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Differential effects of outpatient use of ACE inhibitors and angiotensin receptor blockers on outcomes of acute respiratory illness during the COVID-19 pandemic: a cohort study

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Title: Differential effects of outpatient use of ACE inhibitors and angiotensin receptor blockers on outcomes of acute respiratory illness during the COVID-19 pandemic: a cohort study

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Competing interests

None.

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Not applicable / Not required.

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ABSTRACT

Objectives: Evaluate the associations between patients taking ACE inhibitors (ACEis) 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 vs. 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 hypertension had a greater increase in poor outcomes during the COVID-19 pandemic than those using other medications to treat hypertension. The small absolute magnitude of the differences likely does not support changes in clinical practice.

Keywords: ACE inhibitors, angiotensin receptor blockers, COVID-19, acute viral respiratory illness.

ARTICLE SUMMARY

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 coronavirus disease 2019 (COVID-19) pandemic, pre-clinical 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 severe acute respiratory syndrome coronavirus 2 (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 randomized 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. In this study, we aimed to evaluate the associations between patients taking ACEis and ARBs and their clinical outcomes after an acute viral respiratory illness (AVRI) due to COVID-19. We assessed severity of illness and mortality in AVRI across cohorts of patients with hypertension (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 United States.

METHODS

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

Data source and study setting

We used de-identified 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 United States. The OLDW includes medical and pharmacy claims, laboratory results, and enrollment 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.

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 October 1, 2017, and November 30, 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. (**Supplementary 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 enrollment before the index date of the AVRI episode. Insurance claims during this period were used to identify hypertension 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 hypertension, as explained below.

Variables and measurements

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

Hypertension and comorbidities

Hypertension 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 the **Supplementary Material S1.** Hypertension 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 (HEDIS) performance measures.[29]

Hypertension medications

We developed a comprehensive list of hypertension medications (see **Supplementary Material S1**), then identified all National Drug Codes (NDCs) 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 categorized fill patterns as ACEi or ARB only, ACEi or ARB with other (i.e., not ACEi or ARB) hypertension medications, other hypertension medications only, or no hypertension medications. In primary analyses, ACEi or ARB users with and without other hypertension medications were combined and compared with people using only other hypertension medications; information on people who did not use hypertension 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 5 outcomes associated with more serious cases of AVRI: death, hospitalization, and, conditional on hospitalization: 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 acute respiratory distress 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 enrollment 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 hypertension using hypertension 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 hypertension. 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 3 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 standard errors 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 risk difference may have different importance for an event with an incidence of 10% (relative increase 10%) compared to one with an incidence of 1% (relative increase 100%). To ease interpretation of results, we calculated average marginal effects for each flu 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 flu season and the 2019/2020/COVID-19 flu season versus the baseline 2017/2018 flu season, along with p-values for the hypothesis test that the ratios were equal to 1 (i.e., 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 2017/18 season, which would suggest that COVID-19 is fundamentally different from the general year-to-year shifts in flu 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 version 16.0 was used for all analyses (StataCorp College Station, TX, 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 hypertension. Of these, 15.1% (187,919) did not fill a hypertension 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).

Compared to 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 hypertension, 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 to 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=167,330), including 14.0% of episodes in ACEi/ARB users (n=91,660) and 18.7% in other HTN medication users (n=75,670; **Table 1**). Episode mortality rates were 5.2% overall (n=55,164), 4.0% for ACEi/ARB users (n=26,411), and 7.1% in other HTN medication users (n=28,753). 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 **Supplementary Material S2**. The ACEi/ARB cohort had a somewhat lower risk of three of the five outcomes in the baseline 2017-2018 flu season compared to the other HTN medication cohort, with a 1.9 percentage point (pp) (95% CI -2.2 to -1.6 percentage points) 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 flu 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 vs. 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]). 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. (**Supplementary 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 hypertension). 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=7,696 episodes). (**Supplementary Material S3**)

Strict flu season

Limiting the 2017/18 and 2018/19 cohorts to cases of AVRI occurring in the strict flu season (generally October to May) had minimal effect on the results, which were similar to the primary analysis. (**Supplementary 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 to 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 hypertension 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 to people on other antihypertensives at baseline.

During the COVID-19 flu season, all patients (ACEi/ARB and other HTN) had higher risk of all outcomes, compared to prior years. This is consistent with evidence that patients with hypertension experience worse outcomes from COVID-19.[31-35] The ACEi/ARB group had a larger increase in poor outcomes from baseline compared to patients taking other HTN medication, including higher rates of hospitalization, 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 percentage points. 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

hypertension 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 OptumLabs Data Warehouse; in particular, we do not observe outcomes of people who are uninsured or those who have Medicaid insurance (i.e., people with low incomes and no employer-based insurance). The study only captures people who received health care for AVRI, which may be different in important ways during COVID-19 compared to 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.[36] 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 hypertension who used ACEi/ARB and those who used other medications changed their care seeking behavior in similar ways, this effect should be minimized.

CONCLUSIONS

People with acute viral respiratory illnesses using ACEi/ARBs to treat hypertension had a greater increase in poor outcomes during the COVID-19 pandemic than those using other medications to treat hypertension. 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 hospitalization, ICU use, and diagnosis of ARD or ARDS suggest that this effect likely does not warrant changes in clinical practice.

CONTRIBUTORSHIP STATEMENT

Conceptualization: MMJ, LOJS, FB, VDG, TMD, AHL, NWC. Formal analysis: MMJ. Investigation: MMJ, LOJS, FB, VDG, TMD, AHL, NWC. Methodology: MMJ, LOJS, FB. Project administration: MMJ. Supervision: MMJ, NWC. Validation: MMJ, NWC. Writing-original draft: MMJ. Writing-review and editing: MMJ, LOJS, FB, VSD, TMD, AHL, NWC. Guarantor: MMJ, NWC. All authors provided critical revision and contribution for important intellectual content.

COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

No additional data available.

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LEGENDS

Table 1. Cohort characteristics.

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

Table 1. Cohort characteristics.

	Comparison only (not included sample)	Included Sample		
	No HTN meds	Other HTN meds only	ACEi or ARB	Total included sample
	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	3,922 (2.1%)	3,354 (0.8%)	4,537 (0.7%)	7,891 (0.7%)
35-44	8,337 (4.4%)	9,784 (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	4,449 (2.4%)	8,003 (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	7,217 (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	8,484 (4.5%)	14,224 (3.5%)	27,963 (4.3%)	42,187 (4.0%)
Pacific	5,902 (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				

	Comparison only (not included sample)	Included Sample		
	No HTN meds	Other HTN meds only	ACEi or ARB	Total included sample
	N (%)	N (%)	N (%)	N (%)
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	6,657 (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%)
Hemorrhagic or ischemic stroke	15,912 (8.5%)	34,297 (8.5%)	39,064 (6.0%)	73,361 (6.9%)
Coagulopathy	10,197 (5.4%)	25,467 (6.3%)	22,109 (3.4%)	47,576 (4.5%)
Lymphoma	2,928 (1.6%)	6,095 (1.5%)	6,086 (.9%)	12,181 (1.1%)
Metastatic cancer	6,506 (3.5%)	11,323 (2.8%)	11,808 (1.8%)	23,131 (2.2%)
Solid tumor without mets	17,654 (9.4%)	35,097 (8.7%)	42,177 (6.5%)	77,274 (7.3%)
Renal failure	29,431 (15.7%)	104,877 (25.9%)	107,485 (16.4%)	212,362 (20.0%)
Liver failure	8,676 (4.6%)	19,071 (4.7%)	19,875 (3.0%)	38,946 (3.7%)
Rheumatoid arthritis/collagen vascular diseases	8,584 (4.6%)	20,953 (5.2%)	27,768 (4.2%)	48,721 (4.6%)
Obesity	17,709 (9.4%)	44,279 (10.9%)	72,278 (11.1%)	116,557 (11.0%)
Total	187,919 (100.0%)	405,677 (100.0%)	653,797 (100.0%)	1,059,474 (100.0%)
Unadjusted outcome incidence				
Inpatient stay	33,058 (17.6%)	75,670 (18.7%)	91,660 (14.0%)	167,330 (15.8%)
ICU/CCU services during inpatient stay	15,360 (46.5%)	37,894 (50.1%)	45,129 (49.2%)	83,023 (49.6%)
ARDS diagnosis during inpatient stay	1,051 (3.2%)	2,598 (3.4%)	3,403 (3.7%)	6,001 (3.6%)
ARD diagnosis during inpatient stay	1,781 (5.4%)	4,749 (6.3%)	5,388 (5.9%)	10,137 (6.1%)
Died same or following calendar month	12,933 (6.9%)	28,753 (7.1%)	26,411 (4.0%)	55,164 (5.2%)

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% confidence interval)					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001 (-0.004,0.002)	0.008 (-0.002,0.018)	0.013*** (0.008,0.017)	-0.007*** (-0.010,-0.004)	0.000 (-0.002,0.002)
2019-2020 flu season	0.018*** (0.015,0.021)	0.035*** (0.026,0.044)	0.013*** (0.008,0.017)	0.013*** (0.009,0.016)	0.016*** (0.014,0.017)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.019*** (-0.022,-0.016)	-0.009 (-0.019,0.001)	-0.007** (-0.011,-0.002)	-0.003 (-0.007,0.000)	-0.009*** (-0.011,-0.008)
Season/medication interactions					
2018-2019 season: ACEi or ARB plus/minus other medications	0.004* (0.001,0.008)	0.010 (-0.004,0.023)	0.004 (-0.003,0.010)	0.000 (-0.004,0.004)	0.000 (-0.002,0.002)
2019-2020 season: ACEi or ARB plus/minus other medications	0.015*** (0.012,0.019)	0.015* (0.003,0.027)	0.007* (0.001,0.012)	0.009*** (0.004,0.013)	-0.002 (-0.004,0.001)

Note: p-value for coefficients is for the null hypothesis that the coefficient = 0; presented in probability units (e.g., coefficient of -0.001 represents -0.1 percentage points)

Marginal effects/predicted probability (95% confidence interval)					
Other hypertension medications only					
2017/18	0.179 (0.177,0.181)	0.482 (0.474,0.489)	0.053 (0.050,0.056)	0.030 (0.028,0.033)	0.064 (0.062,0.065)
2018/19	0.178 (0.176,0.180)	0.490 (0.483,0.496)	0.066 (0.062,0.069)	0.023 (0.021,0.025)	0.064 (0.063,0.065)
2019/20	0.196	0.516	0.066	0.043	0.080

	(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
	(0.195,0.198)	(0.511,0.521)	(0.063,0.068)	(0.041,0.045)	(0.078,0.081)
ACEi or ARB plus/minus other medications					
2017/18	0.125	0.463	0.045	0.029	0.035
	(0.124,0.127)	(0.456,0.470)	(0.042,0.048)	(0.027,0.031)	(0.034,0.035)
2018/19	0.128	0.481	0.061	0.021	0.034
	(0.127,0.130)	(0.475,0.487)	(0.058,0.064)	(0.020,0.023)	(0.034,0.035)
2019/20	0.158	0.512	0.064	0.050	0.049
	(0.157,0.160)	(0.508,0.517)	(0.062,0.066)	(0.048,0.052)	(0.048,0.049)
Ratios of marginal effects (95% confidence interval)					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977,1.011)	(0.996,1.038)	(1.136,1.337)	(0.668,0.850)	(0.969,1.030)
2019/20 season vs. 2017/18	1.099***	1.072***	1.238***	1.414***	1.244***
	(1.081,1.116)	(1.053,1.092)	(1.147,1.330)	(1.278,1.550)	(1.210,1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.025**	1.039***	1.360***	0.739***	0.993
	(1.009,1.042)	(1.019,1.058)	(1.251,1.469)	(0.656,0.822)	(0.961,1.025)
2019/20 season vs. 2017/18	1.264***	1.107***	1.437***	1.731***	1.404***
	(1.245,1.282)	(1.088,1.126)	(1.332,1.542)	(1.580,1.882)	(1.363,1.444)

Note: 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

SUPPLEMENTARY MATERIAL S1

SUPPLEMENT T1: Codes used to define AVRI, CAD, stroke, DVT, and PE

Condition	**Codes**
Acute viral respiratory illness (AVRI)	B9721, B9729, J09*, J10*, J11*, J12*, J16, J168, J18, J180, J181, J182, J188, J189, J20, J201, J203, J204, J205, J206, J207, J208, J209, J22, J40, J440, J470, J8411, J84111, U071, U072
Coronary artery disease (CAD)	I20*, I21*, I22*, I23*, I24*, I25*
Stroke	I63*, Z8673*, I60*, I61*, I62*
Deep vein thrombosis (DVT) and pulmonary embolism (PE)	I8249, I824Y, I824Z, I8251, I8259, I825Y, I825Z, I8262, I8272, I26*, I2782

SUPPLEMENT T2: Hypertension medications

Medication type	**Included medications (generic name)**
ACEi	captopril, lisinopril, enalapril, benazepril, perindopril, quinapril, fosinopril, moexipril, ramipril, trandolapril
ARB	losartan, valsartan, irbesartan, candesartan, eprosartan, telmisartan, azilsartan, Olmesartan
Other (excluding topical, ophthalmic, and drops preparations)	Bendroflumethiazide, chlorothiazide, indapamide, metolazone, bumetanide, furosemide, torsemide, ethacrynic, amiloride, triamterene, eplerenone, spironolactone, aliskiren, diltiazem, verapamil, amlodipine, nicardipine, felodipine, nifedipine, torsemide, ethacrynic, isradipine, nisoldipine, doxazosin, prazosin, terazosin, clonidine, guanfacine, methyldopa, reserpine, hydralazine, minoxidil, acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol

	Primary analysis				
	(1) Inpatient stay (95% confidence interval)	(2) Inpatient stay with ICU/CCU (95% confidence interval)	(3) Inpatient stay with ARD dx (95% confidence interval)	(4) Inpatient stay with ARDS dx (95% confidence interval)	(5) Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001 (-0.004,0.002)	0.008 (-0.002,0.018)	0.013*** (0.008,0.017)	-0.007*** (-0.010,-0.004)	0.000 (-0.002,0.002)
2019-2020 flu season	0.018*** (0.015,0.021)	0.035*** (0.026,0.044)	0.013*** (0.008,0.017)	0.013*** (0.009,0.016)	0.016*** (0.014,0.017)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.019*** (-0.022,-0.016)	-0.009 (-0.019,0.001)	-0.007** (-0.011,-0.002)	-0.003 (-0.007,0.000)	-0.009*** (-0.011,-0.008)
ACEi or ARB monotherapy					
2018-2019 season: ACEi or ARB +- other	0.004* (0.001,0.008)	0.01 (-0.004,0.023)	0.004 (-0.003,0.010)	0 (-0.004,0.004)	0 (-0.002,0.002)
2018-2019 season: ACEi or ARB monotherapy					
2019-2020 season: ACEi or ARB +/- other	0.015*** (0.012,0.019)	0.015* (0.003,0.027)	0.007* (0.001,0.012)	0.009*** (0.004,0.013)	-0.002 (-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy					
Demographics					
Female	-0.016*** (-0.017,-0.014)	-0.023*** (-0.028,-0.018)	0 (-0.002,0.003)	-0.004*** (-0.006,-0.002)	-0.011*** (-0.012,-0.010)
Age categories					
<35	-0.006* (-0.011,-0.000)	-0.029 (-0.078,0.019)	0.02 (-0.006,0.045)	-0.01 (-0.028,0.008)	-0.001 (-0.003,0.001)
35-44	-0.008*** (-0.012,-0.005)	-0.028 (-0.056,0.000)	0.006 (-0.008,0.019)	-0.004 (-0.016,0.008)	0.001 (-0.000,0.002)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.010*** (0.008,0.013)	0.005 (-0.009,0.020)	0.001 (-0.005,0.008)	0.001 (-0.005,0.007)	0.001* (0.000,0.002)
65-74	0.011*** (0.008,0.014)	-0.003 (-0.017,0.011)	0.001 (-0.006,0.008)	-0.001 (-0.007,0.004)	0.009*** (0.007,0.010)
75-84	0.029*** (0.025,0.032)	-0.026*** (-0.041,-0.012)	-0.002 (-0.009,0.004)	-0.005 (-0.011,0.001)	0.024*** (0.023,0.026)
85+	0.045*** (0.041,0.048)	-0.071*** (-0.086,-0.056)	-0.010** (-0.017,-0.003)	-0.014*** (-0.020,-0.008)	0.063*** (0.061,0.065)
Insurance coverage type					
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.032*** (-0.034,-0.030)	0.01 (-0.001,0.020)	0.001 (-0.004,0.006)	0.003 (-0.002,0.007)	-0.001* (-0.002,-0.000)
Census region					
Unknown/other	-0.046** (-0.075,-0.016)	0.194* (0.014,0.373)	-0.011 (-0.086,0.064)	0.009 (-0.068,0.087)	-0.023* (-0.044,-0.002)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	-0.008*** (-0.012,-0.003)	0.017* (0.003,0.031)	0.021*** (0.015,0.028)	0.021*** (0.016,0.026)	-0.005** (-0.008,-0.002)
South Atlantic	-0.001 (-0.005,0.003)	0.122*** (0.110,0.134)	0.016*** (0.011,0.021)	0.003 (-0.002,0.007)	-0.016*** (-0.018,-0.013)

	Primary analysis				
	(1)	(2)	(3)	(4)	(5)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.018***	0.073***	0.003	0	-0.009***
	(0.013,0.022)	(0.060,0.086)	(-0.002,0.009)	(-0.004,0.004)	(-0.012,-0.007)
E South Central	0.011***	0.071***	0.018***	-0.001	-0.009***
	(0.007,0.016)	(0.056,0.085)	(0.011,0.024)	(-0.006,0.005)	(-0.011,-0.006)
W North Central	0.027***	0.093***	0.004	0.006*	-0.007***
	(0.022,0.032)	(0.079,0.107)	(-0.002,0.010)	(0.001,0.011)	(-0.010,-0.004)
W South Central	0.014***	0.111***	0.017***	0.003	-0.011***
	(0.010,0.018)	(0.097,0.124)	(0.011,0.023)	(-0.002,0.007)	(-0.014,-0.009)
Mountain	-0.033***	0.122***	-0.007	0.008*	-0.019***
	(-0.037,-0.028)	(0.103,0.140)	(-0.015,0.000)	(0.001,0.016)	(-0.022,-0.016)
Pacific	-0.002	0.170***	0.008	0.001	-0.016***
Race/ethnicity	(-0.007,0.004)	(0.151,0.189)	(-0.000,0.017)	(-0.006,0.007)	(-0.019,-0.013)
Unknown/other	-0.007***	0.020***	0.004*	0.009***	-0.002**
	(-0.010,-0.005)	(0.013,0.028)	(0.001,0.008)	(0.006,0.012)	(-0.003,-0.001)
White	ref.	ref.	ref.	ref.	ref.
Black	0.011***	-0.010**	0.005**	0.008***	0.004***
	(0.009,0.013)	(-0.017,-0.003)	(0.002,0.008)	(0.006,0.011)	(0.002,0.005)
Hispanic	-0.016***	0.086***	0.011***	0.010***	-0.008***
	(-0.018,-0.013)	(0.077,0.095)	(0.006,0.015)	(0.007,0.014)	(-0.009,-0.006)
Asian	-0.011***	0.020*	0.002	0.007	-0.001
Comorbidities	(-0.016,-0.007)	(0.002,0.039)	(-0.007,0.010)	(-0.000,0.014)	(-0.004,0.002)
No diabetes	ref.	ref.	ref.	ref.	ref.
Diabetes without CC	0.011***	0.012**	0.005**	0.004**	0.005***
	(0.009,0.013)	(0.004,0.019)	(0.001,0.009)	(0.001,0.007)	(0.004,0.006)
Diabetes with CC	0.029***	0.008**	-0.002	0.002	0.008***
	(0.027,0.031)	(0.002,0.014)	(-0.005,0.001)	(-0.000,0.004)	(0.006,0.009)
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.023***	-0.012**	-0.003	-0.003*	-0.001
	(0.020,0.026)	(-0.018,-0.005)	(-0.006,0.000)	(-0.005,-0.000)	(-0.003,0.001)
Coronary artery disease	0.020***	0.028***	0.001	-0.002	0.007***
	(0.018,0.022)	(0.022,0.033)	(-0.001,0.004)	(-0.004,0.000)	(0.006,0.009)
Congestive heart failure	0.093***	0.077***	0.018***	0.002*	0.036***
	(0.090,0.095)	(0.072,0.083)	(0.015,0.020)	(0.000,0.004)	(0.034,0.037)
Chronic pulmonary diseases	0.061***	-0.010***	0.015***	-0.007***	-0.002***
	(0.059,0.063)	(-0.015,-0.005)	(0.013,0.018)	(-0.009,-0.006)	(-0.003,-0.001)
Renal failure	0.019***	0.012***	-0.001	0.001	0.023***
	(0.017,0.022)	(0.005,0.018)	(-0.004,0.003)	(-0.001,0.004)	(0.021,0.025)
Liver failure	0.046***	0.035***	-0.003	0	0.059***
	(0.042,0.051)	(0.025,0.045)	(-0.008,0.002)	(-0.004,0.004)	(0.056,0.063)
Metastatic cancer	0.122***	0.01	0.003	-0.010***	0.136***
	(0.115,0.130)	(-0.003,0.024)	(-0.004,0.009)	(-0.014,-0.006)	(0.130,0.142)
Lymphoma	0.064***	-0.008	-0.001	-0.010***	0.027***
	(0.056,0.073)	(-0.025,0.009)	(-0.009,0.007)	(-0.015,-0.004)	(0.021,0.033)
Non-metastatic solid tumor	0.036***	0.018***	0	-0.003*	0.028***
	(0.033,0.040)	(0.009,0.027)	(-0.004,0.005)	(-0.006,-0.000)	(0.026,0.030)
Peripheral vascular disorders	-0.008***	0.017***	0.004**	0.001	0.018***
	(-0.011,-0.006)	(0.010,0.023)	(0.001,0.008)	(-0.001,0.003)	(0.017,0.020)
Cardiac arrhythmias	0.062***	0.062***	0.005***	-0.002*	0.024***

	Primary analysis				
	(1)	(2)	(3)	(4)	(5)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
	(0.060,0.064)	(0.057,0.067)	(0.002,0.007)	(-0.004,-0.000)	(0.023,0.025)
Rheumatoid arthritis/collagen vascular diseases	0.016***	-0.005	-0.007**	0	0.004***
	(0.013,0.020)	(-0.016,0.005)	(-0.012,-0.002)	(-0.004,0.004)	(0.002,0.006)
Coagulopathy	0.029***	0.032***	-0.004	0.002	0.035***
	(0.024,0.033)	(0.023,0.041)	(-0.008,0.000)	(-0.001,0.005)	(0.032,0.038)
Obesity	-0.002	0.013***	0.004	0.009***	-0.009***
	(-0.005,0.000)	(0.006,0.021)	(-0.000,0.007)	(0.006,0.012)	(-0.010,-0.007)
Chronic/acute deep vein thrombosis or pulmonary embolism	0.061***	0.050***	0.003	0.002	0.030***
	(0.056,0.067)	(0.039,0.061)	(-0.003,0.009)	(-0.003,0.006)	(0.026,0.034)
Hemorrhagic or ischemic stroke	0.016***	0.032***	0.002	-0.004**	0.043***
	(0.013,0.020)	(0.024,0.040)	(-0.001,0.006)	(-0.007,-0.001)	(0.040,0.045)
Valvular disease	-0.009***	0.045***	0.007***	-0.002	0.017***
	(-0.012,-0.006)	(0.038,0.052)	(0.003,0.010)	(-0.004,0.001)	(0.015,0.019)
Constant	0.058***	0.310***	0.020***	0.034***	0.012***
	(0.053,0.063)	(0.291,0.330)	(0.011,0.029)	(0.027,0.041)	(0.009,0.015)
N	1059474	167330	167330	167330	1057707
N_clust	728455	147846	147846	147846	727311
p	<0.001	<0.001	<0.001	<0.001	<0.001
R-squared	0.081	0.037	0.006	0.008	0.076

	Sensitivity analysis: ACEi/ARB monotherapy				
	(6)	(7)	(8)	(9)	(10)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001	0.008	0.013***	-0.007***	0
	(-0.004,0.002)	(-0.002,0.018)	(0.008,0.017)	(-0.010,-0.004)	(-0.002,0.002)
2019-2020 flu season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015,0.021)	(0.026,0.044)	(0.008,0.017)	(0.009,0.016)	(0.014,0.017)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.020***	-0.004	-0.007**	-0.002	-0.010***
	(-0.023,-0.017)	(-0.014,0.006)	(-0.011,-0.002)	(-0.006,0.001)	(-0.012,-0.009)
ACEi or ARB monotherapy	-0.016***	-0.039***	-0.007	-0.009**	-0.004***
	(-0.020,-0.012)	(-0.057,-0.020)	(-0.015,0.001)	(-0.015,-0.003)	(-0.006,-0.002)
2018-2019 season: ACEi or ARB +- other	0.004*	0.004	0.004	-0.001	-0.001
	(0.000,0.008)	(-0.009,0.018)	(-0.003,0.010)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy	0.005	0.040**	0.002	0.002	0.001
	(-0.001,0.010)	(0.015,0.065)	(-0.009,0.013)	(-0.006,0.009)	(-0.002,0.004)
2019-2020 season: ACEi or ARB +/- other	0.015***	0.011	0.007*	0.008***	-0.001
	(0.011,0.019)	(-0.001,0.024)	(0.002,0.013)	(0.003,0.013)	(-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy	0.017***	0.035**	0.004	0.012**	-0.003*
	(0.012,0.022)	(0.013,0.057)	(-0.006,0.013)	(0.004,0.020)	(-0.006,-0.000)
Demographics					
Female	-0.016***	-0.023***	0	-0.004***	-0.011***
	(-0.017,-0.014)	(-0.028,-0.018)	(-0.002,0.003)	(-0.006,-0.002)	(-0.012,-0.010)
Age categories					
<35	-0.006*	-0.029	0.02	-0.01	-0.001
	(-0.012,-0.000)	(-0.078,0.020)	(-0.005,0.045)	(-0.028,0.008)	(-0.003,0.001)
35-44	-0.008***	-0.028	0.006	-0.004	0.001
	(-0.012,-0.005)	(-0.056,0.000)	(-0.008,0.019)	(-0.016,0.008)	(-0.001,0.002)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.010***	0.005	0.001	0.001	0.001*
	(0.008,0.013)	(-0.009,0.020)	(-0.005,0.008)	(-0.005,0.007)	(0.000,0.002)
65-74	0.011***	-0.003	0.001	-0.001	0.009***
	(0.008,0.014)	(-0.017,0.011)	(-0.006,0.008)	(-0.007,0.004)	(0.007,0.010)
75-84	0.029***	-0.026***	-0.002	-0.005	0.024***
	(0.026,0.032)	(-0.041,-0.012)	(-0.009,0.004)	(-0.011,0.001)	(0.023,0.026)
85+	0.045***	-0.072***	-0.010**	-0.014***	0.063***
Insurance coverage type	(0.041,0.049)	(-0.087,-0.057)	(-0.017,-0.003)	(-0.020,-0.008)	(0.061,0.065)
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.032***	0.01	0.001	0.003	-0.001**
Census region	(-0.035,-0.030)	(-0.001,0.021)	(-0.004,0.006)	(-0.002,0.007)	(-0.002,-0.000)
Unknown/other	-0.045**	0.196*	-0.011	0.009	-0.023*
	(-0.075,-0.016)	(0.016,0.375)	(-0.086,0.064)	(-0.068,0.087)	(-0.044,-0.002)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	-0.008***	0.017*	0.021***	0.021***	-0.005**
	(-0.012,-0.003)	(0.003,0.031)	(0.015,0.028)	(0.016,0.026)	(-0.008,-0.002)
South Atlantic	-0.001	0.122***	0.016***	0.003	-0.016***
	(-0.005,0.003)	(0.110,0.134)	(0.011,0.021)	(-0.002,0.007)	(-0.018,-0.013)

Sensitivity analysis: ACEi/ARB monotherapy

	(6) Inpatient stay (95% confidence interval)	(7) Inpatient stay with ICU/CCU (95% confidence interval)	(8) Inpatient stay with ARD dx (95% confidence interval)	(9) Inpatient stay with ARDS dx (95% confidence interval)	(10) Died same or following month (95% confidence interval)
E North Central	0.018***	0.073***	0.003	0	-0.009***
	(0.013,0.022)	(0.060,0.086)	(-0.002,0.009)	(-0.004,0.004)	(-0.012,-0.007)
E South Central	0.011***	0.070***	0.018***	-0.001	-0.008***
	(0.007,0.016)	(0.056,0.085)	(0.011,0.024)	(-0.006,0.004)	(-0.011,-0.006)
W North Central	0.027***	0.093***	0.004	0.006*	-0.007***
	(0.022,0.032)	(0.079,0.107)	(-0.002,0.010)	(0.001,0.011)	(-0.010,-0.004)
W South Central	0.014***	0.111***	0.017***	0.003	-0.011***
	(0.010,0.018)	(0.097,0.124)	(0.011,0.023)	(-0.002,0.007)	(-0.014,-0.009)
Mountain	-0.033***	0.122***	-0.007	0.008*	-0.019***
	(-0.037,-0.028)	(0.103,0.141)	(-0.015,0.000)	(0.001,0.016)	(-0.022,-0.016)
Pacific	-0.002	0.170***	0.008	0.001	-0.016***
Race/ethnicity	(-0.007,0.004)	(0.151,0.189)	(-0.000,0.017)	(-0.006,0.007)	(-0.019,-0.013)
Unknown/other	-0.007***	0.020***	0.004*	0.009***	-0.002**
	(-0.010,-0.005)	(0.013,0.028)	(0.001,0.008)	(0.006,0.012)	(-0.003,-0.001)
White	ref.	ref.	ref.	ref.	ref.
Black	0.011***	-0.010**	0.005**	0.008***	0.004***
	(0.009,0.013)	(-0.017,-0.003)	(0.002,0.008)	(0.006,0.011)	(0.003,0.005)
Hispanic	-0.016***	0.086***	0.011***	0.010***	-0.008***
	(-0.018,-0.013)	(0.077,0.095)	(0.006,0.015)	(0.007,0.014)	(-0.009,-0.006)
Asian	-0.012***	0.020*	0.002	0.007	-0.001
Comorbidities	(-0.016,-0.007)	(0.002,0.039)	(-0.007,0.010)	(-0.000,0.014)	(-0.004,0.001)
No diabetes	ref.	ref.	ref.	ref.	ref.
Diabetes without CC	0.011***	0.012**	0.005**	0.004**	0.005***
	(0.009,0.013)	(0.004,0.019)	(0.001,0.009)	(0.001,0.007)	(0.004,0.006)
Diabetes with CC	0.029***	0.008**	-0.002	0.002	0.008***
	(0.027,0.031)	(0.002,0.014)	(-0.005,0.001)	(-0.000,0.004)	(0.006,0.009)
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.023***	-0.012**	-0.003	-0.003*	-0.001
	(0.020,0.026)	(-0.019,-0.005)	(-0.006,0.000)	(-0.005,-0.000)	(-0.003,0.001)
Coronary artery disease	0.020***	0.027***	0.001	-0.002	0.008***
	(0.018,0.022)	(0.022,0.033)	(-0.001,0.004)	(-0.004,0.000)	(0.006,0.009)
Congestive heart failure	0.093***	0.077***	0.017***	0.002	0.036***
	(0.091,0.096)	(0.071,0.082)	(0.015,0.020)	(-0.000,0.004)	(0.035,0.038)
Chronic pulmonary diseases	0.061***	-0.010***	0.015***	-0.007***	-0.002***
	(0.059,0.063)	(-0.015,-0.005)	(0.013,0.018)	(-0.009,-0.006)	(-0.003,-0.001)
Renal failure	0.019***	0.012***	-0.001	0.001	0.023***
	(0.017,0.022)	(0.005,0.018)	(-0.004,0.003)	(-0.001,0.003)	(0.021,0.025)
Liver failure	0.046***	0.035***	-0.003	0	0.059***
	(0.042,0.051)	(0.025,0.045)	(-0.008,0.002)	(-0.004,0.004)	(0.056,0.063)
Metastatic cancer	0.122***	0.01	0.003	-0.010***	0.136***
	(0.115,0.130)	(-0.003,0.024)	(-0.004,0.009)	(-0.014,-0.006)	(0.130,0.142)
Lymphoma	0.064***	-0.008	-0.001	-0.010***	0.027***
	(0.056,0.073)	(-0.025,0.009)	(-0.009,0.007)	(-0.015,-0.004)	(0.021,0.033)
Non-metastatic solid tumor	0.036***	0.018***	0	-0.003*	0.028***
	(0.033,0.040)	(0.009,0.027)	(-0.004,0.005)	(-0.006,-0.000)	(0.026,0.030)
Peripheral vascular disorders	-0.008***	0.017***	0.004**	0.001	0.018***
	(-0.011,-0.006)	(0.010,0.023)	(0.001,0.008)	(-0.001,0.003)	(0.017,0.020)
Cardiac arrhythmias	0.062***	0.062***	0.005***	-0.002*	0.024***

Sensitivity analysis: ACEi/ARB monotherapy

	(6)	(7)	(8)	(9)	(10)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
	(95% confidence interval)	(95% confidence interval)	(95% confidence interval)	(95% confidence interval)	(95% confidence interval)
	(0.060,0.064)	(0.057,0.067)	(0.002,0.007)	(-0.004,-0.000)	(0.023,0.026)
Rheumatoid arthritis/collagen vascular diseases	0.016***	-0.005	-0.007**	0	0.004***
	(0.013,0.020)	(-0.016,0.006)	(-0.012,-0.002)	(-0.004,0.004)	(0.002,0.006)
Coagulopathy	0.029***	0.032***	-0.004	0.002	0.035***
	(0.024,0.033)	(0.023,0.041)	(-0.008,0.000)	(-0.001,0.005)	(0.032,0.038)
Obesity	-0.002	0.013***	0.004	0.009***	-0.008***
	(-0.004,0.000)	(0.006,0.021)	(-0.000,0.007)	(0.006,0.012)	(-0.010,-0.007)
Chronic/acute deep vein thrombosis or pulmonary embolism	0.061***	0.050***	0.003	0.002	0.030***
	(0.055,0.067)	(0.039,0.061)	(-0.003,0.009)	(-0.002,0.006)	(0.026,0.034)
Hemorrhagic or ischemic stroke	0.016***	0.032***	0.002	-0.004**	0.043***
	(0.013,0.019)	(0.024,0.040)	(-0.001,0.006)	(-0.007,-0.001)	(0.040,0.045)
Valvular disease	-0.009***	0.045***	0.007***	-0.002	0.017***
	(-0.012,-0.006)	(0.038,0.052)	(0.003,0.010)	(-0.004,0.001)	(0.015,0.019)
Constant	0.058***	0.312***	0.020***	0.034***	0.012***
	(0.053,0.063)	(0.292,0.332)	(0.011,0.029)	(0.027,0.042)	(0.009,0.015)
N	1059474	167330	167330	167330	1057707
N_clust	728455	147846	147846	147846	727311
p	<0.001	<0.001	<0.001	<0.001	<0.001
R-squared	0.081	0.037	0.006	0.008	0.076

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11) Inpatient stay (95% confidence interval)	(12) Inpatient stay with ICU/CCU (95% confidence interval)	(13) Inpatient stay with ARD dx (95% confidence interval)	(14) Inpatient stay with ARDS dx (95% confidence interval)	(15) Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0.002 (-0.001,0.006)	0.02 (-0.032,0.072)	0.030** (0.009,0.051)	0.006 (-0.005,0.017)	0 (-0.002,0.002)
2019-2020 flu season	0.032*** (0.028,0.035)	0.068** (0.024,0.111)	0.029*** (0.014,0.045)	0.052*** (0.039,0.065)	0.007*** (0.005,0.009)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.006*** (-0.009,-0.003)	-0.001 (-0.049,0.046)	0.009 (-0.008,0.026)	0.003 (-0.007,0.013)	-0.003*** (-0.004,-0.001)
ACEi or ARB monotherapy					
2018-2019 season: ACEi or ARB +- other	-0.003 (-0.007,0.001)	0.004 (-0.062,0.071)	-0.013 (-0.041,0.014)	0.001 (-0.015,0.017)	0.001 (-0.001,0.003)
2018-2019 season: ACEi or ARB monotherapy					
2019-2020 season: ACEi or ARB +/- other	-0.001 (-0.006,0.003)	0.05 (-0.006,0.106)	-0.022* (-0.043,-0.001)	-0.001 (-0.019,0.016)	-0.001 (-0.003,0.001)
2019-2020 season: ACEi or ARB monotherapy					
Demographics					
Female	-0.010*** (-0.012,-0.008)	-0.025* (-0.048,-0.003)	-0.01 (-0.019,0.000)	-0.008 (-0.018,0.002)	-0.003*** (-0.004,-0.002)
Age categories					
<35	-0.013*** (-0.017,-0.010)	-0.125 (-0.286,0.037)	0.089 (-0.025,0.202)	-0.017 (-0.074,0.040)	-0.001** (-0.002,-0.000)
35-44	-0.007*** (-0.009,-0.004)	-0.151*** (-0.229,-0.074)	0.014 (-0.026,0.055)	-0.022 (-0.053,0.009)	-0.001 (-0.001,0.000)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.003** (0.001,0.006)	-0.041 (-0.091,0.009)	-0.004 (-0.027,0.018)	0.006 (-0.018,0.029)	0.001*** (0.001,0.002)
65-74	0.006*** (0.003,0.009)	-0.056* (-0.109,-0.003)	-0.017 (-0.041,0.008)	0.009 (-0.015,0.032)	0.001* (0.000,0.002)
75-84	0.028*** (0.024,0.032)	-0.077** (-0.132,-0.022)	-0.011 (-0.037,0.014)	0.005 (-0.019,0.029)	0.008*** (0.007,0.010)
85+	0.074*** (0.068,0.079)	-0.139*** (-0.196,-0.083)	-0.022 (-0.048,0.004)	-0.007 (-0.032,0.017)	0.036*** (0.032,0.039)
Insurance coverage type					
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.013*** (-0.015,-0.010)	-0.043* (-0.083,-0.002)	-0.01 (-0.028,0.009)	0.006 (-0.011,0.024)	-0.004*** (-0.005,-0.003)
Census region					
Unknown/other	-0.034*** (-0.053,-0.014)	0.755*** (0.693,0.816)	-0.025* (-0.050,-0.000)	-0.062*** (-0.089,-0.035)	0.008 (-0.018,0.034)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	-0.002 (-0.007,0.004)	0.065* (0.008,0.123)	0.015 (-0.008,0.038)	0.025 (-0.003,0.053)	0.002 (-0.001,0.005)
South Atlantic	-0.004 (-0.009,0.001)	0.164*** (0.113,0.214)	0.012 (-0.007,0.032)	-0.009 (-0.032,0.014)	-0.001 (-0.004,0.001)

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.007**	0.111***	0.018	0	0
	(0.002,0.013)	(0.058,0.165)	(-0.003,0.039)	(-0.024,0.024)	(-0.003,0.002)
E South Central	0.001	0.116***	0.01	-0.004	-0.001
	(-0.005,0.007)	(0.055,0.176)	(-0.014,0.034)	(-0.030,0.023)	(-0.003,0.002)
W North Central	0.009**	0.124***	0.021	-0.002	0.002
	(0.003,0.015)	(0.063,0.184)	(-0.004,0.046)	(-0.028,0.025)	(-0.001,0.004)
W South Central	0.001	0.142***	0.025*	0.007	0
	(-0.004,0.007)	(0.086,0.199)	(0.002,0.049)	(-0.019,0.034)	(-0.002,0.003)
Mountain	-0.005	0.161***	-0.005	0.019	-0.002
	(-0.011,0.001)	(0.087,0.235)	(-0.031,0.020)	(-0.017,0.055)	(-0.005,0.001)
Pacific	0	0.173***	-0.004	-0.008	-0.003
Race/ethnicity	(-0.007,0.006)	(0.093,0.253)	(-0.032,0.024)	(-0.041,0.025)	(-0.005,0.000)
Unknown/other	0.001	0.056**	0.002	0.009	0
	(-0.002,0.004)	(0.022,0.089)	(-0.012,0.016)	(-0.006,0.023)	(-0.001,0.001)
White	ref.	ref.	ref.	ref.	ref.
Black	0.008***	0	0.003	0.01	0.001
	(0.006,0.011)	(-0.031,0.032)	(-0.010,0.016)	(-0.003,0.023)	(-0.000,0.002)
Hispanic	-0.001	0.092***	0.016	0.035***	-0.001*
	(-0.004,0.001)	(0.054,0.130)	(-0.001,0.034)	(0.015,0.055)	(-0.003,-0.000)
Asian	-0.007**	0.029	-0.018	0.018	-0.002
Comorbidities	(-0.011,-0.002)	(-0.045,0.103)	(-0.042,0.007)	(-0.018,0.055)	(-0.004,0.000)
No diabetes					
Diabetes without CC					
Diabetes with CC					
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.014***	-0.009	-0.009	-0.017	0.006**
	(0.007,0.021)	(-0.068,0.050)	(-0.032,0.013)	(-0.036,0.003)	(0.002,0.010)
Coronary artery disease					
Congestive heart failure					
Chronic pulmonary diseases					
Renal failure					
Liver failure					
Metastatic cancer					
Lymphoma					
Non-metastatic solid tumor					
Peripheral vascular disorders					
Cardiac arrhythmias					

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Rheumatoid arthritis/collagen vascular diseases					
Coagulopathy					
Obesity					
Chronic/acute deep vein thrombosis or pulmonary embolism					
Hemorrhagic or ischemic stroke					
Valvular disease					
Constant	0.027***	0.268***	0.027	0.006	0.006***
	(0.020,0.033)	(0.190,0.347)	(-0.003,0.058)	(-0.026,0.038)	(0.003,0.009)
N	200778	7696	7696	7696	200508
N_clust	175494	7647	7647	7647	175251
p	<0.001				<0.001
R-squared	0.022	0.033	0.007	0.023	0.015

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0	0.009	0.017***	-0.007***	0
	(-0.004,0.003)	(-0.002,0.019)	(0.012,0.022)	(-0.010,-0.003)	(-0.002,0.002)
2019-2020 flu season	0.003*	0.030***	0.017***	0.010***	0.017***
	(0.000,0.007)	(0.020,0.041)	(0.011,0.022)	(0.006,0.014)	(0.015,0.020)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.016***	-0.01	-0.007**	-0.003	-0.009***
	(-0.019,-0.013)	(-0.021,0.000)	(-0.011,-0.002)	(-0.006,0.001)	(-0.010,-0.007)
ACEi or ARB monotherapy					
2018-2019 season: ACEi or ARB +- other	0.002	0.01	0.001	0	0
	(-0.002,0.006)	(-0.004,0.025)	(-0.006,0.008)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy					
2019-2020 season: ACEi or ARB +/- other	0.008***	0.012	0.008*	0.008**	-0.005***
	(0.004,0.012)	(-0.003,0.026)	(0.001,0.014)	(0.002,0.013)	(-0.008,-0.002)
2019-2020 season: ACEi or ARB monotherapy					
Demographics					
Female	-0.011***	-0.024***	0.001	-0.001	-0.009***
	(-0.012,-0.009)	(-0.030,-0.017)	(-0.002,0.004)	(-0.003,0.001)	(-0.010,-0.008)
Age categories					
<35	0	-0.051	0.012	-0.014	-0.001
	(-0.006,0.006)	(-0.111,0.009)	(-0.020,0.044)	(-0.035,0.006)	(-0.003,0.001)
35-44	-0.005**	-0.027	0.005	-0.008	0.001
	(-0.009,-0.002)	(-0.063,0.009)	(-0.013,0.023)	(-0.022,0.006)	(-0.000,0.002)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.009***	0.005	0	-0.002	0
	(0.006,0.012)	(-0.014,0.023)	(-0.009,0.009)	(-0.009,0.005)	(-0.001,0.001)
65-74	0.009***	-0.009	-0.002	-0.003	0.006***
	(0.006,0.012)	(-0.027,0.009)	(-0.011,0.007)	(-0.010,0.004)	(0.005,0.008)
75-84	0.027***	-0.033***	-0.005	-0.007	0.022***
	(0.023,0.030)	(-0.051,-0.015)	(-0.013,0.004)	(-0.014,0.000)	(0.020,0.023)
85+	0.049***	-0.078***	-0.012*	-0.015***	0.062***
Insurance coverage type	(0.045,0.053)	(-0.097,-0.059)	(-0.021,-0.003)	(-0.022,-0.008)	(0.060,0.065)
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.028***	0.006	0.002	0.004	0.001
Census region	(-0.030,-0.025)	(-0.007,0.019)	(-0.005,0.008)	(-0.001,0.009)	(-0.000,0.002)
Unknown/other	-0.035	0.219*	-0.003	0.016	-0.024*
	(-0.071,0.000)	(0.012,0.426)	(-0.099,0.094)	(-0.085,0.117)	(-0.048,-0.000)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	0	0.018*	0.021***	0.022***	0.002
	(-0.005,0.005)	(0.002,0.035)	(0.014,0.029)	(0.015,0.028)	(-0.001,0.006)
South Atlantic	-0.012***	0.121***	0.014***	-0.004	-0.019***
	(-0.017,-0.008)	(0.107,0.135)	(0.007,0.020)	(-0.009,0.001)	(-0.022,-0.016)

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.008***	0.073***	0.004	-0.008**	-0.012***
	(0.003,0.013)	(0.058,0.089)	(-0.003,0.011)	(-0.013,-0.002)	(-0.015,-0.009)
E South Central	-0.006*	0.069***	0.015***	-0.010**	-0.014***
	(-0.011,-0.001)	(0.051,0.087)	(0.007,0.023)	(-0.016,-0.004)	(-0.017,-0.010)
W North Central	0.013***	0.091***	0.003	-0.004	-0.012***
	(0.008,0.018)	(0.074,0.109)	(-0.005,0.011)	(-0.010,0.002)	(-0.015,-0.009)
W South Central	-0.002	0.100***	0.016***	-0.008**	-0.017***
	(-0.007,0.002)	(0.083,0.116)	(0.008,0.024)	(-0.014,-0.003)	(-0.020,-0.014)
Mountain	-0.040***	0.115***	-0.009	-0.006	-0.020***
	(-0.046,-0.035)	(0.091,0.138)	(-0.019,0.001)	(-0.014,0.002)	(-0.024,-0.017)
Pacific	-0.008*	0.180***	0.005	-0.006	-0.017***
Race/ethnicity	(-0.014,-0.001)	(0.158,0.203)	(-0.006,0.015)	(-0.014,0.002)	(-0.021,-0.013)
Unknown/other	-0.007***	0.013*	0.003	0.005**	0
	(-0.010,-0.005)	(0.003,0.023)	(-0.002,0.009)	(0.001,0.009)	(-0.001,0.002)
White	ref.	ref.	ref.	ref.	ref.
Black	0.011***	-0.012**	0.005*	0.010***	0.004***
	(0.009,0.014)	(-0.021,-0.004)	(0.000,0.009)	(0.007,0.014)	(0.002,0.005)
Hispanic	-0.015***	0.079***	0.010***	0.007**	-0.008***
	(-0.018,-0.013)	(0.068,0.090)	(0.004,0.015)	(0.003,0.011)	(-0.010,-0.007)
Asian	-0.011***	0.005	0.002	0.006	-0.002
Comorbidities	(-0.016,-0.005)	(-0.017,0.027)	(-0.009,0.012)	(-0.002,0.015)	(-0.005,0.001)
No diabetes	ref.	ref.	ref.	ref.	ref.
Diabetes without CC	0.006***	0.012*	0.004	0.003	0.004***
	(0.004,0.009)	(0.003,0.022)	(-0.000,0.009)	(-0.001,0.006)	(0.003,0.005)
Diabetes with CC	0.026***	0.006	-0.003	0	0.007***
	(0.024,0.028)	(-0.001,0.013)	(-0.006,0.001)	(-0.002,0.003)	(0.006,0.008)
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.023***	-0.009*	-0.004	0	-0.001
	(0.020,0.026)	(-0.018,-0.000)	(-0.008,0.000)	(-0.003,0.003)	(-0.003,0.001)
Coronary artery disease	0.018***	0.031***	0	-0.001	0.006***
	(0.016,0.020)	(0.025,0.038)	(-0.003,0.004)	(-0.003,0.001)	(0.004,0.007)
Congestive heart failure	0.101***	0.078***	0.018***	0.004***	0.038***
	(0.098,0.104)	(0.072,0.085)	(0.015,0.022)	(0.002,0.007)	(0.037,0.040)
Chronic pulmonary diseases	0.074***	-0.010**	0.015***	-0.005***	0
	(0.072,0.076)	(-0.016,-0.004)	(0.012,0.018)	(-0.007,-0.002)	(-0.001,0.001)
Renal failure	0.019***	0.012**	0	0.001	0.023***
	(0.016,0.022)	(0.004,0.020)	(-0.004,0.004)	(-0.002,0.004)	(0.021,0.025)
Liver failure	0.041***	0.037***	0	0.004	0.057***
	(0.036,0.047)	(0.024,0.050)	(-0.006,0.007)	(-0.001,0.009)	(0.053,0.062)
Metastatic cancer	0.118***	0.007	0.001	-0.008**	0.138***
	(0.109,0.127)	(-0.010,0.023)	(-0.007,0.010)	(-0.013,-0.003)	(0.131,0.146)
Lymphoma	0.064***	-0.009	-0.001	-0.009**	0.023***
	(0.054,0.073)	(-0.030,0.012)	(-0.011,0.009)	(-0.015,-0.002)	(0.016,0.029)
Non-metastatic solid tumor	0.038***	0.021***	0.002	-0.004*	0.030***
	(0.034,0.042)	(0.010,0.032)	(-0.003,0.008)	(-0.007,-0.000)	(0.027,0.033)
Peripheral vascular disorders	-0.001	0.016***	0.005*	0.004**	0.023***
	(-0.004,0.002)	(0.008,0.024)	(0.001,0.009)	(0.001,0.007)	(0.021,0.025)
Cardiac arrhythmias	0.063***	0.065***	0.005**	-0.001	0.023***

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
	(0.061,0.066)	(0.058,0.071)	(0.002,0.008)	(-0.003,0.002)	(0.021,0.025)
Rheumatoid arthritis/collagen vascular diseases	0.015***	-0.013	-0.008*	-0.001	0.002
	(0.010,0.019)	(-0.026,0.001)	(-0.014,-0.002)	(-0.005,0.004)	(-0.000,0.005)
Coagulopathy	0.035***	0.032***	-0.002	0.001	0.039***
	(0.030,0.041)	(0.021,0.043)	(-0.008,0.003)	(-0.004,0.005)	(0.035,0.043)
Obesity	-0.002	0.016***	0.004	0.008***	-0.008***
	(-0.005,0.000)	(0.007,0.026)	(-0.001,0.009)	(0.005,0.012)	(-0.010,-0.006)
Chronic/acute deep vein thrombosis or pulmonary embolism	0.053***	0.052***	0.005	0.002	0.026***
	(0.046,0.061)	(0.038,0.066)	(-0.003,0.012)	(-0.004,0.007)	(0.021,0.031)
Hemorrhagic or ischemic stroke	0.018***	0.030***	0.005	-0.003	0.044***
	(0.014,0.022)	(0.020,0.040)	(-0.000,0.010)	(-0.007,0.000)	(0.041,0.047)
Valvular disease	-0.008***	0.053***	0.008***	-0.001	0.016***
	(-0.012,-0.005)	(0.044,0.061)	(0.003,0.012)	(-0.004,0.003)	(0.014,0.019)
Constant	0.057***	0.314***	0.022***	0.037***	0.013***
	(0.051,0.063)	(0.290,0.338)	(0.010,0.033)	(0.028,0.046)	(0.010,0.017)
N	738240	106917	106917	106917	737059
N_clust	556579	97383	97383	97383	555729
p	<0.001	<0.001	<0.001	<0.001	<0.001
R-squared	0.094	0.039	0.007	0.008	0.082

	Primary analysis				
	(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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001	0.008	0.013***	-0.007***	0.000
	(-0.004,0.002)	(-0.002,0.018)	(0.008,0.017)	(-0.010,-0.004)	(-0.002,0.002)
2019-2020 flu season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015,0.021)	(0.026,0.044)	(0.008,0.017)	(0.009,0.016)	(0.014,0.017)
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,-0.016)	(-0.019,0.001)	(-0.011,-0.002)	(-0.007,0.000)	(-0.011,-0.008)
ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	0.004*	0.01	0.004	0	0
	(0.001,0.008)	(-0.004,0.023)	(-0.003,0.010)	(-0.004,0.004)	(-0.002,0.002)
2018-2019 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
2019-2020 season: ACEi or ARB +/- other	0.015***	0.015*	0.007*	0.009***	-0.002
	(0.012,0.019)	(0.003,0.027)	(0.001,0.012)	(0.004,0.013)	(-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Note: p-value for coefficients is for the null hypothesis that the coefficient = 0					
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.179	0.482	0.053	0.030	0.064
	(0.177,0.181)	(0.474,0.489)	(0.050,0.056)	(0.028,0.033)	(0.062,0.065)
2018/19	0.178	0.490	0.066	0.023	0.064
	(0.176,0.180)	(0.483,0.496)	(0.062,0.069)	(0.021,0.025)	(0.063,0.065)
2019/20	0.196	0.516	0.066	0.043	0.080
	(0.195,0.198)	(0.511,0.521)	(0.063,0.068)	(0.041,0.045)	(0.078,0.081)

	Primary analysis				
	(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
ACEi or ARB plus/minus other medications					
2017/18	0.125	0.463	0.045	0.029	0.035
	(0.124,0.127)	(0.456,0.470)	(0.042,0.048)	(0.027,0.031)	(0.034,0.035)
2018/19	0.128	0.481	0.061	0.021	0.034
	(0.127,0.130)	(0.475,0.487)	(0.058,0.064)	(0.020,0.023)	(0.034,0.035)
2019/20	0.158	0.512	0.064	0.050	0.049
	(0.157,0.160)	(0.508,0.517)	(0.062,0.066)	(0.048,0.052)	(0.048,0.049)
ACEi or ARB monotherapy					
2017/18	N/A	N/A	N/A	N/A	N/A
2018/19	N/A	N/A	N/A	N/A	N/A
2019/20	N/A	N/A	N/A	N/A	N/A
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977,1.011)	(0.996,1.038)	(1.136,1.337)	(0.668,0.850)	(0.969,1.030)
2019/20 season vs. 2017/18	1.099***	1.072***	1.238***	1.414***	1.244***
	(1.081,1.116)	(1.053,1.092)	(1.147,1.330)	(1.278,1.550)	(1.210,1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.025**	1.039***	1.360***	0.739***	0.993
	(1.009,1.042)	(1.019,1.058)	(1.251,1.469)	(0.656,0.822)	(0.961,1.025)
2019/20 season vs. 2017/18	1.264***	1.107***	1.437***	1.731***	1.404***
	(1.245,1.282)	(1.088,1.126)	(1.332,1.542)	(1.580,1.882)	(1.363,1.444)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
2019/20 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
Number of episodes	1,059,474	167,330	167,330	167,330	1,057,707
Number of people	728,455	147,846	147,846	147,846	727,311

Note: p-value for risk ratios is for the null hypothesis that the risk ratio = 1

N/A: variable not included in model

* p<0.05, ** p<0.01, *** p<0.001

	Sensitivity analysis: ACEi/ARB monotherapy				
	(6)	(7)	(8)	(9)	(10)
	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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001	0.008	0.013***	-0.007***	0
	(-0.004,0.002)	(-0.002,0.018)	(0.008,0.017)	(-0.010,-0.004)	(-0.002,0.002)
2019-2020 flu season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015,0.021)	(0.026,0.044)	(0.008,0.017)	(0.009,0.016)	(0.014,0.017)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.020***	-0.004	-0.007**	-0.002	-0.010***
	(-0.023,-0.017)	(-0.014,0.006)	(-0.011,-0.002)	(-0.006,0.001)	(-0.012,-0.009)
ACEi or ARB monotherapy	-0.016***	-0.039***	-0.007	-0.009**	-0.004***
	(-0.020,-0.012)	(-0.057,-0.020)	(-0.015,0.001)	(-0.015,-0.003)	(-0.006,-0.002)
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	0.004*	0.004	0.004	-0.001	-0.001
	(0.000,0.008)	(-0.009,0.018)	(-0.003,0.010)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy	0.005	0.040**	0.002	0.002	0.001
	(-0.001,0.010)	(0.015,0.065)	(-0.009,0.013)	(-0.006,0.009)	(-0.002,0.004)
2019-2020 season: ACEi or ARB +/- other	0.015***	0.011	0.007*	0.008***	-0.001
	(0.011,0.019)	(-0.001,0.024)	(0.002,0.013)	(0.003,0.013)	(-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy	0.017***	0.035**	0.004	0.012**	-0.003*
Note: p-value for coefficients is for the null hypotl	(0.012,0.022)	(0.013,0.057)	(-0.006,0.013)	(0.004,0.020)	(-0.006,-0.000)
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.179	0.481	0.053	0.030	0.064
	(0.177,0.181)	(0.474,0.489)	(0.050,0.056)	(0.028,0.033)	(0.062,0.065)
2018/19	0.178	0.490	0.066	0.023	0.064
	(0.176,0.180)	(0.483,0.496)	(0.062,0.069)	(0.021,0.025)	(0.063,0.065)
2019/20	0.196	0.516	0.066	0.043	0.079
	(0.195,0.198)	(0.511,0.521)	(0.063,0.068)	(0.041,0.045)	(0.078,0.081)

	Sensitivity analysis: ACEi/ARB monotherapy				
	(6)	(7)	(8)	(9)	(10)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
ACEi or ARB plus/minus other medications					
2017/18	0.133	0.473	0.046	0.030	0.037
	(0.132,0.135)	(0.466,0.480)	(0.043,0.049)	(0.027,0.032)	(0.036,0.038)
2018/19	0.136	0.486	0.062	0.022	0.037
	(0.135,0.138)	(0.479,0.492)	(0.059,0.065)	(0.020,0.024)	(0.036,0.038)
2019/20	0.166	0.519	0.066	0.050	0.052
	(0.164,0.167)	(0.514,0.524)	(0.063,0.068)	(0.048,0.052)	(0.051,0.053)
ACEi or ARB monotherapy					
2017/18	0.093	0.408	0.040	0.024	0.024
	(0.090,0.096)	(0.392,0.425)	(0.033,0.047)	(0.019,0.029)	(0.022,0.025)
2018/19	0.096	0.456	0.054	0.018	0.025
	(0.094,0.099)	(0.441,0.472)	(0.047,0.061)	(0.014,0.022)	(0.023,0.026)
2019/20	0.127	0.478	0.056	0.048	0.036
	(0.125,0.130)	(0.467,0.489)	(0.051,0.061)	(0.043,0.053)	(0.034,0.037)
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977,1.011)	(0.996,1.038)	(1.136,1.337)	(0.668,0.850)	(0.969,1.030)
2019/20 season vs. 2017/18	1.098***	1.072***	1.238***	1.414***	1.243***
	(1.081,1.116)	(1.053,1.092)	(1.147,1.330)	(1.278,1.550)	(1.209,1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.023*	1.027*	1.360***	0.735***	0.985
	(1.005,1.041)	(1.006,1.048)	(1.243,1.476)	(0.647,0.824)	(0.950,1.019)
2019/20 season vs. 2017/18	1.244***	1.097***	1.441***	1.690***	1.382***
	(1.225,1.264)	(1.077,1.118)	(1.329,1.554)	(1.532,1.848)	(1.339,1.425)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	1.037	1.117***	1.358*	0.766	1.047
	(0.993,1.080)	(1.058,1.177)	(1.055,1.660)	(0.526,1.006)	(0.958,1.136)
2019/20 season vs. 2017/18	1.369***	1.170***	1.412**	2.028***	1.526***
	(1.318,1.420)	(1.115,1.226)	(1.129,1.694)	(1.537,2.519)	(1.412,1.640)
Number of episodes	1,059,474	167,330	167,330	167,330	1,057,707
Number of people	728,455	147,846	147,846	147,846	727,311

Note: p-value for risk ratios is for the null hypothe

N/A: variable not included in model

* p<0.05, ** p<0.01, *** p<0.001

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0.002	0.02	0.030**	0.006	0
	(-0.001,0.006)	(-0.032,0.072)	(0.009,0.051)	(-0.005,0.017)	(-0.002,0.002)
2019-2020 flu season	0.032***	0.068**	0.029***	0.052***	0.007***
	(0.028,0.035)	(0.024,0.111)	(0.014,0.045)	(0.039,0.065)	(0.005,0.009)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.006***	-0.001	0.009	0.003	-0.003***
	(-0.009,-0.003)	(-0.049,0.046)	(-0.008,0.026)	(-0.007,0.013)	(-0.004,-0.001)
ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	-0.003	0.004	-0.013	0.001	0.001
	(-0.007,0.001)	(-0.062,0.071)	(-0.041,0.014)	(-0.015,0.017)	(-0.001,0.003)
2018-2019 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
2019-2020 season: ACEi or ARB +/- other	-0.001	0.05	-0.022*	-0.001	-0.001
	(-0.006,0.003)	(-0.006,0.106)	(-0.043,-0.001)	(-0.019,0.016)	(-0.003,0.001)
2019-2020 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Note: p-value for coefficients is for the null hypotl					
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.031	0.312	0.023	0.009	0.007
	(0.029,0.034)	(0.275,0.350)	(0.011,0.035)	(0.002,0.016)	(0.006,0.009)
2018/19	0.033	0.332	0.053	0.015	0.007
	(0.031,0.036)	(0.296,0.368)	(0.036,0.070)	(0.006,0.024)	(0.006,0.008)
2019/20	0.063	0.380	0.053	0.061	0.014
	(0.060,0.066)	(0.357,0.403)	(0.042,0.063)	(0.050,0.073)	(0.013,0.016)

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
ACEi or ARB plus/minus other medications					
2017/18	0.023	0.319	0.033	0.016	0.004
	(0.022,0.025)	(0.289,0.349)	(0.021,0.044)	(0.008,0.023)	(0.003,0.004)
2018/19	0.022	0.343	0.049	0.023	0.004
	(0.021,0.024)	(0.313,0.373)	(0.036,0.063)	(0.014,0.032)	(0.004,0.005)
2019/20	0.054	0.436	0.040	0.067	0.010
	(0.052,0.055)	(0.418,0.454)	(0.033,0.048)	(0.058,0.076)	(0.009,0.011)
ACEi or ARB monotherapy					
2017/18	N/A	N/A	N/A	N/A	N/A
2018/19	N/A	N/A	N/A	N/A	N/A
2019/20	N/A	N/A	N/A	N/A	N/A
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	1.069	1.064	2.291	1.633	0.973
	(0.953,1.186)	(0.893,1.235)	(0.893,3.688)	(0.078,3.189)	(0.744,1.203)
2019/20 season vs. 2017/18	2.008***	1.216**	2.270*	6.718*	1.942***
	(1.823,2.193)	(1.053,1.379)	(1.013,3.526)	(1.473,11.963)	(1.561,2.323)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	0.961	1.076	1.510	1.432	1.128
	(0.875,1.047)	(0.939,1.213)	(0.842,2.177)	(0.544,2.320)	(0.879,1.377)
2019/20 season vs. 2017/18	2.291***	1.369***	1.234	4.210**	2.624***
	(2.124,2.458)	(1.228,1.509)	(0.754,1.713)	(2.113,6.308)	(2.142,3.107)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
2019/20 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
Number of episodes	200,778	7,696	7,696	7,696	200,508
Number of people	175,494	7,647	7,647	7,647	175,251

Note: p-value for risk ratios is for the null hypothe

N/A: variable not included in model

* p<0.05, ** p<0.01, *** p<0.001

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0	0.009	0.017***	-0.007***	0
	(-0.004,0.003)	(-0.002,0.019)	(0.012,0.022)	(-0.010,-0.003)	(-0.002,0.002)
2019-2020 flu season	0.003*	0.030***	0.017***	0.010***	0.017***
	(0.000,0.007)	(0.020,0.041)	(0.011,0.022)	(0.006,0.014)	(0.015,0.020)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.016***	-0.01	-0.007**	-0.003	-0.009***
	(-0.019,-0.013)	(-0.021,0.000)	(-0.011,-0.002)	(-0.006,0.001)	(-0.010,-0.007)
ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	0.002	0.01	0.001	0	0
	(-0.002,0.006)	(-0.004,0.025)	(-0.006,0.008)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
2019-2020 season: ACEi or ARB +/- other	0.008***	0.012	0.008*	0.008**	-0.005***
	(0.004,0.012)	(-0.003,0.026)	(0.001,0.014)	(0.002,0.013)	(-0.008,-0.002)
2019-2020 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Note: p-value for coefficients is for the null hypotl					
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.175	0.480	0.053	0.030	0.061
	(0.173,0.178)	(0.472,0.487)	(0.049,0.056)	(0.028,0.033)	(0.060,0.063)
2018/19	0.175	0.488	0.070	0.024	0.061
	(0.172,0.177)	(0.480,0.496)	(0.066,0.074)	(0.021,0.026)	(0.060,0.063)
2019/20	0.179	0.510	0.069	0.041	0.079
	(0.176,0.181)	(0.503,0.517)	(0.066,0.073)	(0.038,0.044)	(0.077,0.080)

Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)

	(16)	(17)	(18)	(19)	(20)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
ACEi or ARB plus/minus other medications					
2017/18	0.122	0.459	0.044	0.028	0.033
	(0.120,0.123)	(0.452,0.466)	(0.041,0.047)	(0.026,0.031)	(0.032,0.033)
2018/19	0.124	0.478	0.063	0.021	0.032
	(0.122,0.125)	(0.470,0.485)	(0.059,0.066)	(0.019,0.023)	(0.032,0.033)
2019/20	0.133	0.501	0.069	0.046	0.045
	(0.131,0.134)	(0.494,0.508)	(0.065,0.072)	(0.044,0.049)	(0.044,0.046)
ACEi or ARB monotherapy					
2017/18	N/A	N/A	N/A	N/A	N/A
2018/19	N/A	N/A	N/A	N/A	N/A
2019/20	N/A	N/A	N/A	N/A	N/A
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.998	1.018	1.324***	0.776***	1.002
	(0.979,1.017)	(0.995,1.041)	(1.208,1.440)	(0.673,0.879)	(0.967,1.036)
2019/20 season vs. 2017/18	1.019	1.064***	1.313***	1.343***	1.282***
	(1.000,1.039)	(1.041,1.087)	(1.201,1.425)	(1.190,1.495)	(1.241,1.324)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.017	1.041***	1.411***	0.750***	0.997
	(0.999,1.035)	(1.019,1.063)	(1.289,1.533)	(0.655,0.846)	(0.960,1.034)
2019/20 season vs. 2017/18	1.091***	1.092***	1.542***	1.634***	1.380***
	(1.071,1.110)	(1.069,1.114)	(1.413,1.671)	(1.465,1.803)	(1.331,1.428)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
2019/20 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
Number of episodes	738,240	106,917	106,917	106,917	737,059
Number of people	556,579	97,383	97,383	97,383	555,729

Note: p-value for risk ratios is for the null hypothe

N/A: variable not included in model

* p<0.05, ** p<0.01, *** p<0.001

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			
Objectives	3	State specific objectives, including any prespecified hypotheses			
Methods					
Study Design	4	Present key elements of study design early in the paper			
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			
Participants	6	*(a) Cohort study* - Give the		RECORD 6.1: The methods of study	

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			

Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the	

				study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or			

		summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			

Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

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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Title: 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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Competing interests

None.

Patient consent for publication

Not applicable / Not required.

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ABSTRACT

Objectives: Evaluate the associations between patients taking ACE inhibitors (ACEis) 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 vs. 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 hypertension had a greater increase in poor outcomes during the COVID-19 pandemic than those using other medications to treat hypertension. The small absolute magnitude of the differences likely does not support changes in clinical practice.

Keywords: ACE inhibitors, angiotensin receptor blockers, COVID-19, acute viral respiratory illness.

ARTICLE SUMMARY

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 coronavirus disease 2019 (COVID-19) pandemic, pre-clinical 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 severe acute respiratory syndrome coronavirus 2 (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 randomized 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 hospitalized with COVID-19, while reassuring for clinicians and patients, do not directly address the question of whether the risk of hospitalization may be increased in this population. In this study, we aimed to evaluate the associations between prescription fills for 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 vs. other HTN medications in order to control for otherwise unobserved differences in underlying health and healthcare seeking behavior between the medication cohorts. We assessed severity of illness and mortality in AVRI across cohorts of patients with hypertension (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 United States.

METHODS

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

Data source and study setting

We used de-identified 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 United States. The OLDW includes medical and pharmacy claims, laboratory results, and enrollment 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 October 1, 2017, and November 30, 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. (**Supplementary 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 enrollment before the index date of the AVRI episode. Insurance claims during this period were used to identify hypertension 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 hypertension, as explained below.

Variables and measurements

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

Hypertension and comorbidities

Hypertension 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 the **Supplementary Material S1.** Hypertension 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 (HEDIS) performance measures.[29]

Hypertension medications

We developed a comprehensive list of hypertension medications (see **Supplementary Material S1**), then identified all National Drug Codes (NDCs) 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 categorized fill patterns as ACEi or ARB only, ACEi or ARB with other (i.e., not ACEi or ARB) hypertension medications, other hypertension medications only, or no hypertension medications. In primary analyses, ACEi or ARB users with and without other hypertension medications were combined and compared with people using only other hypertension medications; information on people who did not use hypertension 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 5 outcomes associated with more serious cases of AVRI: death, hospitalization, and, conditional on hospitalization: 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 acute respiratory distress 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 enrollment 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 hypertension using hypertension 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 hypertension. 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 3 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 standard errors 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 risk difference may have different importance for an event with an incidence of 10% (relative increase 10%) compared to one with an incidence of 1% (relative increase 100%). To ease interpretation of results, we calculated average marginal effects for each flu 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 flu season and the 2019/2020/COVID-19 flu season versus the baseline 2017/2018 flu season, along with p-values for the hypothesis test that the ratios were equal to 1 (i.e., 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 2017/18 season, which would suggest that COVID-19 is fundamentally different from the general year-to-year shifts in flu 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 version 16.0 was used for all analyses (StataCorp College Station, TX, 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 hypertension. Of these, 15.1% (187,919) did not fill a hypertension 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).

Compared to 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 hypertension, 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 to 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=167,330), including 14.0% of episodes in ACEi/ARB users (n=91,660) and 18.7% in other HTN medication users (n=75,670; **Table 1**). Episode mortality rates were 5.2% overall (n=55,164), 4.0% for ACEi/ARB users (n=26,411), and 7.1% in other HTN medication users (n=28,753). 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 **Supplementary Material S2**. The ACEi/ARB cohort had a somewhat lower risk of three of the five outcomes in the baseline 2017-2018 flu season compared to the other HTN medication cohort, with a 1.9 percentage point (pp) (95% CI -2.2 to -1.6 percentage points) 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 flu 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 vs. 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]). 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. (**Supplementary 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 hypertension). 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=7,696 episodes). (**Supplementary Material S3**)

Strict flu season

Limiting the 2017/18 and 2018/19 cohorts to cases of AVRI occurring in the strict flu season (generally October to May) had minimal effect on the results, which were similar to the primary analysis. (**Supplementary 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 to 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 hypertension 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 to 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 health care seeking behavior.

During the COVID-19 flu season, all patients (ACEi/ARB and other HTN) had higher risk of all outcomes, compared to prior years. This is consistent with evidence that patients with hypertension experience worse outcomes from COVID-19.[36-40] The ACEi/ARB group had a larger increase in poor outcomes from baseline compared to patients taking other HTN medication, including higher rates of hospitalization, 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 percentage points. 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 hypertension 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 OptumLabs Data Warehouse; in particular, we do not observe outcomes of people who are uninsured or those who have Medicaid insurance (i.e., people with low incomes and no employer-based insurance). The study only captures people who received health care for

AVRI, which may be different in important ways during COVID-19 compared to 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 hypertension who used ACEi/ARB and those who used other medications changed their care seeking behavior in similar ways, this effect should be minimized. Lastly, 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 that were not evaluated such as number of previous respiratory infections, number of previous hospitalization, and duration of treatment with ACEi/ARBs.

CONCLUSIONS

People with acute viral respiratory illnesses using ACEi/ARBs to treat hypertension had a greater increase in poor outcomes during the COVID-19 pandemic than those using other medications to treat hypertension. 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 hospitalization, ICU use, and diagnosis of ARD or ARDS suggest that this effect likely does not warrant changes in clinical practice.

CONTRIBUTORSHIP STATEMENT

Conceptualization: MMJ, LOJS, FB, VDG, TMD, AHL, NWC. Formal analysis: MMJ. Investigation: MMJ, LOJS, FB, VDG, TMD, AHL, NWC. Methodology: MMJ, LOJS, FB. Project administration: MMJ. Supervision: MMJ, NWC. Validation: MMJ, NWC. Writing-

original draft: MMJ. Writing-review and editing: MMJ, LOJS, FB, VSD, TMD, AHL, NWC. Guarantor: MMJ, NWC. All authors provided critical revision and contribution for important intellectual content.

COMPETING INTERESTS

None.

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DATA SHARING STATEMENT

No additional data available.

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LEGENDS

Table 1. Cohort characteristics.

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

Table 1. Cohort characteristics.

	Comparison only (not included sample)	Included Sample		
	No HTN meds	Other HTN meds only	ACEi or ARB	Total included sample
	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	3,922 (2.1%)	3,354 (0.8%)	4,537 (0.7%)	7,891 (0.7%)
35-44	8,337 (4.4%)	9,784 (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	4,449 (2.4%)	8,003 (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	7,217 (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	8,484 (4.5%)	14,224 (3.5%)	27,963 (4.3%)	42,187 (4.0%)
Pacific	5,902 (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				

	Comparison only (not included sample)	Included Sample		
	No HTN meds	Other HTN meds only	ACEi or ARB	Total included sample
	N (%)	N (%)	N (%)	N (%)
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	6,657 (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%)
Hemorrhagic or ischemic stroke	15,912 (8.5%)	34,297 (8.5%)	39,064 (6.0%)	73,361 (6.9%)
Coagulopathy	10,197 (5.4%)	25,467 (6.3%)	22,109 (3.4%)	47,576 (4.5%)
Lymphoma	2,928 (1.6%)	6,095 (1.5%)	6,086 (.9%)	12,181 (1.1%)
Metastatic cancer	6,506 (3.5%)	11,323 (2.8%)	11,808 (1.8%)	23,131 (2.2%)
Solid tumor without mets	17,654 (9.4%)	35,097 (8.7%)	42,177 (6.5%)	77,274 (7.3%)
Renal failure	29,431 (15.7%)	104,877 (25.9%)	107,485 (16.4%)	212,362 (20.0%)
Liver failure	8,676 (4.6%)	19,071 (4.7%)	19,875 (3.0%)	38,946 (3.7%)
Rheumatoid arthritis/collagen vascular diseases	8,584 (4.6%)	20,953 (5.2%)	27,768 (4.2%)	48,721 (4.6%)
Obesity	17,709 (9.4%)	44,279 (10.9%)	72,278 (11.1%)	116,557 (11.0%)
Total	187,919 (100.0%)	405,677 (100.0%)	653,797 (100.0%)	1,059,474 (100.0%)
Unadjusted outcome incidence				
Inpatient stay	33,058 (17.6%)	75,670 (18.7%)	91,660 (14.0%)	167,330 (15.8%)
ICU/CCU services during inpatient stay	15,360 (46.5%)	37,894 (50.1%)	45,129 (49.2%)	83,023 (49.6%)
ARDS diagnosis during inpatient stay	1,051 (3.2%)	2,598 (3.4%)	3,403 (3.7%)	6,001 (3.6%)
ARD diagnosis during inpatient stay	1,781 (5.4%)	4,749 (6.3%)	5,388 (5.9%)	10,137 (6.1%)
Died same or following calendar month	12,933 (6.9%)	28,753 (7.1%)	26,411 (4.0%)	55,164 (5.2%)

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% confidence interval)					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001 (-0.004,0.002)	0.008 (-0.002,0.018)	0.013*** (0.008,0.017)	-0.007*** (-0.010,-0.004)	0.000 (-0.002,0.002)
2019-2020 flu season	0.018*** (0.015,0.021)	0.035*** (0.026,0.044)	0.013*** (0.008,0.017)	0.013*** (0.009,0.016)	0.016*** (0.014,0.017)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.019*** (-0.022,-0.016)	-0.009 (-0.019,0.001)	-0.007** (-0.011,-0.002)	-0.003 (-0.007,0.000)	-0.009*** (-0.011,-0.008)
Season/medication interactions					
2018-2019 season: ACEi or ARB plus/minus other medications	0.004* (0.001,0.008)	0.010 (-0.004,0.023)	0.004 (-0.003,0.010)	0.000 (-0.004,0.004)	0.000 (-0.002,0.002)
2019-2020 season: ACEi or ARB plus/minus other medications	0.015*** (0.012,0.019)	0.015* (0.003,0.027)	0.007* (0.001,0.012)	0.009*** (0.004,0.013)	-0.002 (-0.004,0.001)

Note: p-value for coefficients is for the null hypothesis that the coefficient = 0; presented in probability units (e.g., coefficient of -0.001 represents -0.1 percentage points)

Marginal effects/predicted probability (95% confidence interval)					
Other hypertension medications only					
2017/18	0.179 (0.177,0.181)	0.482 (0.474,0.489)	0.053 (0.050,0.056)	0.030 (0.028,0.033)	0.064 (0.062,0.065)
2018/19	0.178 (0.176,0.180)	0.490 (0.483,0.496)	0.066 (0.062,0.069)	0.023 (0.021,0.025)	0.064 (0.063,0.065)
2019/20	0.196	0.516	0.066	0.043	0.080

	(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
	(0.195,0.198)	(0.511,0.521)	(0.063,0.068)	(0.041,0.045)	(0.078,0.081)
ACEi or ARB plus/minus other medications					
2017/18	0.125	0.463	0.045	0.029	0.035
	(0.124,0.127)	(0.456,0.470)	(0.042,0.048)	(0.027,0.031)	(0.034,0.035)
2018/19	0.128	0.481	0.061	0.021	0.034
	(0.127,0.130)	(0.475,0.487)	(0.058,0.064)	(0.020,0.023)	(0.034,0.035)
2019/20	0.158	0.512	0.064	0.050	0.049
	(0.157,0.160)	(0.508,0.517)	(0.062,0.066)	(0.048,0.052)	(0.048,0.049)
Ratios of marginal effects (95% confidence interval)					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977,1.011)	(0.996,1.038)	(1.136,1.337)	(0.668,0.850)	(0.969,1.030)
2019/20 season vs. 2017/18	1.099***	1.072***	1.238***	1.414***	1.244***
	(1.081,1.116)	(1.053,1.092)	(1.147,1.330)	(1.278,1.550)	(1.210,1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.025**	1.039***	1.360***	0.739***	0.993
	(1.009,1.042)	(1.019,1.058)	(1.251,1.469)	(0.656,0.822)	(0.961,1.025)
2019/20 season vs. 2017/18	1.264***	1.107***	1.437***	1.731***	1.404***
	(1.245,1.282)	(1.088,1.126)	(1.332,1.542)	(1.580,1.882)	(1.363,1.444)

Note: 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

SUPPLEMENTARY MATERIAL S1

SUPPLEMENT T1: Codes used to define AVRI, CAD, stroke, DVT, and PE

Condition	**Codes**
Acute viral respiratory illness (AVRI)	B9721, B9729, J09*, J10*, J11*, J12*, J16, J168, J18, J180, J181, J182, J188, J189, J20, J201, J203, J204, J205, J206, J207, J208, J209, J22, J40, J440, J470, J8411, J84111, U071, U072
Coronary artery disease (CAD)	I20*, I21*, I22*, I23*, I24*, I25*
Stroke	I63*, Z8673*, I60*, I61*, I62*
Deep vein thrombosis (DVT) and pulmonary embolism (PE)	I8249, I824Y, I824Z, I8251, I8259, I825Y, I825Z, I8262, I8272, I26*, I2782

SUPPLEMENT T2: Hypertension medications

Medication type	**Included medications (generic name)**
ACEi	captopril, lisinopril, enalapril, benazepril, perindopril, quinapril, fosinopril, moexipril, ramipril, trandolapril
ARB	losartan, valsartan, irbesartan, candesartan, eprosartan, telmisartan, azilsartan, Olmesartan
Other (excluding topical, ophthalmic, and drops preparations)	Bendroflumethiazide, chlorothiazide, indapamide, metolazone, bumetanide, furosemide, torsemide, ethacrynic, amiloride, triamterene, eplerenone, spironolactone, aliskiren, diltiazem, verapamil, amlodipine, nicardipine, felodipine, nifedipine, torsemide, ethacrynic, isradipine, nisoldipine, doxazosin, prazosin, terazosin, clonidine, guanfacine, methyldopa, reserpine, hydralazine, minoxidil, acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol

	Primary analysis				
	(1) Inpatient stay (95% confidence interval)	(2) Inpatient stay with ICU/CCU (95% confidence interval)	(3) Inpatient stay with ARD dx (95% confidence interval)	(4) Inpatient stay with ARDS dx (95% confidence interval)	(5) Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001 (-0.004,0.002)	0.008 (-0.002,0.018)	0.013*** (0.008,0.017)	-0.007*** (-0.010,-0.004)	0.000 (-0.002,0.002)
2019-2020 flu season	0.018*** (0.015,0.021)	0.035*** (0.026,0.044)	0.013*** (0.008,0.017)	0.013*** (0.009,0.016)	0.016*** (0.014,0.017)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.019*** (-0.022,-0.016)	-0.009 (-0.019,0.001)	-0.007** (-0.011,-0.002)	-0.003 (-0.007,0.000)	-0.009*** (-0.011,-0.008)
ACEi or ARB monotherapy					
2018-2019 season: ACEi or ARB +- other	0.004* (0.001,0.008)	0.01 (-0.004,0.023)	0.004 (-0.003,0.010)	0 (-0.004,0.004)	0 (-0.002,0.002)
2018-2019 season: ACEi or ARB monotherapy					
2019-2020 season: ACEi or ARB +/- other	0.015*** (0.012,0.019)	0.015* (0.003,0.027)	0.007* (0.001,0.012)	0.009*** (0.004,0.013)	-0.002 (-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy					
Demographics					
Female	-0.016*** (-0.017,-0.014)	-0.023*** (-0.028,-0.018)	0 (-0.002,0.003)	-0.004*** (-0.006,-0.002)	-0.011*** (-0.012,-0.010)
Age categories					
<35	-0.006* (-0.011,-0.000)	-0.029 (-0.078,0.019)	0.02 (-0.006,0.045)	-0.01 (-0.028,0.008)	-0.001 (-0.003,0.001)
35-44	-0.008*** (-0.012,-0.005)	-0.028 (-0.056,0.000)	0.006 (-0.008,0.019)	-0.004 (-0.016,0.008)	0.001 (-0.000,0.002)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.010*** (0.008,0.013)	0.005 (-0.009,0.020)	0.001 (-0.005,0.008)	0.001 (-0.005,0.007)	0.001* (0.000,0.002)
65-74	0.011*** (0.008,0.014)	-0.003 (-0.017,0.011)	0.001 (-0.006,0.008)	-0.001 (-0.007,0.004)	0.009*** (0.007,0.010)
75-84	0.029*** (0.025,0.032)	-0.026*** (-0.041,-0.012)	-0.002 (-0.009,0.004)	-0.005 (-0.011,0.001)	0.024*** (0.023,0.026)
85+	0.045*** (0.041,0.048)	-0.071*** (-0.086,-0.056)	-0.010** (-0.017,-0.003)	-0.014*** (-0.020,-0.008)	0.063*** (0.061,0.065)
Insurance coverage type					
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.032*** (-0.034,-0.030)	0.01 (-0.001,0.020)	0.001 (-0.004,0.006)	0.003 (-0.002,0.007)	-0.001* (-0.002,-0.000)
Census region					
Unknown/other	-0.046** (-0.075,-0.016)	0.194* (0.014,0.373)	-0.011 (-0.086,0.064)	0.009 (-0.068,0.087)	-0.023* (-0.044,-0.002)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	-0.008*** (-0.012,-0.003)	0.017* (0.003,0.031)	0.021*** (0.015,0.028)	0.021*** (0.016,0.026)	-0.005** (-0.008,-0.002)
South Atlantic	-0.001 (-0.005,0.003)	0.122*** (0.110,0.134)	0.016*** (0.011,0.021)	0.003 (-0.002,0.007)	-0.016*** (-0.018,-0.013)

	Primary analysis				
	(1)	(2)	(3)	(4)	(5)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.018***	0.073***	0.003	0	-0.009***
	(0.013,0.022)	(0.060,0.086)	(-0.002,0.009)	(-0.004,0.004)	(-0.012,-0.007)
E South Central	0.011***	0.071***	0.018***	-0.001	-0.009***
	(0.007,0.016)	(0.056,0.085)	(0.011,0.024)	(-0.006,0.005)	(-0.011,-0.006)
W North Central	0.027***	0.093***	0.004	0.006*	-0.007***
	(0.022,0.032)	(0.079,0.107)	(-0.002,0.010)	(0.001,0.011)	(-0.010,-0.004)
W South Central	0.014***	0.111***	0.017***	0.003	-0.011***
	(0.010,0.018)	(0.097,0.124)	(0.011,0.023)	(-0.002,0.007)	(-0.014,-0.009)
Mountain	-0.033***	0.122***	-0.007	0.008*	-0.019***
	(-0.037,-0.028)	(0.103,0.140)	(-0.015,0.000)	(0.001,0.016)	(-0.022,-0.016)
Pacific	-0.002	0.170***	0.008	0.001	-0.016***
Race/ethnicity	(-0.007,0.004)	(0.151,0.189)	(-0.000,0.017)	(-0.006,0.007)	(-0.019,-0.013)
Unknown/other	-0.007***	0.020***	0.004*	0.009***	-0.002**
	(-0.010,-0.005)	(0.013,0.028)	(0.001,0.008)	(0.006,0.012)	(-0.003,-0.001)
White	ref.	ref.	ref.	ref.	ref.
Black	0.011***	-0.010**	0.005**	0.008***	0.004***
	(0.009,0.013)	(-0.017,-0.003)	(0.002,0.008)	(0.006,0.011)	(0.002,0.005)
Hispanic	-0.016***	0.086***	0.011***	0.010***	-0.008***
	(-0.018,-0.013)	(0.077,0.095)	(0.006,0.015)	(0.007,0.014)	(-0.009,-0.006)
Asian	-0.011***	0.020*	0.002	0.007	-0.001
Comorbidities	(-0.016,-0.007)	(0.002,0.039)	(-0.007,0.010)	(-0.000,0.014)	(-0.004,0.002)
No diabetes	ref.	ref.	ref.	ref.	ref.
Diabetes without CC	0.011***	0.012**	0.005**	0.004**	0.005***
	(0.009,0.013)	(0.004,0.019)	(0.001,0.009)	(0.001,0.007)	(0.004,0.006)
Diabetes with CC	0.029***	0.008**	-0.002	0.002	0.008***
	(0.027,0.031)	(0.002,0.014)	(-0.005,0.001)	(-0.000,0.004)	(0.006,0.009)
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.023***	-0.012**	-0.003	-0.003*	-0.001
	(0.020,0.026)	(-0.018,-0.005)	(-0.006,0.000)	(-0.005,-0.000)	(-0.003,0.001)
Coronary artery disease	0.020***	0.028***	0.001	-0.002	0.007***
	(0.018,0.022)	(0.022,0.033)	(-0.001,0.004)	(-0.004,0.000)	(0.006,0.009)
Congestive heart failure	0.093***	0.077***	0.018***	0.002*	0.036***
	(0.090,0.095)	(0.072,0.083)	(0.015,0.020)	(0.000,0.004)	(0.034,0.037)
Chronic pulmonary diseases	0.061***	-0.010***	0.015***	-0.007***	-0.002***
	(0.059,0.063)	(-0.015,-0.005)	(0.013,0.018)	(-0.009,-0.006)	(-0.003,-0.001)
Renal failure	0.019***	0.012***	-0.001	0.001	0.023***
	(0.017,0.022)	(0.005,0.018)	(-0.004,0.003)	(-0.001,0.004)	(0.021,0.025)
Liver failure	0.046***	0.035***	-0.003	0	0.059***
	(0.042,0.051)	(0.025,0.045)	(-0.008,0.002)	(-0.004,0.004)	(0.056,0.063)
Metastatic cancer	0.122***	0.01	0.003	-0.010***	0.136***
	(0.115,0.130)	(-0.003,0.024)	(-0.004,0.009)	(-0.014,-0.006)	(0.130,0.142)
Lymphoma	0.064***	-0.008	-0.001	-0.010***	0.027***
	(0.056,0.073)	(-0.025,0.009)	(-0.009,0.007)	(-0.015,-0.004)	(0.021,0.033)
Non-metastatic solid tumor	0.036***	0.018***	0	-0.003*	0.028***
	(0.033,0.040)	(0.009,0.027)	(-0.004,0.005)	(-0.006,-0.000)	(0.026,0.030)
Peripheral vascular disorders	-0.008***	0.017***	0.004**	0.001	0.018***
	(-0.011,-0.006)	(0.010,0.023)	(0.001,0.008)	(-0.001,0.003)	(0.017,0.020)
Cardiac arrhythmias	0.062***	0.062***	0.005***	-0.002*	0.024***

	Primary analysis				
	(1)	(2)	(3)	(4)	(5)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
	(0.060,0.064)	(0.057,0.067)	(0.002,0.007)	(-0.004,-0.000)	(0.023,0.025)
Rheumatoid arthritis/collagen vascular diseases	0.016***	-0.005	-0.007**	0	0.004***
	(0.013,0.020)	(-0.016,0.005)	(-0.012,-0.002)	(-0.004,0.004)	(0.002,0.006)
Coagulopathy	0.029***	0.032***	-0.004	0.002	0.035***
	(0.024,0.033)	(0.023,0.041)	(-0.008,0.000)	(-0.001,0.005)	(0.032,0.038)
Obesity	-0.002	0.013***	0.004	0.009***	-0.009***
	(-0.005,0.000)	(0.006,0.021)	(-0.000,0.007)	(0.006,0.012)	(-0.010,-0.007)
Chronic/acute deep vein thrombosis or pulmonary embolism	0.061***	0.050***	0.003	0.002	0.030***
	(0.056,0.067)	(0.039,0.061)	(-0.003,0.009)	(-0.003,0.006)	(0.026,0.034)
Hemorrhagic or ischemic stroke	0.016***	0.032***	0.002	-0.004**	0.043***
	(0.013,0.020)	(0.024,0.040)	(-0.001,0.006)	(-0.007,-0.001)	(0.040,0.045)
Valvular disease	-0.009***	0.045***	0.007***	-0.002	0.017***
	(-0.012,-0.006)	(0.038,0.052)	(0.003,0.010)	(-0.004,0.001)	(0.015,0.019)
Constant	0.058***	0.310***	0.020***	0.034***	0.012***
	(0.053,0.063)	(0.291,0.330)	(0.011,0.029)	(0.027,0.041)	(0.009,0.015)
N	1059474	167330	167330	167330	1057707
N_clust	728455	147846	147846	147846	727311
p	<0.001	<0.001	<0.001	<0.001	<0.001
R-squared	0.081	0.037	0.006	0.008	0.076

	Sensitivity analysis: ACEi/ARB monotherapy				
	(6)	(7)	(8)	(9)	(10)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001	0.008	0.013***	-0.007***	0
	(-0.004,0.002)	(-0.002,0.018)	(0.008,0.017)	(-0.010,-0.004)	(-0.002,0.002)
2019-2020 flu season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015,0.021)	(0.026,0.044)	(0.008,0.017)	(0.009,0.016)	(0.014,0.017)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.020***	-0.004	-0.007**	-0.002	-0.010***
	(-0.023,-0.017)	(-0.014,0.006)	(-0.011,-0.002)	(-0.006,0.001)	(-0.012,-0.009)
ACEi or ARB monotherapy	-0.016***	-0.039***	-0.007	-0.009**	-0.004***
	(-0.020,-0.012)	(-0.057,-0.020)	(-0.015,0.001)	(-0.015,-0.003)	(-0.006,-0.002)
2018-2019 season: ACEi or ARB +- other	0.004*	0.004	0.004	-0.001	-0.001
	(0.000,0.008)	(-0.009,0.018)	(-0.003,0.010)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy	0.005	0.040**	0.002	0.002	0.001
	(-0.001,0.010)	(0.015,0.065)	(-0.009,0.013)	(-0.006,0.009)	(-0.002,0.004)
2019-2020 season: ACEi or ARB +/- other	0.015***	0.011	0.007*	0.008***	-0.001
	(0.011,0.019)	(-0.001,0.024)	(0.002,0.013)	(0.003,0.013)	(-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy	0.017***	0.035**	0.004	0.012**	-0.003*
	(0.012,0.022)	(0.013,0.057)	(-0.006,0.013)	(0.004,0.020)	(-0.006,-0.000)
Demographics					
Female	-0.016***	-0.023***	0	-0.004***	-0.011***
	(-0.017,-0.014)	(-0.028,-0.018)	(-0.002,0.003)	(-0.006,-0.002)	(-0.012,-0.010)
Age categories					
<35	-0.006*	-0.029	0.02	-0.01	-0.001
	(-0.012,-0.000)	(-0.078,0.020)	(-0.005,0.045)	(-0.028,0.008)	(-0.003,0.001)
35-44	-0.008***	-0.028	0.006	-0.004	0.001
	(-0.012,-0.005)	(-0.056,0.000)	(-0.008,0.019)	(-0.016,0.008)	(-0.001,0.002)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.010***	0.005	0.001	0.001	0.001*
	(0.008,0.013)	(-0.009,0.020)	(-0.005,0.008)	(-0.005,0.007)	(0.000,0.002)
65-74	0.011***	-0.003	0.001	-0.001	0.009***
	(0.008,0.014)	(-0.017,0.011)	(-0.006,0.008)	(-0.007,0.004)	(0.007,0.010)
75-84	0.029***	-0.026***	-0.002	-0.005	0.024***
	(0.026,0.032)	(-0.041,-0.012)	(-0.009,0.004)	(-0.011,0.001)	(0.023,0.026)
85+	0.045***	-0.072***	-0.010**	-0.014***	0.063***
Insurance coverage type	(0.041,0.049)	(-0.087,-0.057)	(-0.017,-0.003)	(-0.020,-0.008)	(0.061,0.065)
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.032***	0.01	0.001	0.003	-0.001**
Census region	(-0.035,-0.030)	(-0.001,0.021)	(-0.004,0.006)	(-0.002,0.007)	(-0.002,-0.000)
Unknown/other	-0.045**	0.196*	-0.011	0.009	-0.023*
	(-0.075,-0.016)	(0.016,0.375)	(-0.086,0.064)	(-0.068,0.087)	(-0.044,-0.002)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	-0.008***	0.017*	0.021***	0.021***	-0.005**
	(-0.012,-0.003)	(0.003,0.031)	(0.015,0.028)	(0.016,0.026)	(-0.008,-0.002)
South Atlantic	-0.001	0.122***	0.016***	0.003	-0.016***
	(-0.005,0.003)	(0.110,0.134)	(0.011,0.021)	(-0.002,0.007)	(-0.018,-0.013)

Sensitivity analysis: ACEi/ARB monotherapy

	(6)	(7)	(8)	(9)	(10)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.018***	0.073***	0.003	0	-0.009***
	(0.013,0.022)	(0.060,0.086)	(-0.002,0.009)	(-0.004,0.004)	(-0.012,-0.007)
E South Central	0.011***	0.070***	0.018***	-0.001	-0.008***
	(0.007,0.016)	(0.056,0.085)	(0.011,0.024)	(-0.006,0.004)	(-0.011,-0.006)
W North Central	0.027***	0.093***	0.004	0.006*	-0.007***
	(0.022,0.032)	(0.079,0.107)	(-0.002,0.010)	(0.001,0.011)	(-0.010,-0.004)
W South Central	0.014***	0.111***	0.017***	0.003	-0.011***
	(0.010,0.018)	(0.097,0.124)	(0.011,0.023)	(-0.002,0.007)	(-0.014,-0.009)
Mountain	-0.033***	0.122***	-0.007	0.008*	-0.019***
	(-0.037,-0.028)	(0.103,0.141)	(-0.015,0.000)	(0.001,0.016)	(-0.022,-0.016)
Pacific	-0.002	0.170***	0.008	0.001	-0.016***
Race/ethnicity	(-0.007,0.004)	(0.151,0.189)	(-0.000,0.017)	(-0.006,0.007)	(-0.019,-0.013)
Unknown/other	-0.007***	0.020***	0.004*	0.009***	-0.002**
	(-0.010,-0.005)	(0.013,0.028)	(0.001,0.008)	(0.006,0.012)	(-0.003,-0.001)
White	ref.	ref.	ref.	ref.	ref.
Black	0.011***	-0.010**	0.005**	0.008***	0.004***
	(0.009,0.013)	(-0.017,-0.003)	(0.002,0.008)	(0.006,0.011)	(0.003,0.005)
Hispanic	-0.016***	0.086***	0.011***	0.010***	-0.008***
	(-0.018,-0.013)	(0.077,0.095)	(0.006,0.015)	(0.007,0.014)	(-0.009,-0.006)
Asian	-0.012***	0.020*	0.002	0.007	-0.001
Comorbidities	(-0.016,-0.007)	(0.002,0.039)	(-0.007,0.010)	(-0.000,0.014)	(-0.004,0.001)
No diabetes	ref.	ref.	ref.	ref.	ref.
Diabetes without CC	0.011***	0.012**	0.005**	0.004**	0.005***
	(0.009,0.013)	(0.004,0.019)	(0.001,0.009)	(0.001,0.007)	(0.004,0.006)
Diabetes with CC	0.029***	0.008**	-0.002	0.002	0.008***
	(0.027,0.031)	(0.002,0.014)	(-0.005,0.001)	(-0.000,0.004)	(0.006,0.009)
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.023***	-0.012**	-0.003	-0.003*	-0.001
	(0.020,0.026)	(-0.019,-0.005)	(-0.006,0.000)	(-0.005,-0.000)	(-0.003,0.001)
Coronary artery disease	0.020***	0.027***	0.001	-0.002	0.008***
	(0.018,0.022)	(0.022,0.033)	(-0.001,0.004)	(-0.004,0.000)	(0.006,0.009)
Congestive heart failure	0.093***	0.077***	0.017***	0.002	0.036***
	(0.091,0.096)	(0.071,0.082)	(0.015,0.020)	(-0.000,0.004)	(0.035,0.038)
Chronic pulmonary diseases	0.061***	-0.010***	0.015***	-0.007***	-0.002***
	(0.059,0.063)	(-0.015,-0.005)	(0.013,0.018)	(-0.009,-0.006)	(-0.003,-0.001)
Renal failure	0.019***	0.012***	-0.001	0.001	0.023***
	(0.017,0.022)	(0.005,0.018)	(-0.004,0.003)	(-0.001,0.003)	(0.021,0.025)
Liver failure	0.046***	0.035***	-0.003	0	0.059***
	(0.042,0.051)	(0.025,0.045)	(-0.008,0.002)	(-0.004,0.004)	(0.056,0.063)
Metastatic cancer	0.122***	0.01	0.003	-0.010***	0.136***
	(0.115,0.130)	(-0.003,0.024)	(-0.004,0.009)	(-0.014,-0.006)	(0.130,0.142)
Lymphoma	0.064***	-0.008	-0.001	-0.010***	0.027***
	(0.056,0.073)	(-0.025,0.009)	(-0.009,0.007)	(-0.015,-0.004)	(0.021,0.033)
Non-metastatic solid tumor	0.036***	0.018***	0	-0.003*	0.028***
	(0.033,0.040)	(0.009,0.027)	(-0.004,0.005)	(-0.006,-0.000)	(0.026,0.030)
Peripheral vascular disorders	-0.008***	0.017***	0.004**	0.001	0.018***
	(-0.011,-0.006)	(0.010,0.023)	(0.001,0.008)	(-0.001,0.003)	(0.017,0.020)
Cardiac arrhythmias	0.062***	0.062***	0.005***	-0.002*	0.024***

Sensitivity analysis: ACEi/ARB monotherapy

	(6)	(7)	(8)	(9)	(10)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
	(95% confidence interval)	(95% confidence interval)	(95% confidence interval)	(95% confidence interval)	(95% confidence interval)
	(0.060,0.064)	(0.057,0.067)	(0.002,0.007)	(-0.004,-0.000)	(0.023,0.026)
Rheumatoid arthritis/collagen vascular diseases	0.016***	-0.005	-0.007**	0	0.004***
	(0.013,0.020)	(-0.016,0.006)	(-0.012,-0.002)	(-0.004,0.004)	(0.002,0.006)
Coagulopathy	0.029***	0.032***	-0.004	0.002	0.035***
	(0.024,0.033)	(0.023,0.041)	(-0.008,0.000)	(-0.001,0.005)	(0.032,0.038)
Obesity	-0.002	0.013***	0.004	0.009***	-0.008***
	(-0.004,0.000)	(0.006,0.021)	(-0.000,0.007)	(0.006,0.012)	(-0.010,-0.007)
Chronic/acute deep vein thrombosis or pulmonary embolism	0.061***	0.050***	0.003	0.002	0.030***
	(0.055,0.067)	(0.039,0.061)	(-0.003,0.009)	(-0.002,0.006)	(0.026,0.034)
Hemorrhagic or ischemic stroke	0.016***	0.032***	0.002	-0.004**	0.043***
	(0.013,0.019)	(0.024,0.040)	(-0.001,0.006)	(-0.007,-0.001)	(0.040,0.045)
Valvular disease	-0.009***	0.045***	0.007***	-0.002	0.017***
	(-0.012,-0.006)	(0.038,0.052)	(0.003,0.010)	(-0.004,0.001)	(0.015,0.019)
Constant	0.058***	0.312***	0.020***	0.034***	0.012***
	(0.053,0.063)	(0.292,0.332)	(0.011,0.029)	(0.027,0.042)	(0.009,0.015)
N	1059474	167330	167330	167330	1057707
N_clust	728455	147846	147846	147846	727311
p	<0.001	<0.001	<0.001	<0.001	<0.001
R-squared	0.081	0.037	0.006	0.008	0.076

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0.002	0.02	0.030**	0.006	0
	(-0.001,0.006)	(-0.032,0.072)	(0.009,0.051)	(-0.005,0.017)	(-0.002,0.002)
2019-2020 flu season	0.032***	0.068**	0.029***	0.052***	0.007***
	(0.028,0.035)	(0.024,0.111)	(0.014,0.045)	(0.039,0.065)	(0.005,0.009)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.006***	-0.001	0.009	0.003	-0.003***
	(-0.009,-0.003)	(-0.049,0.046)	(-0.008,0.026)	(-0.007,0.013)	(-0.004,-0.001)
ACEi or ARB monotherapy					
2018-2019 season: ACEi or ARB +- other	-0.003	0.004	-0.013	0.001	0.001
	(-0.007,0.001)	(-0.062,0.071)	(-0.041,0.014)	(-0.015,0.017)	(-0.001,0.003)
2018-2019 season: ACEi or ARB monotherapy					
2019-2020 season: ACEi or ARB +/- other	-0.001	0.05	-0.022*	-0.001	-0.001
	(-0.006,0.003)	(-0.006,0.106)	(-0.043,-0.001)	(-0.019,0.016)	(-0.003,0.001)
2019-2020 season: ACEi or ARB monotherapy					
Demographics					
Female	-0.010***	-0.025*	-0.01	-0.008	-0.003***
	(-0.012,-0.008)	(-0.048,-0.003)	(-0.019,0.000)	(-0.018,0.002)	(-0.004,-0.002)
Age categories					
<35	-0.013***	-0.125	0.089	-0.017	-0.001**
	(-0.017,-0.010)	(-0.286,0.037)	(-0.025,0.202)	(-0.074,0.040)	(-0.002,-0.000)
35-44	-0.007***	-0.151***	0.014	-0.022	-0.001
	(-0.009,-0.004)	(-0.229,-0.074)	(-0.026,0.055)	(-0.053,0.009)	(-0.001,0.000)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.003**	-0.041	-0.004	0.006	0.001***
	(0.001,0.006)	(-0.091,0.009)	(-0.027,0.018)	(-0.018,0.029)	(0.001,0.002)
65-74	0.006***	-0.056*	-0.017	0.009	0.001*
	(0.003,0.009)	(-0.109,-0.003)	(-0.041,0.008)	(-0.015,0.032)	(0.000,0.002)
75-84	0.028***	-0.077**	-0.011	0.005	0.008***
	(0.024,0.032)	(-0.132,-0.022)	(-0.037,0.014)	(-0.019,0.029)	(0.007,0.010)
85+	0.074***	-0.139***	-0.022	-0.007	0.036***
Insurance coverage type	(0.068,0.079)	(-0.196,-0.083)	(-0.048,0.004)	(-0.032,0.017)	(0.032,0.039)
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.013***	-0.043*	-0.01	0.006	-0.004***
Census region	(-0.015,-0.010)	(-0.083,-0.002)	(-0.028,0.009)	(-0.011,0.024)	(-0.005,-0.003)
Unknown/other	-0.034***	0.755***	-0.025*	-0.062***	0.008
	(-0.053,-0.014)	(0.693,0.816)	(-0.050,-0.000)	(-0.089,-0.035)	(-0.018,0.034)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	-0.002	0.065*	0.015	0.025	0.002
	(-0.007,0.004)	(0.008,0.123)	(-0.008,0.038)	(-0.003,0.053)	(-0.001,0.005)
South Atlantic	-0.004	0.164***	0.012	-0.009	-0.001
	(-0.009,0.001)	(0.113,0.214)	(-0.007,0.032)	(-0.032,0.014)	(-0.004,0.001)

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.007**	0.111***	0.018	0	0
	(0.002,0.013)	(0.058,0.165)	(-0.003,0.039)	(-0.024,0.024)	(-0.003,0.002)
E South Central	0.001	0.116***	0.01	-0.004	-0.001
	(-0.005,0.007)	(0.055,0.176)	(-0.014,0.034)	(-0.030,0.023)	(-0.003,0.002)
W North Central	0.009**	0.124***	0.021	-0.002	0.002
	(0.003,0.015)	(0.063,0.184)	(-0.004,0.046)	(-0.028,0.025)	(-0.001,0.004)
W South Central	0.001	0.142***	0.025*	0.007	0
	(-0.004,0.007)	(0.086,0.199)	(0.002,0.049)	(-0.019,0.034)	(-0.002,0.003)
Mountain	-0.005	0.161***	-0.005	0.019	-0.002
	(-0.011,0.001)	(0.087,0.235)	(-0.031,0.020)	(-0.017,0.055)	(-0.005,0.001)
Pacific	0	0.173***	-0.004	-0.008	-0.003
Race/ethnicity	(-0.007,0.006)	(0.093,0.253)	(-0.032,0.024)	(-0.041,0.025)	(-0.005,0.000)
Unknown/other	0.001	0.056**	0.002	0.009	0
	(-0.002,0.004)	(0.022,0.089)	(-0.012,0.016)	(-0.006,0.023)	(-0.001,0.001)
White	ref.	ref.	ref.	ref.	ref.
Black	0.008***	0	0.003	0.01	0.001
	(0.006,0.011)	(-0.031,0.032)	(-0.010,0.016)	(-0.003,0.023)	(-0.000,0.002)
Hispanic	-0.001	0.092***	0.016	0.035***	-0.001*
	(-0.004,0.001)	(0.054,0.130)	(-0.001,0.034)	(0.015,0.055)	(-0.003,-0.000)
Asian	-0.007**	0.029	-0.018	0.018	-0.002
Comorbidities	(-0.011,-0.002)	(-0.045,0.103)	(-0.042,0.007)	(-0.018,0.055)	(-0.004,0.000)
No diabetes					
Diabetes without CC					
Diabetes with CC					
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.014***	-0.009	-0.009	-0.017	0.006**
	(0.007,0.021)	(-0.068,0.050)	(-0.032,0.013)	(-0.036,0.003)	(0.002,0.010)
Coronary artery disease					
Congestive heart failure					
Chronic pulmonary diseases					
Renal failure					
Liver failure					
Metastatic cancer					
Lymphoma					
Non-metastatic solid tumor					
Peripheral vascular disorders					
Cardiac arrhythmias					

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Rheumatoid arthritis/collagen vascular diseases					
Coagulopathy					
Obesity					
Chronic/acute deep vein thrombosis or pulmonary embolism					
Hemorrhagic or ischemic stroke					
Valvular disease					
Constant	0.027***	0.268***	0.027	0.006	0.006***
	(0.020,0.033)	(0.190,0.347)	(-0.003,0.058)	(-0.026,0.038)	(0.003,0.009)
N	200778	7696	7696	7696	200508
N_clust	175494	7647	7647	7647	175251
p	<0.001				<0.001
R-squared	0.022	0.033	0.007	0.023	0.015

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
Flu season / medication type					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0	0.009	0.017***	-0.007***	0
	(-0.004,0.003)	(-0.002,0.019)	(0.012,0.022)	(-0.010,-0.003)	(-0.002,0.002)
2019-2020 flu season	0.003*	0.030***	0.017***	0.010***	0.017***
	(0.000,0.007)	(0.020,0.041)	(0.011,0.022)	(0.006,0.014)	(0.015,0.020)
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.016***	-0.01	-0.007**	-0.003	-0.009***
	(-0.019,-0.013)	(-0.021,0.000)	(-0.011,-0.002)	(-0.006,0.001)	(-0.010,-0.007)
ACEi or ARB monotherapy					
2018-2019 season: ACEi or ARB +- other	0.002	0.01	0.001	0	0
	(-0.002,0.006)	(-0.004,0.025)	(-0.006,0.008)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy					
2019-2020 season: ACEi or ARB +/- other	0.008***	0.012	0.008*	0.008**	-0.005***
	(0.004,0.012)	(-0.003,0.026)	(0.001,0.014)	(0.002,0.013)	(-0.008,-0.002)
2019-2020 season: ACEi or ARB monotherapy					
Demographics					
Female	-0.011***	-0.024***	0.001	-0.001	-0.009***
	(-0.012,-0.009)	(-0.030,-0.017)	(-0.002,0.004)	(-0.003,0.001)	(-0.010,-0.008)
Age categories					
<35	0	-0.051	0.012	-0.014	-0.001
	(-0.006,0.006)	(-0.111,0.009)	(-0.020,0.044)	(-0.035,0.006)	(-0.003,0.001)
35-44	-0.005**	-0.027	0.005	-0.008	0.001
	(-0.009,-0.002)	(-0.063,0.009)	(-0.013,0.023)	(-0.022,0.006)	(-0.000,0.002)
45-54	ref.	ref.	ref.	ref.	ref.
55-64	0.009***	0.005	0	-0.002	0
	(0.006,0.012)	(-0.014,0.023)	(-0.009,0.009)	(-0.009,0.005)	(-0.001,0.001)
65-74	0.009***	-0.009	-0.002	-0.003	0.006***
	(0.006,0.012)	(-0.027,0.009)	(-0.011,0.007)	(-0.010,0.004)	(0.005,0.008)
75-84	0.027***	-0.033***	-0.005	-0.007	0.022***
	(0.023,0.030)	(-0.051,-0.015)	(-0.013,0.004)	(-0.014,0.000)	(0.020,0.023)
85+	0.049***	-0.078***	-0.012*	-0.015***	0.062***
Insurance coverage type	(0.045,0.053)	(-0.097,-0.059)	(-0.021,-0.003)	(-0.022,-0.008)	(0.060,0.065)
Medicare Advantage	ref.	ref.	ref.	ref.	ref.
Commercial	-0.028***	0.006	0.002	0.004	0.001
Census region	(-0.030,-0.025)	(-0.007,0.019)	(-0.005,0.008)	(-0.001,0.009)	(-0.000,0.002)
Unknown/other	-0.035	0.219*	-0.003	0.016	-0.024*
	(-0.071,0.000)	(0.012,0.426)	(-0.099,0.094)	(-0.085,0.117)	(-0.048,-0.000)
New England	ref.	ref.	ref.	ref.	ref.
Mid Atlantic	0	0.018*	0.021***	0.022***	0.002
	(-0.005,0.005)	(0.002,0.035)	(0.014,0.029)	(0.015,0.028)	(-0.001,0.006)
South Atlantic	-0.012***	0.121***	0.014***	-0.004	-0.019***
	(-0.017,-0.008)	(0.107,0.135)	(0.007,0.020)	(-0.009,0.001)	(-0.022,-0.016)

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
E North Central	0.008***	0.073***	0.004	-0.008**	-0.012***
	(0.003,0.013)	(0.058,0.089)	(-0.003,0.011)	(-0.013,-0.002)	(-0.015,-0.009)
E South Central	-0.006*	0.069***	0.015***	-0.010**	-0.014***
	(-0.011,-0.001)	(0.051,0.087)	(0.007,0.023)	(-0.016,-0.004)	(-0.017,-0.010)
W North Central	0.013***	0.091***	0.003	-0.004	-0.012***
	(0.008,0.018)	(0.074,0.109)	(-0.005,0.011)	(-0.010,0.002)	(-0.015,-0.009)
W South Central	-0.002	0.100***	0.016***	-0.008**	-0.017***
	(-0.007,0.002)	(0.083,0.116)	(0.008,0.024)	(-0.014,-0.003)	(-0.020,-0.014)
Mountain	-0.040***	0.115***	-0.009	-0.006	-0.020***
	(-0.046,-0.035)	(0.091,0.138)	(-0.019,0.001)	(-0.014,0.002)	(-0.024,-0.017)
Pacific	-0.008*	0.180***	0.005	-0.006	-0.017***
Race/ethnicity	(-0.014,-0.001)	(0.158,0.203)	(-0.006,0.015)	(-0.014,0.002)	(-0.021,-0.013)
Unknown/other	-0.007***	0.013*	0.003	0.005**	0
	(-0.010,-0.005)	(0.003,0.023)	(-0.002,0.009)	(0.001,0.009)	(-0.001,0.002)
White	ref.	ref.	ref.	ref.	ref.
Black	0.011***	-0.012**	0.005*	0.010***	0.004***
	(0.009,0.014)	(-0.021,-0.004)	(0.000,0.009)	(0.007,0.014)	(0.002,0.005)
Hispanic	-0.015***	0.079***	0.010***	0.007**	-0.008***
	(-0.018,-0.013)	(0.068,0.090)	(0.004,0.015)	(0.003,0.011)	(-0.010,-0.007)
Asian	-0.011***	0.005	0.002	0.006	-0.002
Comorbidities	(-0.016,-0.005)	(-0.017,0.027)	(-0.009,0.012)	(-0.002,0.015)	(-0.005,0.001)
No diabetes	ref.	ref.	ref.	ref.	ref.
Diabetes without CC	0.006***	0.012*	0.004	0.003	0.004***
	(0.004,0.009)	(0.003,0.022)	(-0.000,0.009)	(-0.001,0.006)	(0.003,0.005)
Diabetes with CC	0.026***	0.006	-0.003	0	0.007***
	(0.024,0.028)	(-0.001,0.013)	(-0.006,0.001)	(-0.002,0.003)	(0.006,0.008)
Uncomp hypertension	ref.	ref.	ref.	ref.	ref.
Comp hypertension	0.023***	-0.009*	-0.004	0	-0.001
	(0.020,0.026)	(-0.018,-0.000)	(-0.008,0.000)	(-0.003,0.003)	(-0.003,0.001)
Coronary artery disease	0.018***	0.031***	0	-0.001	0.006***
	(0.016,0.020)	(0.025,0.038)	(-0.003,0.004)	(-0.003,0.001)	(0.004,0.007)
Congestive heart failure	0.101***	0.078***	0.018***	0.004***	0.038***
	(0.098,0.104)	(0.072,0.085)	(0.015,0.022)	(0.002,0.007)	(0.037,0.040)
Chronic pulmonary diseases	0.074***	-0.010**	0.015***	-0.005***	0
	(0.072,0.076)	(-0.016,-0.004)	(0.012,0.018)	(-0.007,-0.002)	(-0.001,0.001)
Renal failure	0.019***	0.012**	0	0.001	0.023***
	(0.016,0.022)	(0.004,0.020)	(-0.004,0.004)	(-0.002,0.004)	(0.021,0.025)
Liver failure	0.041***	0.037***	0	0.004	0.057***
	(0.036,0.047)	(0.024,0.050)	(-0.006,0.007)	(-0.001,0.009)	(0.053,0.062)
Metastatic cancer	0.118***	0.007	0.001	-0.008**	0.138***
	(0.109,0.127)	(-0.010,0.023)	(-0.007,0.010)	(-0.013,-0.003)	(0.131,0.146)
Lymphoma	0.064***	-0.009	-0.001	-0.009**	0.023***
	(0.054,0.073)	(-0.030,0.012)	(-0.011,0.009)	(-0.015,-0.002)	(0.016,0.029)
Non-metastatic solid tumor	0.038***	0.021***	0.002	-0.004*	0.030***
	(0.034,0.042)	(0.010,0.032)	(-0.003,0.008)	(-0.007,-0.000)	(0.027,0.033)
Peripheral vascular disorders	-0.001	0.016***	0.005*	0.004**	0.023***
	(-0.004,0.002)	(0.008,0.024)	(0.001,0.009)	(0.001,0.007)	(0.021,0.025)
Cardiac arrhythmias	0.063***	0.065***	0.005**	-0.001	0.023***

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	Inpatient stay (95% confidence interval)	Inpatient stay with ICU/CCU (95% confidence interval)	Inpatient stay with ARD dx (95% confidence interval)	Inpatient stay with ARDS dx (95% confidence interval)	Died same or following month (95% confidence interval)
	(0.061,0.066)	(0.058,0.071)	(0.002,0.008)	(-0.003,0.002)	(0.021,0.025)
Rheumatoid arthritis/collagen vascular diseases	0.015***	-0.013	-0.008*	-0.001	0.002
	(0.010,0.019)	(-0.026,0.001)	(-0.014,-0.002)	(-0.005,0.004)	(-0.000,0.005)
Coagulopathy	0.035***	0.032***	-0.002	0.001	0.039***
	(0.030,0.041)	(0.021,0.043)	(-0.008,0.003)	(-0.004,0.005)	(0.035,0.043)
Obesity	-0.002	0.016***	0.004	0.008***	-0.008***
	(-0.005,0.000)	(0.007,0.026)	(-0.001,0.009)	(0.005,0.012)	(-0.010,-0.006)
Chronic/acute deep vein thrombosis or pulmonary embolism	0.053***	0.052***	0.005	0.002	0.026***
	(0.046,0.061)	(0.038,0.066)	(-0.003,0.012)	(-0.004,0.007)	(0.021,0.031)
Hemorrhagic or ischemic stroke	0.018***	0.030***	0.005	-0.003	0.044***
	(0.014,0.022)	(0.020,0.040)	(-0.000,0.010)	(-0.007,0.000)	(0.041,0.047)
Valvular disease	-0.008***	0.053***	0.008***	-0.001	0.016***
	(-0.012,-0.005)	(0.044,0.061)	(0.003,0.012)	(-0.004,0.003)	(0.014,0.019)
Constant	0.057***	0.314***	0.022***	0.037***	0.013***
	(0.051,0.063)	(0.290,0.338)	(0.010,0.033)	(0.028,0.046)	(0.010,0.017)
N	738240	106917	106917	106917	737059
N_clust	556579	97383	97383	97383	555729
p	<0.001	<0.001	<0.001	<0.001	<0.001
R-squared	0.094	0.039	0.007	0.008	0.082

	Primary analysis				
	(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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001	0.008	0.013***	-0.007***	0.000
	(-0.004,0.002)	(-0.002,0.018)	(0.008,0.017)	(-0.010,-0.004)	(-0.002,0.002)
2019-2020 flu season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015,0.021)	(0.026,0.044)	(0.008,0.017)	(0.009,0.016)	(0.014,0.017)
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,-0.016)	(-0.019,0.001)	(-0.011,-0.002)	(-0.007,0.000)	(-0.011,-0.008)
ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	0.004*	0.01	0.004	0	0
	(0.001,0.008)	(-0.004,0.023)	(-0.003,0.010)	(-0.004,0.004)	(-0.002,0.002)
2018-2019 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
2019-2020 season: ACEi or ARB +/- other	0.015***	0.015*	0.007*	0.009***	-0.002
	(0.012,0.019)	(0.003,0.027)	(0.001,0.012)	(0.004,0.013)	(-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Note: p-value for coefficients is for the null hypothesis that the coefficient = 0					
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.179	0.482	0.053	0.030	0.064
	(0.177,0.181)	(0.474,0.489)	(0.050,0.056)	(0.028,0.033)	(0.062,0.065)
2018/19	0.178	0.490	0.066	0.023	0.064
	(0.176,0.180)	(0.483,0.496)	(0.062,0.069)	(0.021,0.025)	(0.063,0.065)
2019/20	0.196	0.516	0.066	0.043	0.080
	(0.195,0.198)	(0.511,0.521)	(0.063,0.068)	(0.041,0.045)	(0.078,0.081)

	Primary analysis				
	(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
ACEi or ARB plus/minus other medications					
2017/18	0.125	0.463	0.045	0.029	0.035
	(0.124,0.127)	(0.456,0.470)	(0.042,0.048)	(0.027,0.031)	(0.034,0.035)
2018/19	0.128	0.481	0.061	0.021	0.034
	(0.127,0.130)	(0.475,0.487)	(0.058,0.064)	(0.020,0.023)	(0.034,0.035)
2019/20	0.158	0.512	0.064	0.050	0.049
	(0.157,0.160)	(0.508,0.517)	(0.062,0.066)	(0.048,0.052)	(0.048,0.049)
ACEi or ARB monotherapy					
2017/18	N/A	N/A	N/A	N/A	N/A
2018/19	N/A	N/A	N/A	N/A	N/A
2019/20	N/A	N/A	N/A	N/A	N/A
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977,1.011)	(0.996,1.038)	(1.136,1.337)	(0.668,0.850)	(0.969,1.030)
2019/20 season vs. 2017/18	1.099***	1.072***	1.238***	1.414***	1.244***
	(1.081,1.116)	(1.053,1.092)	(1.147,1.330)	(1.278,1.550)	(1.210,1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.025**	1.039***	1.360***	0.739***	0.993
	(1.009,1.042)	(1.019,1.058)	(1.251,1.469)	(0.656,0.822)	(0.961,1.025)
2019/20 season vs. 2017/18	1.264***	1.107***	1.437***	1.731***	1.404***
	(1.245,1.282)	(1.088,1.126)	(1.332,1.542)	(1.580,1.882)	(1.363,1.444)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
2019/20 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
Number of episodes	1,059,474	167,330	167,330	167,330	1,057,707
Number of people	728,455	147,846	147,846	147,846	727,311

Note: p-value for risk ratios is for the null hypothesis that the risk ratio = 1

N/A: variable not included in model
* p<0.05, ** p<0.01, *** p<0.001

	Sensitivity analysis: ACEi/ARB monotherapy				
	(6)	(7)	(8)	(9)	(10)
	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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	-0.001	0.008	0.013***	-0.007***	0
	(-0.004,0.002)	(-0.002,0.018)	(0.008,0.017)	(-0.010,-0.004)	(-0.002,0.002)
2019-2020 flu season	0.018***	0.035***	0.013***	0.013***	0.016***
	(0.015,0.021)	(0.026,0.044)	(0.008,0.017)	(0.009,0.016)	(0.014,0.017)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.020***	-0.004	-0.007**	-0.002	-0.010***
	(-0.023,-0.017)	(-0.014,0.006)	(-0.011,-0.002)	(-0.006,0.001)	(-0.012,-0.009)
ACEi or ARB monotherapy	-0.016***	-0.039***	-0.007	-0.009**	-0.004***
	(-0.020,-0.012)	(-0.057,-0.020)	(-0.015,0.001)	(-0.015,-0.003)	(-0.006,-0.002)
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	0.004*	0.004	0.004	-0.001	-0.001
	(0.000,0.008)	(-0.009,0.018)	(-0.003,0.010)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy	0.005	0.040**	0.002	0.002	0.001
	(-0.001,0.010)	(0.015,0.065)	(-0.009,0.013)	(-0.006,0.009)	(-0.002,0.004)
2019-2020 season: ACEi or ARB +/- other	0.015***	0.011	0.007*	0.008***	-0.001
	(0.011,0.019)	(-0.001,0.024)	(0.002,0.013)	(0.003,0.013)	(-0.004,0.001)
2019-2020 season: ACEi or ARB monotherapy	0.017***	0.035**	0.004	0.012**	-0.003*
Note: p-value for coefficients is for the null hypotl	(0.012,0.022)	(0.013,0.057)	(-0.006,0.013)	(0.004,0.020)	(-0.006,-0.000)
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.179	0.481	0.053	0.030	0.064
	(0.177,0.181)	(0.474,0.489)	(0.050,0.056)	(0.028,0.033)	(0.062,0.065)
2018/19	0.178	0.490	0.066	0.023	0.064
	(0.176,0.180)	(0.483,0.496)	(0.062,0.069)	(0.021,0.025)	(0.063,0.065)
2019/20	0.196	0.516	0.066	0.043	0.079
	(0.195,0.198)	(0.511,0.521)	(0.063,0.068)	(0.041,0.045)	(0.078,0.081)

	Sensitivity analysis: ACEi/ARB monotherapy				
	(6)	(7)	(8)	(9)	(10)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
ACEi or ARB plus/minus other medications					
2017/18	0.133	0.473	0.046	0.030	0.037
	(0.132,0.135)	(0.466,0.480)	(0.043,0.049)	(0.027,0.032)	(0.036,0.038)
2018/19	0.136	0.486	0.062	0.022	0.037
	(0.135,0.138)	(0.479,0.492)	(0.059,0.065)	(0.020,0.024)	(0.036,0.038)
2019/20	0.166	0.519	0.066	0.050	0.052
	(0.164,0.167)	(0.514,0.524)	(0.063,0.068)	(0.048,0.052)	(0.051,0.053)
ACEi or ARB monotherapy					
2017/18	0.093	0.408	0.040	0.024	0.024
	(0.090,0.096)	(0.392,0.425)	(0.033,0.047)	(0.019,0.029)	(0.022,0.025)
2018/19	0.096	0.456	0.054	0.018	0.025
	(0.094,0.099)	(0.441,0.472)	(0.047,0.061)	(0.014,0.022)	(0.023,0.026)
2019/20	0.127	0.478	0.056	0.048	0.036
	(0.125,0.130)	(0.467,0.489)	(0.051,0.061)	(0.043,0.053)	(0.034,0.037)
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.994	1.017	1.236***	0.759***	0.999
	(0.977,1.011)	(0.996,1.038)	(1.136,1.337)	(0.668,0.850)	(0.969,1.030)
2019/20 season vs. 2017/18	1.098***	1.072***	1.238***	1.414***	1.243***
	(1.081,1.116)	(1.053,1.092)	(1.147,1.330)	(1.278,1.550)	(1.209,1.278)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.023*	1.027*	1.360***	0.735***	0.985
	(1.005,1.041)	(1.006,1.048)	(1.243,1.476)	(0.647,0.824)	(0.950,1.019)
2019/20 season vs. 2017/18	1.244***	1.097***	1.441***	1.690***	1.382***
	(1.225,1.264)	(1.077,1.118)	(1.329,1.554)	(1.532,1.848)	(1.339,1.425)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	1.037	1.117***	1.358*	0.766	1.047
	(0.993,1.080)	(1.058,1.177)	(1.055,1.660)	(0.526,1.006)	(0.958,1.136)
2019/20 season vs. 2017/18	1.369***	1.170***	1.412**	2.028***	1.526***
	(1.318,1.420)	(1.115,1.226)	(1.129,1.694)	(1.537,2.519)	(1.412,1.640)
Number of episodes	1,059,474	167,330	167,330	167,330	1,057,707
Number of people	728,455	147,846	147,846	147,846	727,311

Note: p-value for risk ratios is for the null hypothe

N/A: variable not included in model
* p<0.05, ** p<0.01, *** p<0.001

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0.002	0.02	0.030**	0.006	0
	(-0.001,0.006)	(-0.032,0.072)	(0.009,0.051)	(-0.005,0.017)	(-0.002,0.002)
2019-2020 flu season	0.032***	0.068**	0.029***	0.052***	0.007***
	(0.028,0.035)	(0.024,0.111)	(0.014,0.045)	(0.039,0.065)	(0.005,0.009)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.006***	-0.001	0.009	0.003	-0.003***
	(-0.009,-0.003)	(-0.049,0.046)	(-0.008,0.026)	(-0.007,0.013)	(-0.004,-0.001)
ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	-0.003	0.004	-0.013	0.001	0.001
	(-0.007,0.001)	(-0.062,0.071)	(-0.041,0.014)	(-0.015,0.017)	(-0.001,0.003)
2018-2019 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
2019-2020 season: ACEi or ARB +/- other	-0.001	0.05	-0.022*	-0.001	-0.001
	(-0.006,0.003)	(-0.006,0.106)	(-0.043,-0.001)	(-0.019,0.016)	(-0.003,0.001)
2019-2020 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Note: p-value for coefficients is for the null hypotl					
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.031	0.312	0.023	0.009	0.007
	(0.029,0.034)	(0.275,0.350)	(0.011,0.035)	(0.002,0.016)	(0.006,0.009)
2018/19	0.033	0.332	0.053	0.015	0.007
	(0.031,0.036)	(0.296,0.368)	(0.036,0.070)	(0.006,0.024)	(0.006,0.008)
2019/20	0.063	0.380	0.053	0.061	0.014
	(0.060,0.066)	(0.357,0.403)	(0.042,0.063)	(0.050,0.073)	(0.013,0.016)

	Sensitivity analysis: Dropping people with comorbidities (other than hypertension)				
	(11)	(12)	(13)	(14)	(15)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
ACEi or ARB plus/minus other medications					
2017/18	0.023	0.319	0.033	0.016	0.004
	(0.022,0.025)	(0.289,0.349)	(0.021,0.044)	(0.008,0.023)	(0.003,0.004)
2018/19	0.022	0.343	0.049	0.023	0.004
	(0.021,0.024)	(0.313,0.373)	(0.036,0.063)	(0.014,0.032)	(0.004,0.005)
2019/20	0.054	0.436	0.040	0.067	0.010
	(0.052,0.055)	(0.418,0.454)	(0.033,0.048)	(0.058,0.076)	(0.009,0.011)
ACEi or ARB monotherapy					
2017/18	N/A	N/A	N/A	N/A	N/A
2018/19	N/A	N/A	N/A	N/A	N/A
2019/20	N/A	N/A	N/A	N/A	N/A
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	1.069	1.064	2.291	1.633	0.973
	(0.953,1.186)	(0.893,1.235)	(0.893,3.688)	(0.078,3.189)	(0.744,1.203)
2019/20 season vs. 2017/18	2.008***	1.216**	2.270*	6.718*	1.942***
	(1.823,2.193)	(1.053,1.379)	(1.013,3.526)	(1.473,11.963)	(1.561,2.323)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	0.961	1.076	1.510	1.432	1.128
	(0.875,1.047)	(0.939,1.213)	(0.842,2.177)	(0.544,2.320)	(0.879,1.377)
2019/20 season vs. 2017/18	2.291***	1.369***	1.234	4.210**	2.624***
	(2.124,2.458)	(1.228,1.509)	(0.754,1.713)	(2.113,6.308)	(2.142,3.107)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
2019/20 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
Number of episodes	200,778	7,696	7,696	7,696	200,508
Number of people	175,494	7,647	7,647	7,647	175,251

Note: p-value for risk ratios is for the null hypothe

N/A: variable not included in model
* p<0.05, ** p<0.01, *** p<0.001

	Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)				
	(16)	(17)	(18)	(19)	(20)
	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					
Season					
2017-2018 flu season	ref.	ref.	ref.	ref.	ref.
2018-2019 flu season	0	0.009	0.017***	-0.007***	0
	(-0.004,0.003)	(-0.002,0.019)	(0.012,0.022)	(-0.010,-0.003)	(-0.002,0.002)
2019-2020 flu season	0.003*	0.030***	0.017***	0.010***	0.017***
	(0.000,0.007)	(0.020,0.041)	(0.011,0.022)	(0.006,0.014)	(0.015,0.020)
HTN medication group					
Other medications only	ref.	ref.	ref.	ref.	ref.
ACEi or ARB plus/minus other medications	-0.016***	-0.01	-0.007**	-0.003	-0.009***
	(-0.019,-0.013)	(-0.021,0.000)	(-0.011,-0.002)	(-0.006,0.001)	(-0.010,-0.007)
ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Season/medication interactions					
2018-2019 season: ACEi or ARB +- other	0.002	0.01	0.001	0	0
	(-0.002,0.006)	(-0.004,0.025)	(-0.006,0.008)	(-0.005,0.004)	(-0.003,0.002)
2018-2019 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
2019-2020 season: ACEi or ARB +/- other	0.008***	0.012	0.008*	0.008**	-0.005***
	(0.004,0.012)	(-0.003,0.026)	(0.001,0.014)	(0.002,0.013)	(-0.008,-0.002)
2019-2020 season: ACEi or ARB monotherapy	N/A	N/A	N/A	N/A	N/A
Note: p-value for coefficients is for the null hypotl					
Marginal effects/predicted probability					
Other hypertension medications only					
2017/18	0.175	0.480	0.053	0.030	0.061
	(0.173,0.178)	(0.472,0.487)	(0.049,0.056)	(0.028,0.033)	(0.060,0.063)
2018/19	0.175	0.488	0.070	0.024	0.061
	(0.172,0.177)	(0.480,0.496)	(0.066,0.074)	(0.021,0.026)	(0.060,0.063)
2019/20	0.179	0.510	0.069	0.041	0.079
	(0.176,0.181)	(0.503,0.517)	(0.066,0.073)	(0.038,0.044)	(0.077,0.080)

Sensitivity analysis: limiting analysis to strict flu season (dropping summer months)

	(16)	(17)	(18)	(19)	(20)
	Inpatient stay	Inpatient stay with ICU/CCU	Inpatient stay with ARD dx	Inpatient stay with ARDS dx	Died same or following month
ACEi or ARB plus/minus other medications					
2017/18	0.122	0.459	0.044	0.028	0.033
	(0.120,0.123)	(0.452,0.466)	(0.041,0.047)	(0.026,0.031)	(0.032,0.033)
2018/19	0.124	0.478	0.063	0.021	0.032
	(0.122,0.125)	(0.470,0.485)	(0.059,0.066)	(0.019,0.023)	(0.032,0.033)
2019/20	0.133	0.501	0.069	0.046	0.045
	(0.131,0.134)	(0.494,0.508)	(0.065,0.072)	(0.044,0.049)	(0.044,0.046)
ACEi or ARB monotherapy					
2017/18	N/A	N/A	N/A	N/A	N/A
2018/19	N/A	N/A	N/A	N/A	N/A
2019/20	N/A	N/A	N/A	N/A	N/A
Risk ratios of marginal effects					
Other hypertension medications only					
2018/19 season vs. 2017/18	0.998	1.018	1.324***	0.776***	1.002
	(0.979,1.017)	(0.995,1.041)	(1.208,1.440)	(0.673,0.879)	(0.967,1.036)
2019/20 season vs. 2017/18	1.019	1.064***	1.313***	1.343***	1.282***
	(1.000,1.039)	(1.041,1.087)	(1.201,1.425)	(1.190,1.495)	(1.241,1.324)
ACEi or ARB plus/minus other medications					
2018/19 season vs. 2017/18	1.017	1.041***	1.411***	0.750***	0.997
	(0.999,1.035)	(1.019,1.063)	(1.289,1.533)	(0.655,0.846)	(0.960,1.034)
2019/20 season vs. 2017/18	1.091***	1.092***	1.542***	1.634***	1.380***
	(1.071,1.110)	(1.069,1.114)	(1.413,1.671)	(1.465,1.803)	(1.331,1.428)
ACEi or ARB monotherapy					
2018/19 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
2019/20 season vs. 2017/18	N/A	N/A	N/A	N/A	N/A
Number of episodes	738,240	106,917	106,917	106,917	737,059
Number of people	556,579	97,383	97,383	97,383	555,729

Note: p-value for risk ratios is for the null hypothe

N/A: variable not included in model
* p<0.05, ** p<0.01, *** p<0.001

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			
Objectives	3	State specific objectives, including any prespecified hypotheses			
Methods					
Study Design	4	Present key elements of study design early in the paper			
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			
Participants	6	*(a) Cohort study* - Give the		RECORD 6.1: The methods of study	

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			

Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the	

				study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or			

		summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			
Discussion					
Key results	18	Summarise key results with reference to study objectives			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			

Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.