Clinical Kidney Journal, 2024, vol. 17, no. 7, sfae164

https://doi.org/10.1093/ckj/sfae164
Advance Access Publication Date: 8 June 2024
Original Article

ORIGINAL ARTICLE

Effects of ACE inhibitor/ARB therapy and long COVID on kidney disease: a retrospective cohort study using real-world data

Yue Zhang [1], Djibril M. Ba[1], Kathryn Risher[1], Duanping Liao[1], Leslie J. Parent[1,2], Nasrollah Ghahramani [1,2] and Vernon M. Chinchilli[1]

[1]Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA and [2]Department of Medicine, Penn State College of Medicine, Hershey, PA, USA

Correspondence to: Nasrollah Ghahramani; E-mail: nghahramani@pennstatehealth.psu.edu

ABSTRACT

Background. The association between angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and severe acute respiratory syndrome coronavirus 2 susceptibility, particularly via ACE-2 receptor upregulation in the kidneys, raises concerns about potential kidney disease risks in long coronavirus disease (COVID) patients. This study explores the association of ACEI/ARB therapy on acute kidney injury (AKI), chronic kidney disease (CKD) and all-cause mortality in patients with and without long COVID.

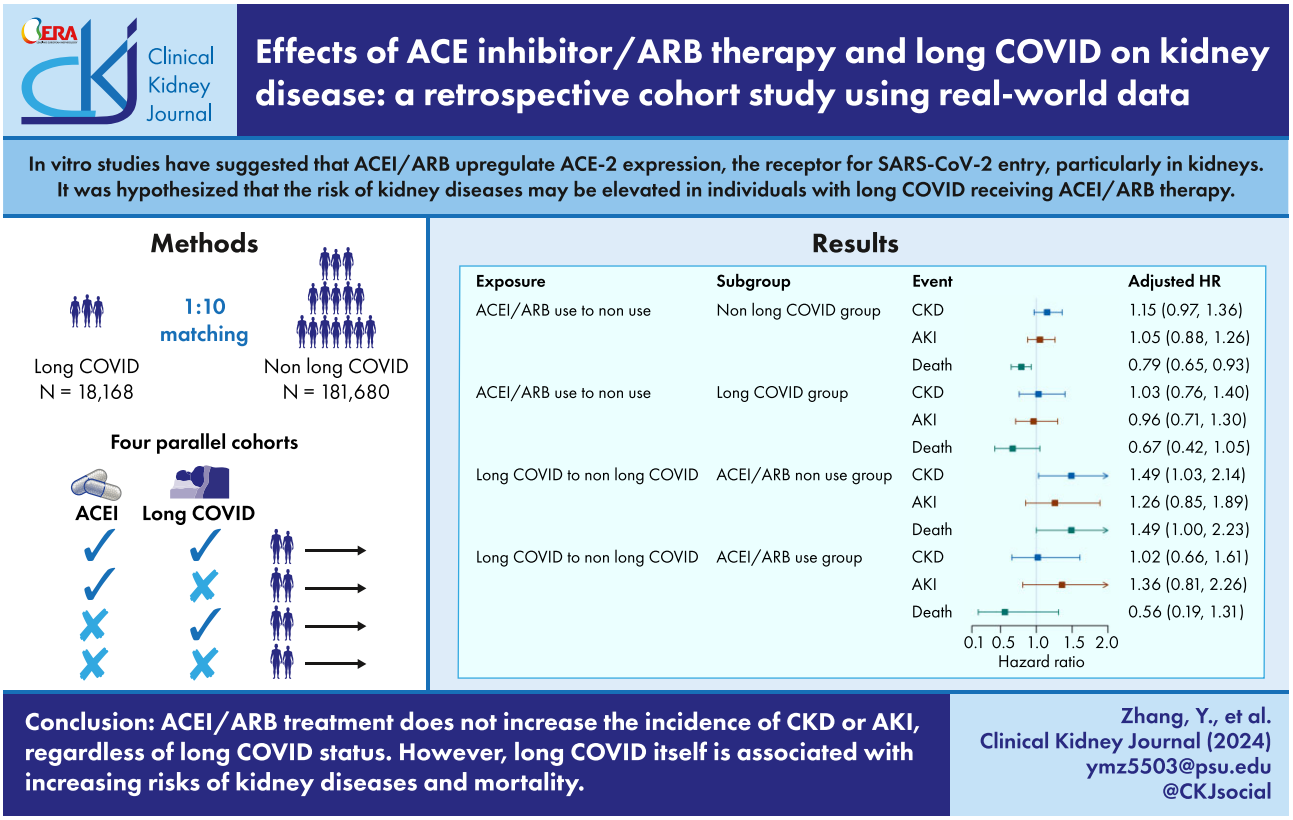
Methods. A retrospective cohort study using TriNetX datasets was conducted, with diagnoses of long COVID via *International Classification of Diseases, Tenth Revision* (ICD-10) codes and prescription for ACEI/ARB as the classification of four cohorts: long COVID ACEI/ARB users (LCAUs), long COVID ACEI/ARB non-users (LCANs), non-long COVID ACEI/ARB users (NLCAUs) and non-long COVID ACEI/ARB non-users (NLCANs). Multivariable stratified Cox proportional hazards regression models assessed the adjusted hazard ratios (aHRs) across groups. Additional analyses were conducted, including time-dependent exposure analysis and comparison with an active comparator, calcium channel blockers.

Results. Our study included 18 168 long COVID and 181 680 propensity score-matched non-long COVID patients from October 2021 to October 2023. ACEI/ARB use did not significantly affect the risk of AKI or CKD when comparing LCAUs with LCANs and NLCAUs with NLCANs. However, a protective effect against all-cause mortality was observed {aHR 0.79 [95% confidence interval (CI) 0.65–0.93]} in the NLCAU group compared with the NLCAN group. Conversely, long COVID was associated with increased risks of CKD [aHR 1.49 (95% CI 1.03–2.14)] and all-cause mortality [aHR 1.49 (95% CI 1.00–2.23)] when comparing LCANs with NLCANs. The additional analyses support the primary findings.

Conclusions. ACEI/ARB treatment does not increase the incidence of CKD or AKI, regardless of long COVID status. However, long COVID itself is associated with increasing risks of kidney diseases and all-cause mortality.

Received: 26.2.2024; Editorial decision: 30.4.2024

GRAPHICAL ABSTRACT



Keywords: acute kidney injury, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), chronic kidney disease, long COVID, real-world analysis

KEY LEARNING POINTS

What was known:

- *In vitro* studies suggest that the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) may increase the risk of severe acute respiratory syndrome coronavirus 2 entering cells, particularly in the kidney, thereby raising safety concerns regarding the use of ACEIs/ARBs.
- Controversial conclusions have been drawn from current studies regarding whether the use of ACEIs/ARBs increases the risk of kidney diseases for patients without coronavirus disease 2019 (COVID-19).
- Current studies indicate that ACEI/ARB use may be safe for COVID-19 patients in the short term, yet evidence remains insufficient from long-term follow-up, especially in cases of long COVID symptoms.

This study adds:

- Utilizing real-world data from >199 848 patients in the USA, while using propensity score matching, this study confirms that the use of ACEIs/ARBs does not increase the risk of chronic kidney disease (CKD), acute kidney injury (AKI) or all-cause mortality.
- This is the first study to demonstrate it is long COVID, not ACEI/ARB use, that increases the risk of CKD and higher mortality.
- By comparing the use of ACEIs/ARBs and calcium channel blockers, our retrospective cohort study suggests that, contrary to findings from *in vitro* studies, the mechanism of ACEIs/ARBs may not increase the risk of kidney disease in a population study.

Potential impact:

- This study provides evidence supporting the safe use of ACEIs/ARBs for both long COVID and non-long COVID patients over lengthy follow-up periods, guiding physician practice.
- It emphasizes the necessity for increased focus on long COVID patients, particularly concerning their risk of progressing to CKD.
- It illustrates the application of comprehensive methodologies through three independent study designs, offering a valuable template for addressing similar research questions in the future.

INTRODUCTION

In the current post- coronavirus disease 2019 (COVID-19) pandemic period, the post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC), colloquially referred to as 'long COVID', has become a significant and ongoing public health challenge [1, 2]. Kidney diseases have been reported as significant in PASC. Several retrospective cohort studies have observed increased risks of chronic kidney disease (CKD) and acute kidney injury (AKI) following COVID-19 infections [3–6]. However, existing research predominantly addresses kidney complications following acute COVID-19 infections and overlooks the potential risk of kidney diseases in patients exhibiting long COVID symptoms. As of 1 October 2021, the introduction of a new *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code, U09.9, in the USA for 'Post COVID-19 condition, unspecified' [7], facilitates more detailed research using real-world data to explore the risks of kidney diseases in patients presenting with post-COVID-19 conditions.

Meanwhile, as studies on the mechanism of SARS-CoV-2 continue, there is growing concern regarding the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) in patients with long COVID. SARS-CoV-2 primarily enters host cells by attaching its spike (S) protein to angiotensin-converting enzyme 2 (ACE2) [8]. ACEI/ARB medications are known to upregulate ACE2 expression, notably in the kidneys [9]. This information has led to widespread discussions about the safety of ACEI/ARB therapy for individuals with COVID-19. Also, given conflicting views on the relationship between ACEIs/ARBs and the occurrence of AKI [10, 11], determining whether ACEI/ARB use increases the risk of kidney diseases in long COVID patients is an urgent question.

In this study, our objective was to utilize national real-world clinical data to investigate whether patients with a long COVID diagnosis, who have a history of ACEI/ARB exposure, are at risk for adverse outcomes with continued use of these medications, considering the potential risk of kidney diseases. We executed three distinct study designs with the intention of thoroughly evaluating the impact of ACEI/ARB use on kidney diseases in individuals with and without long COVID.

MATERIALS AND METHODS

Data source

This analysis was conducted using a TriNetX database with data extracted from 1 October 2020 to 1 October 2023. TriNetX serves as a federated, multi-institutional health research network that compiles de-identified data derived from electronic health records (EHRs) across a broad spectrum of healthcare organizations [12].

Cohort derivation and assessment of exposure

Long COVID patients, >18 years of age, were identified from 1 October 2021 to 1 October 2023 utilizing the ICD-10-CM code U09.9. The Centers for Disease Control and Prevention (CDC) officially characterizes long COVID as a post-COVID condition manifesting in patients with a confirmed or probable history of SARS-CoV-2 infection. The corresponding ICD-10 code for this condition became effective on 1 October 2021 [13]. ACEI/ARB users were defined as patients who had any ACEI/ARB prescription history within 1 year prior to the index dates, based on the medical prescription normalized code (RxNorm) [14] and National Drug Code (NDC) (Supplementary Appendix).

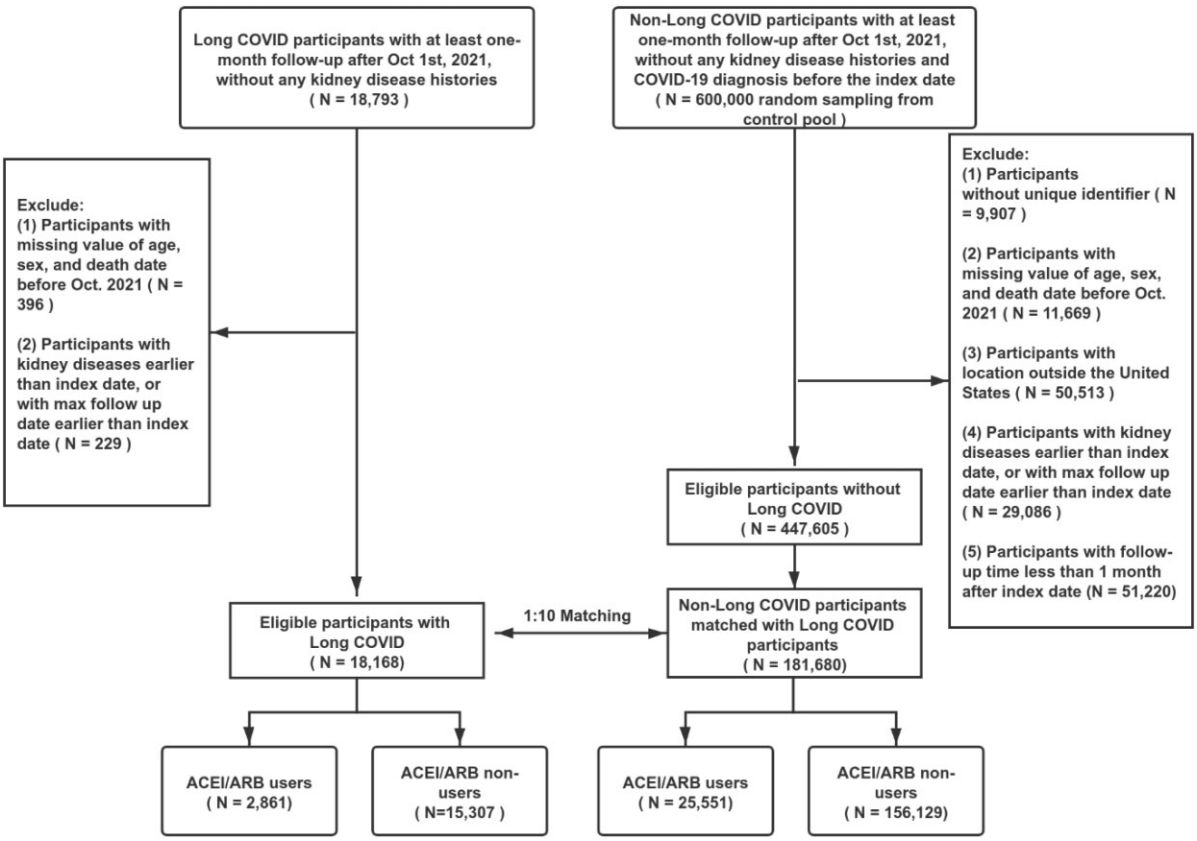


Figure 1: Participant selection flow diagram for long COVID and non-long COVID groups from the TriNetX dataset.

We identified 18 793 patients coded as having long COVID, as well as 600 000 control patients who were not diagnosed with COVID-19 infection or long COVID. Each group had at least 1 month of follow-up after 1 October 2021. The index dates of the long COVID group were defined as the earliest diagnosis dates of long COVID. For the participants without long COVID, the earliest possible index date is 1 October 2021 and the latest index date is the maximum of the recorded dates for each patient, including diagnosis records, lab test results and medication records. Pseudo index dates were randomly assigned between these potential earliest and latest index dates for each patient [15–18]. None of the patients in either group had a history of kidney disease prior to the index dates.

After all of the exclusion criteria were applied, we identified a total of 18 168 eligible patients with long COVID and 447 605 eligible patients without COVID infection or long COVID. Nearest-neighbour propensity score matching methods were further utilized at a 1:10 matching ratio using the 'without replacement' sampling method [19]. This approach led to the final selection of 18 168 patients with long COVID and a corresponding control group of 181 680 patients who were subjected to in-depth analysis (Fig. 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies [20].

Assessment of outcomes

The primary outcomes were the incidence of CKD (ICD-10 code N18) and AKI (ICD-10 code N17) identified after the index dates during the follow-up period. All-cause mortality, captured via the TriNetX platform from death registries or EHR histories, was also assessed.

Assessment of potential covariates

Demographic data on age (years), sex (male/female), race (White/Black or African American/unknown/other) and US regional location (South/West/Midwest/Northeast/unknown) were extracted directly from TriNetX patients' databases. Patients' comorbidities were assessed using the Elixhauser Comorbidity Index (ECI), within 1 year prior to the index dates through ICD-10 codes [21, 22]. The nine most prevalent and potential kidney diseases or long COVID-related conditions, including congestive heart failure (CHF) [23], hypertension [24], diabetes [25], obesity [26], cardiac arrhythmia [27], chronic pulmonary disease [28], hypothyroidism [29], solid tumour [30] and depression [31], were selected from the ECI results. Additionally, we evaluated the history of nine drugs—statins, diuretics, calcium channel blockers (CCBs), antiplatelets, anticoagulants, non-steroidal anti-inflammatory drugs, proton pump inhibitors, insulin and beta-blockers—used within the year preceding the index dates. These medications have been identified as potential risk factors for kidney disease [6, 10, 32].

Study design and statistical analysis

To achieve a thorough evaluation of the impact of ACEI/ARB use on kidney diseases in patients with or without long COVID, we

utilized three independent study designs. This approach was intended to mitigate various biases and facilitate cross-validation among the different methods. A comprehensive study design diagram is presented in Supplementary Fig. S1, illustrating the rationale behind each aspect of the study.

Primary analysis: four parallel cohorts design

We built four parallel cohorts with the status of long COVID and ACEI/ARB use histories, including long COVID ACEI/ARB users (LCAUs), long COVID non-users (LCANs), non-long COVID ACEI/ARB users (NLCAUs) and non-long COVID ACEI/ARB non-users (NLCANs), as shown in Fig. 2. Propensity score matching with a 1:10 ratio was performed with individual covariates [age, gender, race, location, cardiovascular disease (CVD), hypertension and diabetes] and two-way interactions between covariates (race, CVD, hypertension and diabetes) in a binary logistic regression model to better control for baseline demographics and comorbidities [19]. CVD was defined as the combination of one or more of CHF, cardiac arrhythmia, valvular disease, pulmonary circulation disorders and peripheral vascular disorders.

We summarized baseline patients' characteristics across long COVID and non-long COVID groups, presented as before matching and after 1:10 matching. The standardized mean difference (SMD) was used as a measure to evaluate the matching result and an SMD >0.1 was the threshold recommended for declaring imbalance [33].

We calculated the person-time of follow-up for each participant following the index date to the first occurrence of an outcome of interest (CKD, AKI and all-cause death), death date (if applicable) or the maximum follow-up date (the latest date recorded in diagnosis records, lab test results and medication records), whichever occurred first. We conducted subgroup analyses by calculating the unadjusted incidence rates and corresponding 95% confidence intervals (CIs) per 1000 person-years of follow-up for the four cohorts within each subgroup. Subsequently, after confirming no violation of the proportional hazards assumption, we implemented stratified Cox proportional hazards regression models using a matching identifier constructed from the propensity scores for the outcomes of CKD, AKI and all-cause death separately. These models accounted for four demographic variables, nine common comorbidities and histories of the use of nine drugs, delivering an adjusted hazard ratio (aHR) with a 95% CI.

A sensitivity analysis was conducted to assess the impact of ACEI/ARB use and long COVID on kidney diseases, accounting for the competing risk of all-cause mortality, using the Fine–Gray subdistribution hazard model [34]. The primary outcome measured was the time until the development of CKD or AKI as separate events. All-cause mortality was considered a competing event. Instances where neither CKD nor AKI developed, nor all-cause death occurred, were treated as censoring times.

A second sensitivity analysis was adjusted for additional covariates of estimated glomerular filtration rate (eGFR) and proteinuria. Specifically, eGFR was calculated based on creatinine values using the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [35]. If participants had multiple eGFR values within 1 year prior to the index date, the mean eGFR was calculated. The Logical Observation Identifiers Names and Codes (LOINC) were employed to extract creatinine values [36]. The history of proteinuria was identified using the ICD-10 code (R80). However, due to missing values in laboratory test results, this sensitivity analysis was conducted with a reduced sample size.

Additional analysis 1: time-dependent variable design

In the primary analysis, a potential concern was the random assignment of index dates and the possible immortal time bias introduced by the inconsistency between the ACEI/ARB use date and the diagnosed date of long COVID. To address these concerns, we incorporated time-dependent exposures for ACEI/ARB or long COVID separately to verify the results [37, 38].

We extracted the earliest recorded date for each participant from a variety of sources within the dataset, including diagnosis records, laboratory test records and medication records. For those patients whose earliest recorded date fell on or before 1 October 2021, we established 1 October 2021 as their index date. Conversely, if the earliest recorded date occurred after 1 October 2021, we assigned this earliest date as the index date for these patients.

Stratified Cox proportional hazards regression models were implemented for the outcomes of CKD, AKI and all-cause death separately. To address potential biases, we introduced time-dependent variables into our model [39]. Specifically, while investigating the effects of long COVID, time-dependent ACEI/ARB use was included as a covariate. Conversely, in analysing the impact of ACEI/ARB use, time-dependent long COVID status was incorporated as a covariate.

Additional analysis 2: active comparator cohort design

Another potential bias of this observational study design was the unmeasured confounding and selection bias. To mitigate these biases, we adopted a pharmaco-epidemiological approach known as the active comparator cohort design [40]. Instead of comparing ACEI/ARB users with non-users as in previous analyses, this method involved contrasting ACEI/ARB use with CCB use. This approach aimed to examine any potential differences in kidney disease incidence between these groups. The principal strength of this research design was the likelihood of similar baselines between the groups, as both ACEIs/ARBs and CCBs are commonly prescribed drugs for the treatment of hypertension [41, 42]. Moreover, considering that ACEIs/ARBs could potentially facilitate the entry of SARS-CoV-2 into kidney cells [8, 9], this design allowed us to investigate whether the specific mechanism of ACEIs/ARBs could be correlated with an increased risk of kidney diseases in long COVID patients.

We constructed two cohorts: one with ACEI/ARB use and no CCB use and another with exclusive CCB use and no ACEI/ARB. Patients with histories of both ACEI/ARB and CCB use were excluded. The index dates corresponded to the initiation dates of these drugs. Multivariable Cox proportional hazards regression models were applied separately for the outcomes of CKD and AKI comparing the ACEI/ARB and CCB groups. These models adjusted for four demographic factors, nine prevalent comorbidities and the history of eight types of drug use (excluding CCB compared with the primary analysis), providing an aHR with a 95% CI. Due to the sample size limitation, all-cause death was not included in this analysis.

A third sensitivity analysis was conducted that included only patients $\geq$40 years of age, based on the higher prevalence of hypertension in this age group [43].

Data were analysed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute, Cary, NC, USA) using a two-tailed α of 0.05.

Table 1: Distribution of matching variables and SMDs for participants with or without long COVID before and after matching.

	Before matching			After 1:10 matching		
Variables	No long COVID	Long COVID	SMD[a]	No long COVID	Long COVID	SMD[a]
N	447 605	18 168		181 680	18 168	
Age (years), mean (SD)	51.16 (18.0)	50.61 (14.6)	0.033	51.17 (14.7)	50.61 (14.6)	0.033
Female, *n* (%)	271 079 (60.6)	12 439 (68.5)	0.166	121 227 (66.7)	12 439 (68.5)	0.037
Race, *n* (%)			0.131			0.020
White	303 843 (67.9)	13 236 (72.9)		133 605 (73.5)	13 236 (72.9)	
Black or African American	61 237 (13.7)	1801 (9.9)		17 044 (9.4)	1801 (9.9)	
Unknown	62 253 (13.9)	2445 (13.5)		24 109 (13.3)	2445 (13.5)	
Other	20 272 (4.5)	686 (3.8)		6922 (3.8)	686 (3.8)	
Location, *n* (%)			0.235			0.027
Midwest	73 680 (16.5)	3593 (19.8)		36 416 (20.0)	3593 (19.8)	
Northeast	127 131 (28.4)	4958 (27.3)		51 405 (28.3)	4958 (27.3)	
South	188 957 (42.2)	6063 (33.4)		59 077 (32.5)	6063 (33.4)	
West	57 837 (12.9)	3554 (19.6)		34 782 (19.1)	3554 (19.6)	
CVD, *n* (%)	36 920 (8.2)	4280 (23.6)	0.428	30 801 (17.0)	4280 (23.6)	0.165
Hypertension, *n* (%)	74 156 (16.6)	4908 (27.0)	0.255	48 118 (26.5)	4908 (27.0)	0.012
Diabetes, *n* (%)	29 970 (6.7)	2075 (11.4)	0.165	18 706 (10.3)	2075 (11.4)	0.036

[a]An SMD >0.2 is a threshold recommended for declaring imbalance.

Table 2: Demographic and clinical characteristics stratified by ACEI/ARB use and long COVID status after 1:10 matching.

	No long COVID ($n = 181\,680$)		Long COVID (n = 18 168)	
Characteristics	No ACEI/ARB ($n = 156\,129$)	ACEI/ARB ($n = 25\,551$)	No ACEI/ARB ($n = 15\,307$)	ACEI/ARB ($n = 2861$)
Age (years), mean (SD)	50.6 (14.7)	60.2 (11.9)	50.0 (14.6)	59.2 (11.9)
Female, *n* (%)	107 510 (68.9)	13 717 (53.7)	10 773 (70.4)	1666 (58.2)
Race, *n* (%)				
White	114 465 (73.3)	19 140 (74.9)	11 165 (72.9)	2071 (72.4)
Black or African American	14 086 (9.0)	2958 (11.6)	1432 (9.4)	369 (12.9)
Unknown	21 331 (13.7)	2778 (10.9)	2109 (13.8)	336 (11.7)
Other	6247 (4.0)	675 (2.6)	601 (3.9)	85 (3.0)
Location, *n* (%)				
Midwest	30 710 (19.7)	5706 (22.3)	2942 (19.2)	651 (22.8)
Northeast	44 244 (28.3)	7161 (28.0)	4314 (28.2)	644 (22.5)
South	50 193 (32.1)	8884 (34.8)	4947 (32.3)	1116 (39.0)
West	30 982 (19.8)	3800 (14.9)	3104 (20.3)	450 (15.7)
CHF, *n* (%)	2902 (1.8)	2817 (11.0)	357 (2.3)	300 (10.5)
Hypertension, *n* (%)	26 657 (17.1)	21 461 (84.0)	2644 (17.3)	2264 (79.1)
Diabetes, *n* (%)	11 076 (7.1)	7630 (29.9)	1155 (7.5)	920 (32.2)
Obesity, *n* (%)	11 707 (7.5)	5838 (22.8)	2404 (15.7)	1018 (35.6)
Cardiac arrhythmia, *n* (%)	14 302 (9.2)	4983 (19.5)	2416 (15.8)	674 (23.6)
Chronic pulmonary disease, *n* (%)	9669 (6.2)	3426 (13.4)	3027 (19.8)	833 (29.1)
Hypothyroidism, *n* (%)	9384 (6.0)	2917 (11.4)	1356 (8.9)	405 (14.2)
Solid tumour, *n* (%)	6479 (4.2)	1768 (6.9)	392 (2.6)	182 (6.4)
Depression, *n* (%)	11 774 (7.5)	3495 (13.7)	2815 (18.4)	726 (25.4)

RESULTS

Primary analysis results

The present analysis incorporated 181 680 non-long COVID patients {mean age 51.17 years [standard deviation (SD) 14.7], 66.7% female, 73.5% White} and 18 168 long COVID patients [mean age 50.61 years (SD 14.6), 68.5% female, 72.9% White]. Prior to matching, imbalances in distribution were noted for patient regional location (SMD 0.235), baseline CVD status (SMD 0.428) and baseline hypertension status (SMD 0.255). After the matching process, we observed balanced distributions across all covariates, with all SMDs <0.2 (Table 1).

After the matching process, it was evident that the group using ACEIs/ARBs included older individuals and a smaller proportion of females compared with the group not taking ACEIs/ARBs. Furthermore, the ACEI/ARB users exhibited a higher prevalence of all nine comorbidities at baseline. These trends were consistent across both long COVID and non-long COVID patients. Additionally, the LCAU group presented the highest prevalence of CHF (10.5%), hypertension (79.1%), diabetes (32.2%), obesity (35.6%), cardiac arrhythmia (23.6%), chronic pulmonary disease (29.1%), hypothyroidism (14.2%) and depression (25.4%) when compared with the other three parallel cohorts (Table 2). These statistics highlight the comparatively poorer baseline health conditions of the LCAU group.

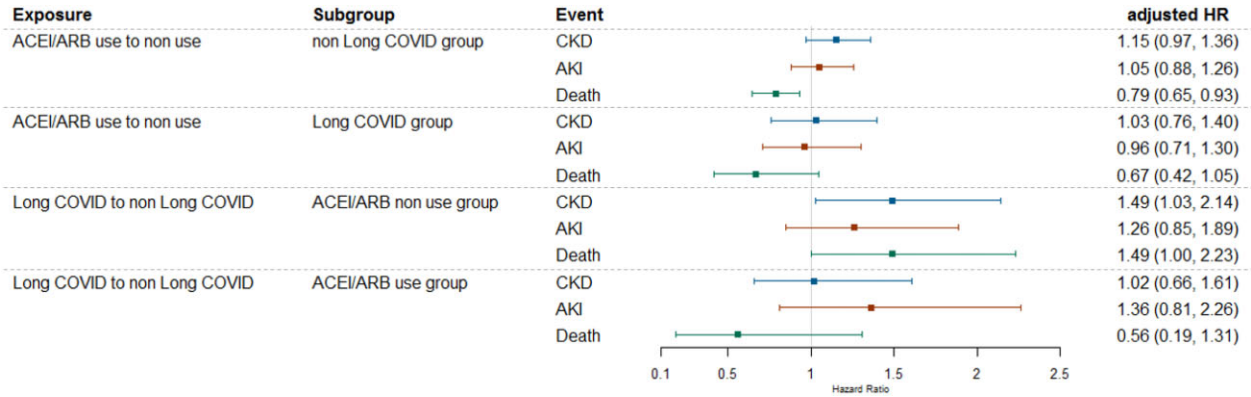


Figure 2: Effects of ACEI/ARB use and long COVID on CKD, AKI and all-cause death. All models were adjusted for four demographic variables (age, gender, race and location), nine common comorbidities at baseline (CHF, hypertension, diabetes, obesity, cardiac arrhythmia, chronic pulmonary disease, hypothyroidism, solid tumour and depression) and histories of the use of nine drugs [statins, diuretics, antiplatelets, anticoagulants, CCBs, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), insulin and beta-blockers].

In evaluating crude incidence rates per 1000 person-years, LCAUs presented incidence rates for CKD (33.2 cases/1000 person-years) and AKI (34.1 cases/1000 person-years), which were higher than the incidence rate for LCANs with CKD (14.3 cases/1000 person-years) and AKI (14.5 cases/1000 person-years) when accounting for long COVID status while comparing the impact of ACEI/ARB use. Similarly, with ACEI/ARB use and assessing long COVID's influence, LCAUs maintained a higher incidence rate than NLCAUs, evidenced by 29.3 cases of CKD and 25.9 cases of AKI per 1000 person-years (Supplementary Table S1).

Stratified Cox proportional hazards models were used to assess the influence of ACEI/ARB use within the long COVID and non-long COVID cohorts, as well as the impact of long COVID among individuals with and without ACEI/ARB use. ACEI/ARB use did not significantly influence the incidence of CKD or AKI in either the long COVID [CKD: aHR 1.03 (95% CI 0.76–1.40), AKI: aHR 0.96 (95% CI 0.71–1.30)] or non-long COVID cohorts [CKD: aHR 1.15 (95% CI 0.97–1.36), AKI: aHR 1.05 (95% CI 0.88–1.26)]. Furthermore, although ACEI/ARB use did not markedly affect all-cause mortality in the long COVID cohort [aHR 0.67 (95% CI 0.42–1.05)], it did exhibit a significant protective effect against all-cause mortality in the non-long COVID cohort [aHR 0.79 (95% CI 0.65–0.93)]. Moreover, in patients without ACEI/ARB use, long COVID had a significant effect on the incidence of CKD [aHR 1.49 (95% CI 1.03–2.14)] and all-cause mortality [aHR 1.49 (95% CI 1.00–2.23)]. However, the effect on AKI was not significant [aHR 1.26 (95% CI 0.85–1.89)]. In contrast, among individuals taking ACEIs/ARBs, these associations were not statistically significant, with aHRs of 1.02 (95% CI 0.66–1.61) for CKD, 1.36 (95% CI 0.81–2.26) for AKI and 0.56 (95% CI 0.19–1.31) for all-cause mortality (Fig. 2).

The first sensitivity analysis, accounting for the competing risk of all-cause mortality, yielded consistent results for CKD across four scenarios. However, when examining the aHR for the impact of long COVID in both the ACEI/ARB use and non-use groups, long COVID demonstrated a significantly increasing effect on the incidence of AKI. This result was observed after adjusting for the competing risk of all-cause mortality and the same covariates in the primary analysis (Supplementary Table S2).

The second sensitivity analysis included 12 732 patients with long COVID and 59 779 control patients. The results of this sensitivity analysis were consistent with those of the primary analysis (Supplementary Table S3).

Additional analysis 1 results

When treating the status of long COVID as a time-dependent variable to assess the effects of ACEI/ARB use in the entire population, we found that ACEI/ARB use did not exhibit significant effects on either CKD [aHR 1.11 (95% CI 0.95–1.29)] or AKI [aHR 0.97 (95% CI 0.83–1.14)]. However, ACEI/ARB use demonstrated a significant protective effect against all-cause mortality [aHR 0.77 (95% CI 0.65, 0.91)]. Furthermore, when considering ACEI/ARB use as a time-dependent variable, long COVID had a significant impact on CKD [aHR 1.47 (95% CI 1.03–2.10)] and AKI [aHR 1.55 (95% CI 1.04–2.31)] but no significant effect on AKI [aHR 1.32 (95% CI 0.89–1.96)], as shown in Fig. 3.

Additional analysis 2 results

Overall, ACEI/ARB users and CCB users exhibited similar demographic distributions and baseline comorbidities. Nevertheless, the ACEI/ARB group had a lower proportion of females compared with the CCB group, a higher proportion of White individuals and a lower proportion of Black individuals and an increased prevalence of diabetes (Supplementary Table S4).

We observed no significantly elevated hazards in patients on ACEIs/ARBs compared with those on CCBs in the long COVID group. The aHR for ACEI/ARB use relative to CCBs on CKD was 0.89 (95% CI 0.57–1.38) and on AKI was 1.06 (95% CI 0.63–1.79), after accounting for demographics, baseline comorbidities and other drug use histories. Comparable non-significant results were also noted in non-long COVID groups (Fig. 4).

The sensitivity analysis conducted on the subgroup ≥40 years of age demonstrated results consistent with those observed in additional analysis 2 (Supplementary Table S5).

DISCUSSION

From our study, our primary conclusion is that the use of ACEIs/ARBs does not appear to elevate the risk of CKD or AKI with long COVID patients. Second, our findings suggest that long COVID may increase the risk of CKD and potentially increase the risk of all-cause mortality. Lastly, ACEI/ARB use appears to offer a protective effect against all-cause mortality in patients without long COVID.

To the best of our knowledge, this study is the first to clearly explain the complex effects of long COVID and the use of ACEIs/ARBs on kidney diseases. Additionally, our research serves

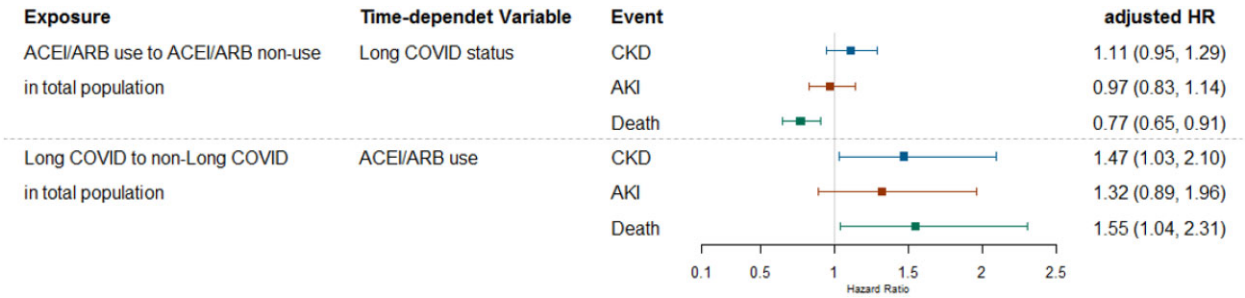


Figure 3: Effects of ACEI/ARB use and long COVID on CKD, AKI and all-cause death with time-dependent long COVID and ACEI/ARB status. All models were adjusted for four demographic variables (age, gender, race and location), nine common comorbidities at baseline (CHF, hypertension, diabetes, obesity, cardiac arrhythmia, chronic pulmonary disease, hypothyroidism, solid tumour and depression) and histories of the use of nine drugs [statins, diuretics, antiplatelets, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), CCBs, proton pump inhibitors (PPIs), insulin and beta-blockers].

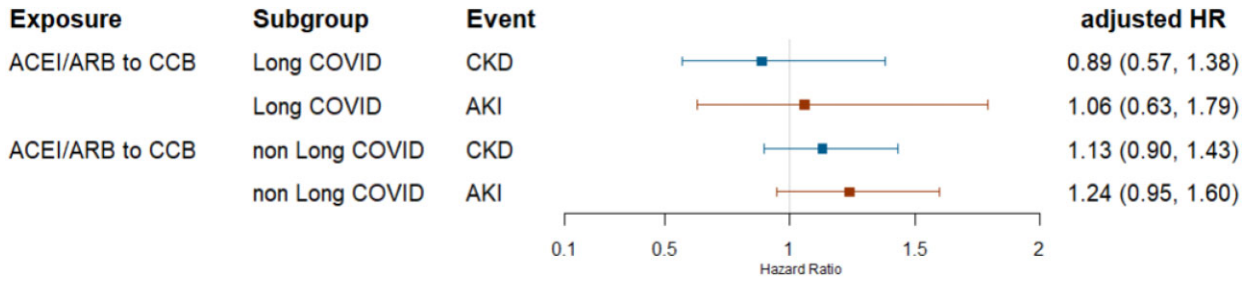


Figure 4: Comparison of ACEI/ARB use with the active comparator, CCBs, with aHRs (95% CIs) for CKD and AKI in both long COVID and non-long COVID subgroups. All models were adjusted for four demographic variables (age, gender, race and location), nine common comorbidities at baseline (CHF, hypertension, diabetes, obesity, cardiac arrhythmia, chronic pulmonary disease, hypothyroidism, solid tumour and depression) and histories of the use of eight drugs [statins, diuretics, antiplatelets, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), insulin and beta-blockers].

as an extension, providing insights into the long-term effects of COVID-19 on kidney diseases, especially accounting for the competing risk of death and time-dependent effects of ACEI/ARB use or a long COVID diagnosis. Moreover, this comparison between ACEIs/ARBs and CCBs is the first to examine the ACEI/ARB mechanism leveraging real-world data with long COVID patients.

Consistency of ACEI/ARB effects with previous studies

Our findings confirm the results of prior studies. First, our findings align with earlier research on the use of ACEIs/ARBs for kidney diseases and all-cause death. A prospective cohort study investigating the link between ACEI/ARB use and recurrent AKI post-hospitalization found that the use of ACEIs/ARBs did not heighten the risk of recurrent AKI [10]. Additionally, several retrospective cohort studies examining ACEI/ARB use following AKI also highlighted their protective effects against all-cause death [44, 45].

In the context of COVID-19 and its acute outcomes, our findings agree with the results of several key studies. A randomized clinical trial involving 659 patients (334 in the discontinuation group and 325 in the continuation group) who were hospitalized with mild–moderate COVID-19 and were on ACEIs/ARBs prior to admission showed no significant difference in the mean number of days alive and out of the hospital between the discontinuation and continuation groups [46]. Additionally, a multicentre prospective cohort study of 1129 hospitalized COVID-19 patients with hypertension revealed that inpatient use of ACEIs/ARBs was linked to a lower risk of all-cause mortality compared with non-users [47]. Although these studies are characterized by relatively short follow-up periods and primarily focus on acute outcomes after COVID-19, their results are consistent with our findings over longer periods, particularly in relation to the effects of long COVID.

Lastly, guidelines from the European [48] and American [49] Societies of Cardiology advised against routinely discontinuing ACEIs/ARBs in response to the COVID-19 pandemic. Our findings further extend this guidance by suggesting that for individuals with long COVID, the routine cessation of ACEI/ARB treatment is not indicated.

Long COVID effects on kidney diseases

Our study primarily revealed that long COVID is associated with an increased risk of CKD and all-cause mortality, but not AKI. Previous cohort studies with 1 726 683 US veterans showed increased risks of AKI, end-stage kidney disease and major adverse kidney events shortly after COVID-19 infections among 30-day survivors, with a median follow-up of ≈172 days [6]. In our study design, we specifically excluded individuals who had a prior diagnosis of AKI or CKD before the index dates, focusing solely on the incidence of new AKI or CKD cases after diagnosis of long COVID. This methodological approach likely explains why our study observed an increased risk of CKD but did not find a significant association with AKI, as we excluded those who developed AKI immediately following COVID-19 infection and only focused on effects of a long COVID diagnosis.

Competing risk effect of all-cause mortality

To assess the competing effect of all-cause mortality on CKD and AKI, we performed sensitivity analyses for both the exposure to

ACEIs/ARBs and long COVID, as outlined in our primary analysis. After adjusting for the competing risk of all-cause death, the association of ACEI/ARB use with both CKD and AKI remained non-significant. This outcome supports the validity of our results with ACEI/ARB use.

In our primary analysis, we found that long COVID increased the risk of all-cause mortality. Subsequently, we performed a sensitivity analysis, adjusting for the competing risk of all-cause death, that revealed a significantly increased risk of AKI. This finding can be seen in the strong correlation between hospitalization for AKI and mortality [50, 51]. It is plausible that all-cause mortality might preclude the development of AKI in some patients. Therefore, when evaluating the impact of long COVID-19, considering the competing risk of all-cause death is crucial, as it may transform an effect from non-significant to significant.

Comparison between ACEI/ARB use and CCB use

We selected CCBs as an active comparator to ACEIs/ARBs due to their common use in treating hypertension, albeit through differing mechanisms [52]. Our underlying assumption was that ACEI/ARB users and CCB users would have comparable comorbidities and health conditions, potentially sharing similar unmeasured confounders. Thus, any observed difference in outcomes likely stems from the mechanistic differences between ACEIs/ARBs and CCBs.

In additional analysis 2, we conducted a sensitivity analysis focusing exclusively on patients ≥40 years of age, a demographic with a higher prevalence of hypertension [43]. The consistency of these results with those of additional analysis 2 further validate our findings.

Strengths and limitations of the study

A strength of this analysis is the use of multiple study designs to increase the rigor of the work. We employed three distinct study designs, mitigating potential biases and yielding consistent conclusions across each one. The four parallel cohorts design (primary analysis) was straightforward, allowing us to compare the effects of ACEI/ARB use and long COVID under different comparisons. Our matching strategy facilitated the creation of cohorts with similar baseline characteristics and reduced the selection bias [53]. The time-dependent variable design (additional analysis 1) addressed the bias introduced by a randomly assigned index for the non-long COVID group in the primary analysis, and it effectively minimized the immortal time bias [37, 38]. The active comparator design (additional analysis 2) was implemented to compare ACEI/ARB and CCB use head to head [40]. All three study designs demonstrated the non-significant association between ACEI/ARB use and kidney diseases, regardless of long COVID status. Both the primary analysis and additional analysis 1 included all-cause mortality, revealing the potential protective effects of ACEIs/ARBs. Primary analysis and additional analysis 1 also assessed the effects of long COVID, with both suggesting that long COVID could increase the risk of CKD.

The interaction term test reinforces the validity of our study results, demonstrating that the observed outcomes can be attributed directly to either ACEI/ARB use or long COVID. Prior to our main analysis, we incorporated an interaction term for long COVID status and ACEI/ARB use into the Cox proportional hazards regression model for CKD and AKI across the total population. We found that the effects of this interaction term were not statistically significant (CKD, $P = .681$; AKI, $P = .438$), indicating that the observed outcomes related to long COVID (or ACEI/ARB use) in our study are attributable to long COVID (or ACEI/ARB use) itself rather than being modified by ACEI/ARB use (or long COVID).

The extensive real-world dataset we used adds considerable strength to our study. With the recent assignment of the ICD-10 code for long COVID, to the best of our knowledge, ours is the first study examining the effects of long COVID on kidney diseases within a substantial real-world sample, including 199 848 patients. Also, our research incorporates the latest data available through 1 October 2023, with a 2-year period of follow-up for long COVID patients from 1 October 2021.

Our study also has some limitations. First, due to the nature of observational studies, causality cannot be definitively established. Second, we acknowledge the potential pitfalls of EHR databases compared with prospective clinical trials: patients might be misclassified due to misreporting or underreporting of diagnostic codes or medications. Third, despite our efforts to exclude patients with long COVID or COVID-19 diagnoses or those testing positive for SARS-CoV-2, it is possible that some individuals in the control group had undiagnosed mild or asymptomatic COVID-19 because they were not tested for infection. Such non-differential misclassification of exposure could potentially underestimate the strength of the association between long COVID and the onset of CKD, AKI or all-cause death.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

The protocol for this study was reviewed and received a determination of non-human subjects' research by the Penn State Institutional Review Board. The individual informed consent requirement was waived for this secondary analysis of de-identified data.

FUNDING

There was no external or internal funding supporting this study.

AUTHORS' CONTRIBUTIONS

Y.Z., D.M.B. and V.M.C. designed the research (project conception, development of overall research plan). Y.Z. and D.M.B. were responsible for data extraction, data analysis and study oversight. Y.Z. performed the statistical analysis and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and read and approved the final manuscript. This study is part of the YZ's doctoral dissertation research project with the Penn State College of Medicine, United States of America.

DATA AVAILABILITY STATEMENT

Data are available from TriNetX.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Ford ND. Long COVID and significant activity limitation among adults, by age—United States, June 1–13, 2022, to June 7–19, 2023. *MMWR Morb Mortal Wkly Rep* 2023;**72**:866–70. https://doi.org/10.15585/mmwr.mm7232a3
2. Groff D, Sun A, Ssentongo AE *et al*. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open* 2021;**4**:e2128568. https://doi.org/10.1001/jamanetworkopen.2021.28568
3. Fisher M, Neugarten J, Bellin E *et al*. AKI in hospitalized patients with and without COVID-19: a comparison study. *J Am Soc Nephrol* 2020;**31**:2145–57. https://doi.org/10.1681/ASN.2020040509
4. Winkelmayer WC, Khairallah P, Charytan DM. Nephrology and COVID-19. *JAMA* 2020;**324**:1137–8. https://doi.org/10.1001/jama.2020.16779
5. Nugent J, Aklilu A, Yamamoto Y *et al*. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. *JAMA Netw Open* 2021;**4**:e211095. https://doi.org/10.1001/jamanetworkopen.2021.1095
6. Bowe B, Xie Y, Xu E *et al*. Kidney outcomes in long COVID. *J Am Soc Nephrol* 2021;**32**:2851–62. https://doi.org/10.1681/ASN.2021060734
7. Pfaff ER, Madlock-Brown C, Baratta JM *et al*. Coding long COVID: characterizing a new disease through an ICD-10 lens. *BMC Med* 2023;**21**:58. https://doi.org/10.1101/2022.04.18.22273968
8. Jackson CB, Farzan M, Chen B *et al*. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* 2022;**23**:3–20. https://doi.org/10.1038/s41580-021-00418-x
9. Khan S, Chen L, Yang CR *et al*. Does SARS-CoV-2 infect the kidney? *J Am Soc Nephrol* 2020;**31**:2746–8. https://doi.org/10.1681/ASN.2020081229
10. Brar S, Liu KD, Go AS *et al*. Prospective cohort study of renin-angiotensin system blocker usage after hospitalized acute kidney injury. *Clin J Am Soc Nephrol* 2021;**16**:26–36. https://doi.org/10.2215/CJN.10840720
11. Bidulka P, Fu EL, Leyrat C *et al*. Stopping renin-angiotensin system blockers after acute kidney injury and risk of adverse outcomes: parallel population-based cohort studies in English and Swedish routine care. *BMC Med* 2020;**18**:195. https://doi.org/10.1186/s12916-020-01659-x
12. TriNetX. Publication guidelines. https://trinetx.com/real-world-resources/publications/trinetx-publication-guidelines/ [accessed 1 July 2023].
13. Centers for Disease Control and Prevention. Clinical overview of long COVID. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html [accessed 2 July 2023].
14. National Library of Medicine. RxNorm overview. https://www.nlm.nih.gov/research/umls/rxnorm/overview.html [accessed 28 October 2023].
15. Harvey R, Jankus DD, Mosley D. Random assignment of proxy event dates to unexposed individuals in observational studies: an automated technique using SAS®. https://mwsug.org/proceedings/2012/PH/MWSUG-2012-PH02.pdf [accessed 18 June 2024].
16. Schubart JR, Schilling A, Schaefer E *et al*. Use of prescription opioid and other drugs among a cohort of persons with Ehlers–Danlos syndrome: a retrospective study. *Am J Med Genet A* 2019;**179**:397–403. https://doi.org/10.1002/ajmg.a.61031
17. Ba DM, Risher KA, Ssentongo P *et al*. Human immunodeficiency virus (HIV) treatment with antiretroviral therapy mitigates the high risk of mental health disorders associated with HIV infection in the US population. *Open Forum Infect Dis* 2023;**10**:ofad555. https://doi.org/10.1093/ofid/ofad555
18. Zhang Y, Chinchilli VM, Ssentongo P *et al*. Association of long COVID with mental health disorders: a retrospective cohort study using real-world data from the USA. *BMJ Open* 2024;**14**:e079267. https://doi.org/10.1136/bmjopen-2023-079267
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res* 2011;**46**:399–424. https://doi.org/10.1080/00273171.2011.568786
20. Elm Ev, Altman DG, Egger M *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;**335**:806–8. https://doi.org/10.1136/bmj.39335.541782.AD
21. Elixhauser A, Steiner C, Harris DR *et al*. Comorbidity measures for use with administrative data. *Med Care* 1998;**36**:8–27. https://doi.org/10.1097/00005650-199801000-00004
22. Garland A, Olafson K, Ramsey CD *et al*. Epidemiology of critically ill patients in intensive care units: a population-based observational study. *Crit Care* 2013;**17**:R212. https://doi.org/10.1186/cc13026
23. House AA, Wanner C, Sarnak MJ *et al*. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019;**95**:1304–17. https://doi.org/10.1016/j.kint.2019.02.022
24. Townsend RR, Taler SJ. Management of hypertension in chronic kidney disease. *Nat Rev Nephrol* 2015;**11**:555–63. https://doi.org/10.1038/nrneph.2015.114
25. Thomas MC, Brownlee M, Susztak K *et al*. Diabetic kidney disease. *Nat Rev Dis Primer* 2015;**1**:15018. https://doi.org/10.1038/nrdp.2015.18
26. Câmara NOS, Iseki K, Kramer H *et al*. Kidney disease and obesity: epidemiology, mechanisms and treatment. *Nat Rev Nephrol* 2017;**13**:181–90. https://doi.org/10.1038/nrneph.2016.191
27. Turakhia MP, Blankestijn PJ, Carrero JJ *et al*. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018;**39**:2314–25. https://doi.org/10.1093/eurheartj/ehy060
28. Chen CY, Liao KM. Chronic obstructive pulmonary disease is associated with risk of chronic kidney disease: a nationwide case-cohort study. *Sci Rep* 2016;**6**:25855. https://doi.org/10.1038/srep25855
29. Kreisman SH, Hennessey JV. Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. *Arch Intern Med* 1999;**159**:79–82. https://doi.org/10.1001/archinte.159.1.79
30. Stengel B. Chronic kidney disease and cancer: a troubling connection. *J Nephrol* 2010;**23**:253–62.
31. Shirazian S, Grant CD, Aina O *et al*. Depression in chronic kidney disease and end-stage renal disease: similarities and differences in diagnosis, epidemiology, and management. *Kidney Int Rep* 2016;**2**:94–107. https://doi.org/10.1016/j.ekir.2016.09.005
32. Zhang Y, Ghahramani N, Razjouyan H *et al*. The association between proton pump inhibitor use and risk of post-hospitalization acute kidney injury: a multicenter

prospective matched cohort study. *BMC Nephrol* 2023;**24**:150. https://doi.org/10.1186/s12882-023-03211-4
33. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;**38**:1228–34. https://doi.org/10.1080/03610910902859574
34. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509. https://doi.org/10.1080/01621459.1999.10474144
35. Inker LA, Eneanya ND, Coresh J *et al.* New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. https://doi.org/10.1056/NEJMoa2102953
36. Agency for Healthcare Research and Quality. LOINC. https://digital.ahrq.gov/loinc [accessed 8 April 2024].
37. Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transpl Int* 2018;**31**:125–30. https://doi.org/10.1111/tri.13081
38. Agarwal P, Moshier E, Ru M *et al.* Immortal time bias in observational studies of time-to-event outcomes. *Cancer Control* 2018;**25**:1073274818789355. https://doi.org/10.1177/1073274818789355
39. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health* 1999;**20**:145–57. https://doi.org/10.1146/annurev.publhealth.20.1.145
40. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep* 2015;**2**:221–8. https://doi.org/10.1007/s40471-015-0053-5
41. Goyal A, Cusick AS, Thielemier B. *ACE inhibitors*. Treasure Island, FL: StatPearls Publishing, 2023. https://www.ncbi.nlm.nih.gov/books/NBK430896/. [accessed 7 February 2024].
42. McKeever RG, Hamilton RJ. Calcium channel blockers. Treasure Island, FL: StatPearls Publishing, 2022. https://www.ncbi.nlm.nih.gov/books/NBK482473/ [accessed 8 December 2023].
43. Ostchega Y, Nguyen DT. Hypertension prevalence among adults aged 18 and over: united States, 2017–2018. *NCHS Data Brief* 2020;**364**:1–8.
44. Brar S, Ye F, James MT *et al.* Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. *JAMA Intern Med* 2018;**178**:1681–90. https://doi.org/10.1001/jamainternmed.2018.4749
45. Pan M, Vasbinder A, Anderson E *et al.* Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and outcomes in patients hospitalized for COVID-19. *J Am Heart Assoc* 2021;**10**:e023535. https://doi.org/10.1161/JAHA.121.023535
46. Lopes RD, Macedo AVS, de Barros E *et al.* Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA* 2021;**325**:254–64. https://doi.org/10.1001/jama.2020.25864
47. Zhang P, Zhu L, Cai J *et al.* Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;**126**:1671–81. https://doi.org/10.1161/CIRCRESAHA.120.317134
48. European Society of Cardiology. Position Statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang [accessed 31 October 2023].
49. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19 [accessed 31 October 2023].
50. Wang HE, Muntner P, Chertow GM *et al.* Acute kidney injury and mortality in hospitalized patients. *Am J Nephrol* 2012;**35**:349–55. https://doi.org/10.1159/000337487
51. Rewa O, Bagshaw SM. Acute kidney injury—epidemiology, outcomes and economics. *Nat Rev Nephrol* 2014;**10**:193–207. https://doi.org/10.1038/nrneph.2013.282
52. McKee PA, Castelli WP, McNamara PM *et al.* The natural history of congestive heart failure: the Framingham Study. *N Engl J Med* 1971;**285**:1441–6. https://doi.org/10.1056/NEJM197112232852601
53. Morgan CJ. Reducing bias using propensity score matching. *J Nucl Cardiol* 2018;**25**:404–6. https://doi.org/10.1007/s12350-017-1012-y

Received: 26.2.2024; Editorial decision: 30.4.2024