpatient or two outpatient diagnoses on different dates of service in the 6 months before the index date. Inpatient and outpatient settings were defined using procedure and revenue codes using code lists developed for use with Healthcare Effectiveness Data and Information Set performance measures.[29]

HTN medications

We developed a comprehensive list of HTN medications (see online supplemental material S1), then identified all National Drug Codes for these medications in a table that is part of the OLDW. We searched for prescription fills in the 90 days before the index date for each episode of AVRI and categorised fill patterns as ACEi or ARB only, ACEi or ARB with other (ie, not ACEi or ARB) HTN medications, other HTN medications only or no HTN medications. In primary analyses, ACEi or ARB users with and without other HTN medications were combined and compared with people using only other HTN medications; information on people who did not use HTN medications is provided in summary tables for reference, but they were excluded from the analyses. A small number of people who filled both an ACEi and an ARB were also excluded from the analysis (N=10 933).

Outcomes

We specified five outcomes associated with more serious cases of AVRI: death, hospitalisation and, conditional on hospitalisation: intensive care unit (ICU) or coronary

care unit (CCU) services (revenue codes 0200 to 0219), a diagnosis of acute respiratory distress (ARD) (ICD-10 diagnosis code R06.03) and a diagnosis of ARD syndrome (ARDS) (ICD-10 diagnosis code J80).

Data on death in OLDW includes only the month and year of death to maintain deidentification. It is sourced from the Death Master File, claims information and insurance enrolment information. The mortality outcome in this study assessed whether the person was reported to have died in the same month as the index date or in the following month.

Data analysis

We used a difference-in-differences approach to assess the association between use of ACEis or ARBs and poor outcomes from COVID-19. The comparison group is people with HTN using HTN medications other than ACEis or ARBs; the exposure of interest is the COVID-19 pandemic. We compared outcomes of AVRI in the 2017/2018 and 2018/2019 influenza seasons to those in the 2019/2020 influenza/COVID-19 season. The premise is that the design will control for both differences in underlying health between the two medication groups (by comparing each to people taking those same medications in the years before COVID-19) and differences in healthcare service use during COVID-19 that are common to all people with HTN. The inclusion of two pre-COVID-19 influenza seasons allows for a comparison of differences in outcomes between the medication groups due to changes in overall AVRI illness mix unrelated to COVID-19. Cases, inpatient admission rates and mortality rates can vary substantially with different influenza strains.[30]

We used a linear probability approach to model each of the five outcomes, in three time periods (2017/2018, 2018/2019 and 2019/2020 seasons) for two patient medication groups (people using ACEis or ARBs vs those using other HTN medications). Regression models included patient sex, age (categorical), insurance type (Medicare Advantage vs commercial), Census region of residence, race/ethnicity and flags for comorbidities described above. Huber-White SEs were specified to adjust for repeated observations of some patients across separate episodes of AVRI. The model is specified such that the coefficient on the interaction between the 2019/2020 influenza/COVID-19 season and the ACEi/ARB group provides a statistical test for whether the ACEi/ARB group was differently affected by COVID-19 than the other HTN medication cohort. A coefficient greater than 0 indicates the ACEi/ARB group had a larger absolute increase in risk of the outcome than the other HTN medication cohort.

A linear probability model provides estimates of absolute risk differences rather than relative changes in risk. As a result, the differences are not scaled to the baseline probability of the event: a one percentage point (pp) risk difference may have different importance for an event with an incidence of 10% (relative increase 10%) compared with one with an incidence of 1% (relative increase 100%). To ease interpretation of results, we calculated average marginal effects for each influenza season over the medication groups (in other words, the adjusted probabilities were calculated keeping the actual medication group rather than changing the medication group of each individual). We calculated ratios of these adjusted probabilities in the 2018/2019 influenza season and the 2019/2020/COVID-19 influenza season versus the baseline 2017/2018 influenza season, along with p values for the hypothesis test that the ratios were equal to 1 (ie, the baseline year and the later year had no difference in outcome risk for that medication group). These ratios provide the percentage relative increase in the outcome risk.

Model result interpretation

If the presence of COVID-19 affects the ACEi/ARB group more than the other HTN medication group, we would expect to see a positive and statistically significant coefficient for the interaction term ACEi/ARB by season=2019/2020. We would place more credence in the COVID-19 season findings if we find that outcomes in the 2018/2019 season did not differ much from those in the 2017/2018 season, which would suggest that COVID-19 is fundamentally different from the general year-to-year shifts in influenza strain. This would be supported by finding (1) a smaller coefficient for season=2018/2019 than for season=2019/2020 and (2) a smaller coefficient for the interaction term ACEi/ARB by season=2018/2019 than for the interaction term ACEi/ARB by season=2019/2020. Stata/MP V.16.0 was used for all analyses (StataCorp College Station, Texas, 2019). The first author (MMJ) conducted all analyses and had access to all study data; all other authors had access to summary data and complete analysis results. No additional data available.

Patient and public involvement

Patients and/or public were not involved in this study.

RESULTS

We identified 1 247 393 episodes of AVRI in the study period among people with HTN. Of these, 15.1% (187 919) did not fill a HTN medication in the 90 days before the index date and were excluded from further analysis. Of the remaining 1 059 474, 61.7% (653 797) filled at least one ACEi or ARB, and 38.3% (405 677) filled no ACEi or ARBs (table 1). Most episodes were in female patients (58.6%; n=620 810) and in older patients, with 72.9% of AVRI episodes in people aged 65 and older (n=772 210). The most common comorbidities were chronic pulmonary diseases (35.2%; n=372 735), cardiac arrhythmias (27.2%, n=288 478), coronary artery disease (26.3%; n=279 098), diabetes with complications (25.6%; n=271 700) and congestive heart failure (24.0%; n=254 773).

Table 1 Cohort characteristics

	Comparison only (not included sample)	Included sample		Total included sample
	No HTN meds	Other HTN meds only	ACEi or ARB	
	N (%)	N (%)	N (%)	N (%)
Insurance type				
Medicare advantage	145 045 (77.2)	348 583 (85.9)	518 670 (79.3)	867 253 (81.9)
Commercial	42 874 (22.8)	57 094 (14.1)	135 127 (20.7)	192 221 (18.1)
Female	99 755 (53.1)	246 659 (60.8)	374 151 (57.2)	620 810 (58.6)
Age (categories)				
<35	3922 (2.1)	3354 (0.8)	4537 (0.7)	7891 (0.7)
35–44	8337 (4.4)	9784 (2.4)	17 780 (2.7)	27 564 (2.6)
45–54	17 704 (9.4)	24 916 (6.1)	51 926 (7.9)	76 842 (7.3)
55–64	32 637 (17.4)	59 872 (14.8)	115 095 (17.6)	174 967 (16.5)
65–74	54 862 (29.2)	120 039 (29.6)	218 160 (33.4)	338 199 (31.9)
75–84	44 330 (23.6)	115 011 (28.4)	171 276 (26.2)	286 287 (27.0)
85+	26 127 (13.9)	72 701 (17.9)	75 023 (11.5)	147 724 (13.9)
Race/ethnicity				
White	109 223 (58.1)	238 439 (58.8)	372 987 (57.0)	611 426 (57.7)
Black	28 990 (15.4)	70 774 (17.4)	103 284 (15.8)	174 058 (16.4)
Hispanic	20 302 (10.8)	36 478 (9.0)	82 374 (12.6)	118 852 (11.2)
Asian	4449 (2.4)	8003 (2.0)	15 063 (2.3)	23 066 (2.2)
Unknown/other	24 955 (13.3)	51 983 (12.8)	80 089 (12.2)	132 072 (12.5)
Census division				
New England	7217 (3.8)	18 358 (4.5)	25 557 (3.9)	43 915 (4.1)
Mid Atlantic	18 655 (9.9)	43 354 (10.7)	59 385 (9.1)	102 739 (9.7)
South Atlantic	66 206 (35.2)	154 483 (38.1)	252 798 (38.7)	407 281 (38.4)
E North Central	24 489 (13.0)	59 277 (14.6)	86 110 (13.2)	145 387 (13.7)
E South Central	12 743 (6.8)	28 786 (7.1)	47 182 (7.2)	75 968 (7.2)
W North Central	18 292 (9.7)	28 065 (6.9)	42 997 (6.6)	71 062 (6.7)
W South Central	25 743 (13.7)	48 406 (11.9)	92 517 (14.2)	140 923 (13.3)
Mountain	8484 (4.5)	14 224 (3.5)	27 963 (4.3)	42 187 (4.0)
Pacific	5902 (3.1)	10 612 (2.6)	19 087 (2.9)	29 699 (2.8)
Unknown/other	188 (0.1)	112 (0.0)	201 (0.0)	313 (<0.1)
Hypertension				
No complications	164 325 (87.4)	334 180 (82.4)	572 570 (87.6)	906 750 (85.6)
With complications	23 594 (12.6)	71 497 (17.6)	81 227 (12.4)	152 724 (14.4)
Comorbidities				
Diabetes				
No complications	22 002 (11.7)	42 302 (10.4)	99 778 (15.3)	142 080 (13.4)
With complications	37 742 (20.1)	99 365 (24.5)	172 335 (26.4)	271 700 (25.6)
Chronic pulmonary disease	66 355 (35.3)	163 682 (40.3)	209 053 (32.0)	372 735 (35.2)
Coronary artery disease	41 083 (21.9)	122 633 (30.2)	156 465 (23.9)	279 098 (26.3)
Congestive heart failure	30 910 (16.4)	123 355 (30.4)	131 418 (20.1)	254 773 (24.0)
Cardia arrhythmia	47 176 (25.1)	138 713 (34.2)	149 765 (22.9)	288 478 (27.2)
Valvular disease	15 929 (8.5)	50 011 (12.3)	55 342 (8.5)	105 353 (9.9)
Chronic/acute deep vein thrombosis or pulmonary embolism	6657 (3.5)	13 846 (3.4)	13 883 (2.1)	27 729 (2.6)
Peripheral vascular disorders	24 473 (13.0)	66 643 (16.4)	74 909 (11.5)	141 552 (13.4)
Haemorrhagic or ischaemic stroke	15 912 (8.5)	34 297 (8.5)	39 064 (6.0)	73 361 (6.9)

Continued

Table 1 Continued

	Comparison only (not included sample)	Included sample		Total included sample
	No HTN meds	Other HTN meds only	ACEi or ARB	
	N (%)	N (%)	N (%)	N (%)
Coagulopathy	10197 (5.4)	25467 (6.3)	22109 (3.4)	47576 (4.5)
Lymphoma	2928 (1.6)	6095 (1.5)	6086 (.9)	12181 (1.1)
Metastatic cancer	6506 (3.5)	11323 (2.8)	11808 (1.8)	23131 (2.2)
Solid tumour without mets	17654 (9.4)	35097 (8.7)	42177 (6.5)	77274 (7.3)
Renal failure	29431 (15.7)	104877 (25.9)	107485 (16.4)	212362 (20.0)
Liver failure	8676 (4.6)	19071 (4.7)	19875 (3.0)	38946 (3.7)
Rheumatoid arthritis/collagen vascular diseases	8584 (4.6)	20953 (5.2)	27768 (4.2)	48721 (4.6)
Obesity	17709 (9.4)	44279 (10.9)	72278 (11.1)	116557 (11.0)
Total	187919 (100.0)	405677 (100.0)	653797 (100.0)	1059474 (100.0)
Unadjusted outcome incidence				
Inpatient stay	33058 (17.6)	75670 (18.7)	91660 (14.0)	167330 (15.8)
ICU/CCU services during inpatient stay	15360 (46.5)	37894 (50.1)	45129 (49.2)	83023 (49.6)
ARDS diagnosis during inpatient stay	1051 (3.2)	2598 (3.4)	3403 (3.7)	6001 (3.6)
ARD diagnosis during inpatient stay	1781 (5.4)	4749 (6.3)	5388 (5.9)	10137 (6.1)
Died same or following calendar month	12933 (6.9)	28753 (7.1)	26411 (4.0)	55164 (5.2)

ACEi, ACE inhibitor; ARD, acute respiratory distress; ARDS, ARD syndrome; CCU, coronary care unit; HTN, hypertension; ICU, intensive care unit.

Compared with AVRI episodes in those using other HTN medications, AVRI episodes in people using ACEi or ARB were more frequently identified in those with Commercial insurance (vs Medicare Advantage), uncomplicated diabetes and Hispanic ethnicity, among other patient characteristics (table 1). AVRI episodes in people using ACEi/ARB were less likely to be associated with the oldest age group and with most comorbidities, including complicated HTN, congestive heart failure, kidney failure, liver failure, cancer, arrhythmia, coagulopathy, deep vein thrombosis or pulmonary embolism, stroke and valvular disease, among other patient characteristics compared with AVRI episodes in people using other HTN medications (table 1).

Unadjusted outcome rates

Across all study years, 15.8% of AVRI episodes included an inpatient stay (n=167330), including 14.0% of episodes in ACEi/ARB users (n=91660) and 18.7% in other HTN medication users (n=75670; table 1). Episode mortality rates were 5.2% overall (n=55164), 4.0% for ACEi/ARB users (n=26411) and 7.1% in other HTN medication users (n=28753). About half of inpatient stays included ICU or CCU use.

Primary analysis

Table 2 presents key model results and marginal effects and ratios for season and medication cohort effects for all five outcomes. Complete regression results are available in online supplemental material S2. The ACEi/ARB cohort had a somewhat lower risk of three of the five outcomes in the baseline 2017–2018 influenza season compared with the other HTN medication cohort, with a 1.9 pp (95% CI −2.2 to −1.6 pps) lower risk of an inpatient stay, a 0.9 pp lower risk of death (95% CI −1.1 to −0.8 pp) and a 0.7 pp (95% CI −1.1 to −0.2 pp) lower risk of an ARD diagnosis conditional on having an inpatient stay. The point estimates for the risk differences of ICU/CCU use or an ARDS diagnosis in an inpatient stay also showed a lower risk for the ACEi/ARB cohort, but this difference was not statistically significant. The COVID-19 influenza season was associated with a higher risk of all five outcomes in both the ACEi/ARB and the other HTN medication cohorts. Risk differences ranged from 1.3 pp higher risk of an ARD (95% CI 0.8 to 1.7 pp) or ARDS (95% CI 0.9 to 1.6 pp) diagnosis in an inpatient stay to a 3.5 pp (2.6 to 4.4 pp) higher risk of ICU/CCU use in an inpatient stay (table 2)

The ACEi/ARB cohort saw a larger risk difference than the other HTN medication cohort in four out of the five outcomes, with an additional 1.5 pp increase in risk of an inpatient stay (95% CI 1.2 to 1.9 pp) and of ICU/CCU use in an inpatient stay (95% CI 0.3 to 2.7 pp) as well as a 0.7 pp (0.1 to 1.2 pp) additional increase in risk of ARD and 0.9 pp (0.4 to 1.3 pp) additional increase in risk of ARDS. There was no statistically significant difference in the absolute risk of death (−0.2 pp, 95% CI −0.4 to 0.1 pp) for the ACEi/ARB group beyond that seen by the other medication group. However, the relative increased risk of death in 2019/2020 versus 2017/2018 for the ACEi/ARB group was larger (1.40 (1.36 to 1.44)) than for the other

Table 2 Main analysis results from linear probability model; full results in supplementary materials

	(1)	(2)	(3)	(4)	(5)
	Inpatient stay	**Inpatient stay with ICU/CCU**	**Inpatient stay with ARD dx**	**Inpatient stay with ARDS dx**	**Died same or following month**
Key coefficient estimates (95% CI)					
Season					
2017 to 2018 influenza season	ref.	ref.	ref.	ref.	ref.
2018 to 2019 influenza season	–0.001	0.008	0.013***	–0.007***	0.000
	(–0.004 to 0.002)	(–0.002 to 0.018)	(0.008 to 0.017)	(–0.010 to 0.004)	(–0.002 to 0.002)
2019 to 2020 influenza season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015 to 0.021)	(0.026 to 0.044)	(0.008 to 0.017)	(0.009 to 0.016)	(0.014 to 0.017)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	–0.019***	–0.009	–0.007**	–0.003	–0.009***
	(–0.022 to to 0.016)	(–0.019 to 0.001)	(–0.011 to 0.002)	(–0.007 to 0.000)	(–0.011 to to 0.008)
Season/medication interactions					
2018 to 2019 season: ACEi or ARB plus/minus other medications	0.004*	0.010	0.004	0.000	0.000
	(0.001 to 0.008)	(–0.004 to 0.023)	(–0.003 to 0.010)	(–0.004 to 0.004)	(–0.002 to 0.002)
2019 to 2020 season: ACEi or ARB plus/minus other medications	0.015***	0.015*	0.007*	0.009***	–0.002
	(0.012 to 0.019)	(0.003 to 0.027)	(0.001 to 0.012)	(0.004 to 0.013)	(–0.004 to 0.001)
Note: p-value for coefficients is for the null hypothesis that the coefficient=0; presented in probability units (eg, coefficient of –0.001 represents –0.1 percentage points)					
Marginal effects/predicted probability (95% CI)					
Other hypertension medications only					
2017/18	0.179	0.482	0.053	0.030	0.064
	(0.177 to 0.181)	(0.474 to 0.489)	(0.050 to 0.056)	(0.028 to 0.033)	(0.062 to 0.065)
2018/19	0.178	0.490	0.066	0.023	0.064
	(0.176 to 0.180)	(0.483 to 0.496)	(0.062 to 0.069)	(0.021 to 0.025)	(0.063 to 0.065)
2019/20	0.196	0.516	0.066	0.043	0.080
	(0.195 to 0.198)	(0.511 to 0.521)	(0.063 to 0.068)	(0.041 to 0.045)	(0.078 to 0.081)
ACEi or ARB plus/minus other medications					
2017/18	0.125	0.463	0.045	0.029	0.035
	(0.124 to 0.127)	(0.456 to 0.470)	(0.042 to 0.048)	(0.027 to 0.031)	(0.034 to 0.035)
2018/19	0.128	0.481	0.061	0.021	0.034
	(0.127 to 0.130)	(0.475 to 0.487)	(0.058 to 0.064)	(0.020 to 0.023)	(0.034 to 0.035)
2019/20	0.158	0.512	0.064	0.050	0.049
	(0.157 to 0.160)	(0.508 to 0.517)	(0.062 to 0.066)	(0.048 to 0.052)	(0.048 to 0.049)
Ratios of marginal effects (95% CI)					
Other hypertension medications only					
2018/19 season vs 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977 to 1.011)	(0.996 to 1.038)	(1.136 to 1.337)	(0.668 to 0.850)	(0.969 to 1.030)
2019/20 season vs 2017/18	1.099***	1.072***	1.238***	1.414***	1.244***
	(1.081 to 1.116)	(1.053 to 1.092)	(1.147 to 1.330)	(1.278 to 1.550)	(1.210 to 1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs 2017/18	1.025**	1.039***	1.360***	0.739***	0.993
	(1.009 to 1.042)	(1.019 to 1.058)	(1.251 to 1.469)	(0.656 to 0.822)	(0.961 to 1.025)

Continued

Table 2 Continued

	(1) Inpatient stay	(2) Inpatient stay with ICU/CCU	(3) Inpatient stay with ARD dx	(4) Inpatient stay with ARDS dx	(5) Died same or following month
2019/20 season vs 2017/18	1.264***	1.107***	1.437***	1.731***	1.404***
	(1.245 to 1.282)	(1.088 to 1.126)	(1.332 to 1.542)	(1.580 to 1.882)	(1.363 to 1.444)

P-value for risk ratios is for the null hypothesis that the risk ratio=1.
*p<0.05, **p<0.01, ***p<0.001.
ref.: reference category.ACEi, ACE inhibitor; ARD, acute respiratory distress; ARDS, ARD syndrome; CCU, coronary care unit; ICU, intensive care unit.

HTN medication cohort (1.24 (1.21 to 1.28)). In other words, each group experienced roughly the same absolute change in risk (an increase of about 1.6 pp), but the baseline risk of death for the ACEi/ARB group was lower, so the relative increase was greater.

Sensitivity analyses

ACEi/ARB monotherapy

When we separated people using only ACEi/ARB from those using ACEi/ARB plus other HTN medications, results were somewhat different for the two groups. In both the 2018/2019 and 2019/2020 seasons, the monotherapy group had a 3.5 to 4.0 pp higher risk of ICU/CCU use in an inpatient stay than the polytherapy group (online supplemental material S3)

People with no comorbidities

The primary effect being studied (ACEi/ARB use during COVID-19) was attenuated when the cohort was limited to people who did not have any of the comorbidities we identified (other than HTN). A large (5.0 pp; 95% CI −0.6 pp to 10.6 pp) increase in the risk of an inpatient stay with ICU/CCU services was not statistically significant because of the small sample size (N=7696 episodes) (online supplemental material S3)

Strict influenza season

Limiting the 2017/2018 and 2018/2019 cohorts to cases of AVRI occurring in the strict influenza season (generally October to May) had minimal effect on the results, which were similar to the primary analysis (online supplemental material S3)

DISCUSSION

In this large observational study, we found that hypertensive patients with an AVRI who were taking ACEis or ARBs for management of their HTN had larger risk differences during the COVID-19 period in the outcomes of inpatient stay, inpatient stay with ICU/CCU, inpatient stay with ARD and inpatient stay with ARDS when compared with people on other antihypertensive medications. This suggests that people taking ACEi/ARB were more affected by COVID-19 than people taking other HTN medications.

People with AVRI who were using ACEi/ARB had fewer comorbidities compared with people taking other medications to control their blood pressure, which might explain their lower baseline risk of poor outcomes. Prior to the COVID-19 season, among people with HTN experiencing an episode of AVRI, those who used ACEi/ARB were less likely to have an inpatient stay, less likely to experience ARDS and ARD and less likely to die compared with people on other antihypertensives at baseline.

Recent observational studies assessing association between ACEi/ARB use and COVID-19 outcomes have generally found lower risk of poor outcomes for ACEi/ARB users;[31–35] however, these studies have differed from ours in important ways. Our finding of lower baseline risk of poor outcomes with AVRI in people taking ACEis/ARBs even after extensively controlling for observed differences in health status highlights the importance of using methods that can control for unobserved differences in health status. Our difference-in-differences approach does this by using non-COVID AVRI outcome differences to control for unobserved differences in underlying health and healthcare seeking behaviour.

During the COVID-19 influenza season, all patients (ACEi/ARB and other HTN) had higher risk of all outcomes, compared with prior years. This is consistent with evidence that patients with HTN experience worse outcomes from COVID-19.[36–40] The ACEi/ARB group had a larger increase in poor outcomes from baseline compared with patients taking other HTN medication, including higher rates of hospitalisation, ICU admission, ARD and ARDS. There was no significant difference in the absolute risk of death for those on ACEi/ARB versus other medication group.

While relative changes in poor AVRI outcomes associated with ACEi/ARB use during COVID-19 were moderate to large, the absolute differences were relatively small, ranging from 0.7 to 1.9 pps. The effects demonstrated in this study may support the theoretical biological effect of ACEi/ARB in the clinical outcomes of people with COVID-19. Nevertheless, it is very uncertain whether these effects were mediated through upregulation of ACE-2 receptors and subsequent susceptibility to SARS-CoV-2, as previously proposed.[1] Moreover, in translating these findings to clinical practice, the small

absolute risk differences observed here are unlikely to outweigh the clinical benefits of ACEi/ARB therapy for managing HTN and heart failure. Therapy selection for these diseases should follow existing clinical guidelines of nephrology, cardiology and other societies.

LIMITATIONS

The use of health insurance claims data limits the findings of this study to the populations included in the OLDW; in particular, we do not observe outcomes of people who are uninsured or those who have Medicaid insurance (ie, people with low incomes and no employer-based insurance). The study only captures people who received healthcare for AVRI, which may be different in important ways during COVID-19 compared with earlier years; early in the pandemic, many people avoided seeking in-person care, likely to avoid exposure to COVID-19 or to preserve access to care for others.[41] However, the difference-in-differences design of the study addresses this problem by comparing changes in outcomes for two similar populations; as long as people with HTN who used ACEi/ARB and those who used other medications changed their care-seeking behaviour in similar ways, this effect should be minimised. Finally, although analyses were adjusted for age, sex, race/ethnicity and comorbidities, residual confounding is still a possibility given the observational study design and other potential confounders who were not evaluated such as number of previous respiratory infections, number of previous hospitalisation and duration of treatment with ACEi/ARBs.

CONCLUSIONS

People with AVRIs using ACEi/ARBs to treat HTN had a greater increase in poor outcomes during the COVID-19 pandemic than those using other medications to treat HTN. This may support the existence of the theoretical biological effect of ACEi/ARB in increasing susceptibility to COVID-19. Small absolute differences in risks of hospitalisation, ICU use and diagnosis of ARD or ARDS suggest that this effect likely does not warrant changes in clinical practice.

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