Renin–Angiotensin System Blockers and the risk of COVID-19 related mortality in patients with kidney failure

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Abstract

Background: There is concern about potential deleterious effects of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) in patients with COVID-19. Patients with kidney failure, who often use ACEi/ARB, are at higher risk of more severe COVID-19. However, there are no data available on the association of ACEi/ARB use with COVID-19 severity in this population.

Methods: Data were retrieved from the ERACODA database of kidney transplant and dialysis patients affected by COVID-19, who presented between February 1 and October 1 2020, and had information on 28-day mortality available. Cox proportional-hazards regression was used to calculate hazard ratios (HRs) for the relation between ACEi/ARB use and 28-day mortality risk. Additionally, we studied the association of ACEi/ARB discontinuation with 28-day mortality.

Results: We evaluated 1,511 patients, 459 kidney transplant recipients and 1,052 dialysis patients. Of them, 332 (22%) died within 28 days of initial presentation (88 [19%] kidney transplant and 244 [23%] dialysis patients). 189 (41%) and 288 (27%) of the transplant and dialysis patients respectively were on ACEi/ARB treatment. In transplant and dialysis patients, there was no association between ACEi/ARB use and 28-day mortality in both crude and adjusted models (adjusted HR=1.12, 95%CI: 0.69-1.83 in transplant and 1.04, 95%CI: 0.73-1.47 in dialysis patients). Among transplant recipients, ACEi/ARB discontinuation was associated with increased mortality risk after adjustment for demographics and comorbidities, but the association was no longer statistically significant after adjustment for COVID-19 severity (adjusted HR=1.36, 95%CI: 0.40-4.58). Among dialysis patients, ACEi/ARB discontinuation was not associated with mortality in any model. Essentially similar

results were obtained across subgroups when ACEi and ARB were studied separately and when other outcomes for COVID-19 severity were studied eg. hospital admission, intensive care unit admission or need for ventilator support.

Conclusions: Amongst kidney transplant and dialysis patients with COVID-19, there was no association between ACEi/ARB use and mortality. Similarly, discontinuation of ACEi/ARB on admission with COVID-19 did not negatively impact the risk of death from COVID-19.

Introduction

Renin-angiotensin system (RAS) blockade either by angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) is the first-choice treatment for patients with heart failure, myocardial infarction and proteinuric kidney disease. Over the past two decades, several studies have suggested that RAS blockade is capable of increasing ACE2 expression in different tissues including the heart, vasculature and lungs[1–3]. Circulating ACE2 activity, in particular, is increased in dialysis patients on ARB treatment[3]. Coronaviruses use ACE2 as a receptor to enter type II pneumocytes[4] thus there is a theoretical concern that ACEi/ARB use may lead to a more severe clinical course following infection with coronaviruses. Conversely, potential protective effects have also been also described[5]. Fang et al. hypothesized that in theory patients with hypertension, diabetes or cardiac diseases treated with RAS blockers might be at higher risk for more severe disease when infected with the novel coronavirus SARS-CoV 2[6]. Without evidence to support this hypothesis, several professional societies, including the European Society of Hypertension, the American College of Physicians, and the European Renal Association issued statements recommending that ACEi/ARBs be continued in patients with COVID-19 whilst simultaneously strongly advocating for research to be undertaken to elucidate any potential role of ACEi/ARB as determinants of COVID-19 severity.

COVID-19 is a new disease which has spread rapidly across the world since its discovery in 2019[7]. Randomized clinical trials (RCTs) aiming to assess the effect of ACEi/ARB discontinuation or initiation on COVID-19 related outcomes are currently ongoing and the results of one, not focused on kidney disease patients, were recently made public[8]. Observational clinical data on this topic are scarce and

limited to non-kidney disease populations. Of note, the use of ACEi/ARB is higher among patients with CKD and increases with the severity of CKD. Moreover, patients with CKD are especially at high risk of developing severe COVID-19; a risk which increases exponentially with the severity of CKD[9]. For these reasons, nephrology community urgently needs to ascertain if RAS blockade can, at least in part, explain the severity of COVID-19 in this patient population.

In response to the COVID-19 pandemic, a European database (ERACODA) was established to investigate the course and outcome of COVID-19 in patients living with a kidney transplant or on maintenance dialysis therapy[10]. This database was used to investigate the association between the use of ACEi/ARB and risk of 28-day mortality in patients with kidney failure and COVID-19. Additionally, we studied the effect of ACEi/ARB discontinuation, at point of admission for COVID-19, on 28-day mortality risk.

Methods

Study design and participants

This observational study included information from the ERACODA database, which is endorsed by the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA). The ERACODA database was established in March 2020 and currently involves the cooperation of approximately 200 physicians representing 128 centers in 28 countries, mostly in Europe or bordering the Mediterranean Sea. Data is gathered on adult patients (≥ 18 years old) with kidney failure, either on long-term dialysis or with a functioning kidney allograft, who have been diagnosed with COVID-19 based on a positive result on a real-time polymerase chain reaction assay of nasal or pharyngeal swab specimens, and/or compatible findings on a computer tomography scan of the lungs. Data are collected from outpatients as well as hospitalized patients. Physicians responsible for the care of these patients register detailed demographic data including information pertaining to disease severity, treatment and outcomes.

The ERACODA database is hosted at the University Medical Center Groningen, the Netherlands, and uses REDCap software (Research Electronic Data Capture, Vanderbilt University Medical Center, Nashville, TN, USA) for data collection[8]. Patient identifiable information is stripped from each record and data are stored pseudonymized. The study was approved by the Institutional Review Board of the University Medical Center Groningen (Netherlands), who deemed the collection and analysis of data exempt from ethics review in the context of the Medical Research Involving Human Subjects Act (WMO).

This observational study was designed by the ERACODA Working Group who also run the database assisted by a Management Team and an Advisory Board (members listed in the Acknowledgements).

Data collection

Dialysis and transplant patients who presented with COVID-19 between 1st February and 1st October 2020 and on whom there was information on status 28 days after initial presentation were included in this analysis. The primary study outcome was 28-day mortality. Secondary outcomes were hospitalization, intensive care unit (ICU) admission and ventilator support. Outcomes were recorded with end of follow-up at day 28, with the last follow-up data entered on October 29, 2020.

Detailed information was collected on patient characteristics (including demographics, height, weight, frailty score, comorbidities and medication use) and COVID-19 related characteristics (reason for COVID-19 screening, presenting symptoms, vital signs and laboratory test results) at presentation. The use of ACEi/ARB and changes in dosing or discontinuation of these drugs during the first 48 hours after hospital admission were recorded. Additionally, data on change in dosing or discontinuation of immunosuppressive drugs, and start of anti-inflammatory therapy and anti-viral therapy were collected. Frailty was assessed on a scale of 1 to 9 based on the Clinical Frailty Scale (CFS).[9] The CFS uses clinical descriptors and pictographs to generate a frailty score for a patient, a score of 1 represents very fit and score of 9 represents terminally ill. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥30 kg/m^2. Comorbidities were recorded from patient records.

Statistical analysis

Baseline characteristics of the patients included in the study are presented according to ACEi/ARB use for dialysis patients and transplant recipients separately. Continuous data are presented as mean ± standard deviation (SD) or as median with interquartile range for non-normally distributed data. Categorical data are presented as percentages. Characteristics between groups were compared using student's t-test for continuous variables (Mann-Whitney U-test for non-normally distributed data) and Pearson chi-2 statistics for categorical variables.

The association of ACEi/ARB use (vs. non-use) with 28-day mortality and secondary outcomes was examined in dialysis and transplant patients separately. Cumulative survival probabilities were plotted in Kaplan-Meier curves and were compared using the log-rank test for 28-day mortality. Cumulative incidence function was calculated for secondary outcomes given the competing risk from mortality. Cox proportional-hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of primary and secondary outcomes. To account for competing risk from mortality, the cause-specific hazard was calculated for secondary outcomes.

Multiple models were constructed to account for potential confounders. Model 1 is a crude (unadjusted) model. In Model 2, we adjusted for age, sex and clinical frailty scale (i.e. the most important factors related to prognosis in previous analyses of the ERACODA database). In model 3, we additionally adjusted for systolic blood pressure, diabetes and heart failure (comorbidities predisposing for use of ACEi/ARB). Model 4 was further adjusted for anti-inflammatory therapy and anti-viral therapy. For the primary outcome (28-day mortality) we also investigated interaction

between the type of kidney replacement therapy and ACEi/ARB use. The assumption of proportionality was confirmed by visual inspection of Schoenfeld residuals.

To assess the robustness of our findings, we performed additional analyses. Firstly, in model 5, we adjusted for variables that showed statistically significant difference in their distribution between ACEi/ARB users and non-users; except variables related to COVID-19 disease severity because disease severity may be a consequence of use/non-use of ACEi/ARB and might thus be causal. Secondly, we investigated whether the association of ACEi/ARB use with 28-day mortality varies across subgroups of age (<65 years versus ≥65 years); sex (male versus female); obesity, hypertension, diabetes or heart failure status (yes versus no).). Thirdly, we examined whether any association with 28-day mortality differed between ACEi users and ARB users.

Finally, we examined characteristics of continuers and discontinuers of ACEi/ARB use and examined the association of continuation/discontinuation of ACEi/ARB use with 28-day mortality. This analysis was performed only in hospitalized patients as a decision to continue or discontinue treatment is more likely in hospitalised patients. A total of 448 hospitalized patients who were on ACEi/ARB and had information on ACEi/ARB continuation or discontinuation upon hospitalization, were analysed. Disease severity could be the reason for ACEi/ARB discontinuation in these patients thus in model 5, we adjusted further for factors related to COVID-19 disease severity including cough, shortness of breath, fever, pulse rate, respiration rate, lymphocyte count, C-reactive protein and >25% serum creatinine rise compared to pre-COVID-19 baseline.

All analyses were performed using Stata version 14.0 (College Station, TX). A 2-sided P value < 0.05 indicated statistical significance.

Results

As of October 29, 2020, data have been collected of 1,804 patients. 1,511 of these patients had complete information on vital status at day 28 and ACEi/ARB use (Supplementary Figure 1). 459 were kidney transplant and 1,052 were dialysis patients. 189 (41%) transplant patients and 288 (27%) dialysis patients were on ACEi/ARB treatment.

Baseline characteristics

Baseline characteristics for users and non-users of ACEi/ARB in kidney transplant and dialysis patients are presented in Table 1.

Kidney transplant recipients included in the study were predominantly male (60%) with an average age of 59 years. Commonest comorbidities were hypertension (84%) and diabetes (31%). Characteristics of ACEi/ARB users and non-users were largely comparable although ACEi/ARB users were less frail with increased prevalence of hypertension and lower prevalence of heart failure and chronic lung disease. They had been transplanted for a longer period, had higher body temperature and were less often on prednisone and more often on mTOR inhibitors.

Dialysis patients were on average 66 years old and the majority were also male (61%). ACEi/ARB users were younger, less frail, more often males and current smokers with higher systolic and diastolic blood pressure and increased prevalence of hypertension, diabetes, and diabetic kidney disease. They were more likely to be on peritoneal dialysis and to have residual diuresis.

Association with 28-day mortality

In transplant recipients, 28-day mortality was 17% (95% CI: 13%-24%) in ACEi/ARB users and 20% (95% CI: 16%-26%) in non-users. In dialysis patients, these numbers were 21% (95% CI: 17%-26%) and 24% (95% CI: 21%-27%), respectively (Supplementary table 1).

There was no statistically significant difference in cumulative survival probabilities between ACEi/ARB users and non-users (p=0.45 in transplant recipients and p=0.26 in dialysis patients) (Figure 1). In transplant patients, Cox regression analysis indicated no statistically significant association between ACEi/ARB use and 28-day mortality. This association was not statistically significant in the crude model nor in any of the multivariable adjusted models (in the final model 4 HR=1.12, 95% CI: 0.69-1.83) (Table 2). Results were similar among dialysis patients (in the final model 4 HR=1.04, 95% CI: 0.73, 1.47) (Table 2) (p for interaction between type of kidney replacement therapy and ACEi/ARB use status = 0.88). Visualization of Schoenfeld residuals did not indicate violation of the proportional-hazards assumption (Supplementary Figure 2).

Association with hospitalization, ICU admission and ventilator support

Distribution of hospitalization, ICU admission and ventilator support among ACEi/ARB users and non-users is shown in Figure 2 and in Supplementary Table 1.

There was no statistically significant difference in cumulative outcome probabilities between ACEi/ARB users and non-users for hospitalization, ICU admission or ventilator support (Supplementary Figures 3-5). Similar to the

association with 28-day mortality, in fully adjusted model, ACEi/ARB use was not associated with any of the secondary outcomes in transplant and dialysis patients (Table 3).

Additional analyses

First, further adjustment for variables that showed statistically significant difference in their distribution between ACEi/ARB users and non-users resulted in similar findings regarding association with primary outcome and secondary outcomes (Supplementary Table 2). Second, association of ACEi/ARB use with 28-day mortality did not vary across subgroups by age (<65 years/65 years and older), sex (male/female), obesity status (yes/no), hypertension status (yes/no), diabetes status (yes/no) or heart failure status (yes/no) (p for interaction for all subgroups >0.05). Third, interaction between ACEi and ARB use for association with 28-day mortality in fully adjusted model was not statistically significant among transplant as well as dialysis patients (p for interaction=0.99 among transplant and dialysis patients). Finally, comparison of continuers vs. discontinuers showed that among transplant patients, the group that discontinued ACEi/ARB use had higher respiratory rate and increased prevalence of shortness of breath and worsening creatinine (>25%). Among dialysis patients, the group that discontinued ACEi/ARB use had higher prevalence of obesity and cough and had higher temperature, respiration rate and pulse rate (Supplementary Table 3). Cox proportional hazards regression analysis in transplant patients indicated significantly higher risk of 28-day mortality in discontinuers compared with continuers in a crude model (model 1) and multivariable models (models 2-4), but this association was no longer statistically significant when

adjusted for COVID-19 disease severity related variables on admission (model 5, Table 4). Among dialysis patients this association was not statistically significant in any of the models (Table 4).

Discussion

Among dialysis patients and kidney transplant recipients diagnosed with COVID-19, we found no significant association between prior ACEi/ARB use or ACEi/ARB continuation and 28-day mortality after adjusting for baseline demographics, comorbidities, and the severity of COVID-19. There was also no substantially higher risk for secondary outcomes, including incidence of hospital admission, ICU admission or mechanical ventilator support. Although unadjusted analyses suggested that ACEi/ARB discontinuation in kidney transplant recipients was associated with worse mortality rates, as expected this association effect was lost after adjusting for COVID-19 disease severity.

ACE2 is a carboxypeptidase homologue of ACE discovered in the year 2000 that promotes the degradation of angiotensin (Ang) II (vasoconstrictor effects) to Ang 1-7 (vasodilatory effects) and Ang I to Ang 1-9[12]. ACE2 expression was initially thought to be restricted to the testis, kidney, and heart, but later studies demonstrated widespread ACE2 distribution in the lung, liver, small intestine, brain, and placenta among others[1]. Whereas ACE is highly expressed in the lungs, ACE2 is abundantly expressed in the kidneys. Within the kidney, ACE2 has been specifically found in the apical membranes of the proximal tubules and in the glomerular epithelial cells (podocytes)[1]. Coronaviruses use ACE2 as a receptor to enter type II pneumocytes or alveolar epithelial type II, thus the presence of ACE2 protein in lungs is important for virus cell entry[4]. Preliminary studies during the past two decades suggest that RAS blockade upregulates ACE2 expression in different organs and tissues[1,2]; however its effect on lungs, mainly in type II pneumocytes, had not been assessed. Reviewing this knowledge in an editorial, Fang et al. hypothesized that in theory patients with chronic

disease such as diabetes and hypertension treated with ACE2-increasing drugs, might be at higher risk for severe COVID-19 infection and suggested that calcium channel blockers may represent a suitable alternative treatment in these patients[6]. The publication of this hypothesis in The Lancet Respiratory Medicine created unrest and led to suggestions that RAS blockade should be stopped not only as part of COVID-19 treatment protocols but in all high risk patients to minimize problems when being infected. However, the advantages of such an approach should be weighed against the effect that the withdrawal of RAS blockade could have on patients not infected with COVID-19, but for instance with chronic kidney disease. In such patients RAS blockade has been proven efficacious to prevent hard clinical outcomes, among which hospital admissions, kidney failure and death. Several research groups and societies advised therefore to continue RAS blockade pending evidence to support or refute Fang's hypothesis[6].

Several studies, including the ERACODA cohort, have demonstrated that the mortality rate in patients with kidney failure, either dialysis or kidney transplant patients, is high[11,21–23]. A study using the OpenSAFELY health analytics platform, which includes data of more than 17 million people in the UK, among whom almost 11,000 died from COVID-19, suggested that dialysis and transplant patients are even at higher risk than those with other known risk factors, including chronic heart and lung disease[9,24]. Given that kidney failure reduces life expectancy after COVID-19 infection, it is crucial to ascertain whether ACEi/ARB use or continuation worsens mortality associated with COVID-19 infection in this specific population.

To date, several observational cohort studies have focused on the effect of RAS blockade on the severity of COVID-19 infected patients[13–17.] However, to our

knowledge none of these studies mention the effect of RAS blockade specifically in patients with kidney failure (treated with dialysis or a kidney transplant). A recent analysis of 12,500 patients who were tested for COVID-19 showed no association of previous treatment with RAS blockade with higher risk of testing positive for COVID-19[13]. In addition, there was no association between RAS blockade treatment and the severity of COVID-19. Similarly, another study found no association of RAS blockade with the risk of COVID-19 nor the severity of the disease[14]. Our study furthers this knowledge because it demonstrates that additionally RAS blockade is not associated with survival in patients with kidney failure and COVID-19.

In another study of 681 patients with hypertension and confirmed or clinically suspected COVID-19[15], ARB treatment was not associated with mortality, severity or other in-hospital complications. Interestingly, this study also assessed the association of ARB discontinuation with mortality and severity of COVID-19. Surprisingly, and in contrast to expectation, ARB discontinuation was associated with increased risk of mortality, invasive ventilation, and AKI[13]. Similarly, in our study RAS discontinuation was associated with increased 28-day mortality in kidney transplant recipients. However, after adjusting for the severity of the disease, this effect was lost. Based on these findings, we suggest that disease severity could be at least in part responsible for discontinuation of ACEi/ARB use and therefore likely responsible for excess risk of mortality in ACEi/ARB discontinuers. One might speculate that patients with severe disease at admission, who are more likely to develop shock and AKI, will be those in whom RAS blockade will be withdrawn.

Our study is observational which, by definition, is a limitation. . RCTs are needed to ascertain the real effect of RAS blockade on COVID-19 risk and severity of COVID-

19. Following the COVID-19 pandemic outbreak, several RCTs have been initiated including the BRACE-CORONA study, ACORES-2, REPLACE COVID, RASCOVID-19 and ACEi-COVID[8,18,19]. However, none have focused on patients with kidney failure. The first study with results, the BRACE CORONA study, examined continuing versus discontinuing ACEi/ARB in patients on these medications who were hospitalized with COVID-19 infection[19]. The results were recently presented at the European Society of Cardiology Congress and demonstrated that among patients hospitalized with COVID-19 and receiving chronic ACEi/ARB, discontinuing ACEi/ARB was neither beneficial nor deleterious with regards to mortality or hospitalization days[20]. Our results specifically in patients with kidney failure extend these data.

In this observational cohort study which includes a large number of dialysis and kidney transplant patients with COVID-19, previous use of ACEi/ARB was not associated with an increased 28-day mortality. Furthermore, the discontinuation of ACEi/ARB was not linked with risk of death in kidney transplant and dialysis patients with COVID-19. In the COVID-19 pandemic era, our study suggests that RAS blockade in patients with kidney failure can be continued. Routine withdrawal of RAS blockade in patients with kidney failure who are at risk of cardiovascular and kidney events will confer significantly more harm.

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Contributors: All authors contributed to data collection, study design, data analysis, interpretation, and drafting of this paper.

The ERACODA collaboration is an initiative to study prognosis and risk factors for mortality due to COVID-19 in patients with a kidney transplant or on dialysis that is endorsed by the ERA-EDTA. ERACODA is an acronym for European Renal Association COVID-19 Database. The organizational structure contains a Working Group assisted by a Management Team and an Advisory Board.

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Data Sharing Statement: Collaborators that entered data in ERACODA remain owner of these data. The database can therefore not be disclosed to any third party without the prior written consent of all data providers. Research proposals can be submitted to the Working Group via COVID.19.KRT@umcg.nl. If deemed of interest and methodological sound by the Working Group and Advisory Board, the analyses needed for the proposal will be carried out by the Management Team.

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Figure legends

Figure 1: Cumulative survival probability in: A) transplant patients (left panel) and B) dialysis patients (right panel) among ACEi/ARB users and non-users.

Figure 2: Distribution of: A) hospitalization; B) ICU admission and C) ventilator support in dialysis and transplant patients by ACEi/ARB use.

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Table 1: Characteristics of kidney transplant and dialysis patients with COVID-19, overall and according to ACEi/ARB use status (non-users/users).

	Kidney transplant recipients				Dialysis patients			
		ACEi/ARB use status				ACEi/ARB use status		
	All N=459	Non-users N=270	Users N=189	p-value	All N=1,052	Non-users N=764	Users N=288	p-value
Patient Characteristics								
Male sex, %	60	57	65	0.11	61	58	70	<0.001
Age, year	59 ± 13	60 ± 14	58 ± 12	0.21	66 ± 15	67 ± 14	63 ± 16	<0.001
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5	0.41	27 ± 5	27 ± 6	27 ± 5	0.79
Race				0.06				<0.001
Asian, %	3	2	4		3	2	6	
Black or African descent, %	7	9	5		5	4	9	
White or Caucasian, %	85	84	88		86	88	80	
Other or unknown, %	4	5	3		6	6	5	
Tobacco use				0.18				0.03
Current, %	4	6	2		7	6	11	
Prior, %	24	25	23		23	22	24	
Never, %	51	51	52		47	47	46	
Unknown, %	20	19	23		23	25	19	
Clinical frailty scale, AU	3.0 ± 1.6	3.2 ± 1.7	2.8 ± 1.5	0.03	4.0 ± 1.8	4.1 ± 1.8	3.7 ± 1.8	0.01
Patient identification				0.34				0.10
Symptoms only, %	88	88	88		65	62	70	
Symptoms and contact, %	8	7	10		17	18	14	
No symptoms but contact, %	1	1	1		9	9	9	
Routine screening, %	3	5	1		10	11	7	
Comorbidities								
Obesity, %	22	20	24	0.36	22	22	24	0.52
Hypertension, %	84	76	95	<0.001	84	81	92	<0.001
Diabetes Mellitus, %	31	33	28	0.30	43	40	49	0.01
Coronary artery disease, %	20	22	16	0.12	33	33	35	0.57
Heart failure, %	9	11	5	0.04	24	23	26	0.33
Chronic lung disease, %	9	11	6	0.04	14	15	11	0.12
Active malignancy, %	6	6	6	0.72	7	7	6	0.55
Auto-immune disease, %	5	6	5	0.71	5	5	5	0.82
Primary kidney disease								
Prim. glomerulonephritis, %	20	21	18	0.42	15	17	11	0.01
Pyelonephritis, %	4	4	4	0.82	2	2	1	0.18

Interstitial nephritis, %	5	6	3	0.22	3	4	3	0.50
Hereditary kidney disease, %	14	12	16	0.19	8	8	7	0.84
Congenital diseases, %	4	3	5	0.22	2	2	1	0.84
Vascular diseases, %	8	8	9	0.67	13	14	11	0.20
Sec. glomerular disease, %	5	4	6	0.20	7	7	6	0.57
Diabetic kidney disease, %	13	16	10	0.10	25	23	31	0.01
Other, %	12	11	13	0.45	18	16	21	0.06
Unknown, %	15	16	15	0.74	8	8	8	0.83
Hemodialysis, %	NA	NA	NA		95	96	93	0.03
Peritoneal dialysis, %	NA	NA	NA		5	4	7	
Residual diuresis ≥200 ml/day, %	NA	NA	NA		33	30	42	<0.001
Transplant waiting list status								<0.001
Active on waiting list, %	NA	NA	NA		11	10	14	
In preparation, %	NA	NA	NA		11	10	16	
Temporarily not on list, %	NA	NA	NA		10	8	14	
Not transplantable, %	NA	NA	NA		66	70	54	
Unknown, %	NA	NA	NA		2	2	2	
Time since transplantation				<0.001				
<1 year, %	6	11	1		NA	NA	NA	
1-5 years, %	33	37	28		NA	NA	NA	
>5 years, %	61	52	72		NA	NA	NA	
Medication use								
Use of immunosuppressive medication								
Prednisone, %	86	89	81	0.03	NA	NA	NA	
Tacrolimus, %	78	80	77	0.46	NA	NA	NA	
Cyclosporine, %	10	10	11	0.44	NA	NA	NA	
Mycophenolate, %	68	68	68	0.99	NA	NA	NA	
Azathioprine, %	4	5	3	0.34	NA	NA	NA	
mTOR inhibitor, %	14	11	19	0.03	NA	NA	NA	
Disease related characteristics								
Presenting symptoms								
Sore throat, %	13	14	13	0.90	12	11	15	0.05
Cough, %	64	60	71	0.05	50	50	51	0.94
Shortness of breath, %	42	41	44	0.70	34	35	30	0.28
Fever, %	73	71	76	0.42	60	60	61	0.65
Headache, %	16	13	20	0.10	11	9	15	0.04
Nausea or vomiting, %	16	17	15	0.88	10	9	13	0.16
Diarrhea, %	29	29	29	0.98	12	13	11	0.28
Myalgia or arthralgia, %	27	26	29	0.85	20	19	23	0.30
Vital signs								

Temperature, °C	37.5 ± 1.1	37.4 ± 1.1	37.7 ± 1.1	0.01	37.5 ± 1.1	37.4 ± 1.0	37.5 ± 1.1	0.24
Respiration rate, /min	21 ± 7	21 ± 7	21 ± 7	0.88	19 ± 5	19 ± 5	20 ± 5	0.19
O2 saturation room air, %	94 ± 8	94 ± 6	93 ± 10	0.05	94 ± 5	93 ± 5	94 ± 5	0.01
SBP, mm Hg	132 ± 21	132 ± 22	132 ± 19	0.84	137 ± 26	135 ± 25	143 ± 28	<0.001
DBP, mm Hg	77 ± 15	77 ± 16	77 ± 13	0.99	75 ± 15	74 ± 15	78 ± 16	0.001
Pulse rate, BPM	86 ± 17	86 ± 18	86 ± 15	0.98	82 ± 15	82 ± 15	82 ± 15	0.85
Laboratory test results								
Creatinine increase (>25%)	30	29	31	0.92	-	-	-	
Lymphocytes, x1000/µL	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)	0.8 (0.5, 1.2)	0.63	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.13
CRP, mg/L	44 (10, 97)	38 (8, 96)	49 (14, 97)	0.18	25 (6, 75)	25 (6, 76)	27 (6, 72)	0.94

Continuous variables are reported as mean ± SD or median (IQR). Continuation/discontinuation groups were compared using Student-t, Wilcoxon or Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. *Abbreviations are:* ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; °C, degree Celsius; DBP, diastolic blood pressure; O2, oxygen; prim., primary; SBP, systolic blood pressure; CRP, C-reactive protein

Table 2: Association of ACEi/ARB use with 28-day mortality. Presented are hazard ratios (95% confidence interval) in transplant and dialysis patients, separately*

	Kidney transplant recipients		Dialysis patients	
Events (n)	**88 (459)**	**p-value**	**244 (1,052)**	**p-value**
Model 1	0.85 (0.55, 1.31)	0.46	0.85 (0.63, 1.13)	0.27
Model 2	1.03 (0.65, 1.64)	0.89	1.05 (0.75, 1.45)	0.79
Model 3	1.11 (0.69, 1.81)	0.66	1.04 (0.73, 1.47)	0.82
Model 4	1.12 (0.69, 1.83)	0.64	1.04 (0.73, 1.47)	0.84

ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker;
*Non-use as reference group
Model 1=Crude
Model 2=Model 1 + age, sex and frailty
Model 3=Model 2 + systolic blood pressure, diabetes, heart failure
Model 4=Model 3 + anti-inflammatory therapy, anti-viral therapy

Table 3: Association of ACEi/ARB use with incidence of the secondary outcomes hospitalization, ICU admission and ventilator support. Presented are hazard ratios (95% confidence interval) in transplant and dialysis patients, separately*

	Transplant recipients		Dialysis patients	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Hospitalization: events (n)	**379 (459)**		**724 (1,047)**	
Model 1	1.04 (0.85, 1.27)	0.71	0.85 (0.72, 1.01)	0.06
Model 2	1.04 (0.84, 1.29)	0.71	0.85 (0.71, 1.02)	0.08
Model 3	1.05 (0.84, 1.31)	0.66	0.82 (0.67, 1.00)	0.05
Model 4	1.04 (0.83, 1.30)	0.74	0.89 (0.73, 1.08)	0.23
ICU admission: events (n)	**77 (459)**		**100 (1,047)**	
Model 1	1.22 (0.78, 1.91)	0.39	0.78 (0.49, 1.24)	0.29
Model 2	1.29 (0.81, 2.06)	0.28	0.81 (0.49, 1.33)	0.40
Model 3	1.39 (0.87, 2.24)	0.17	0.66 (0.38, 1.15)	0.14
Model 4	1.28 (0.79, 2.06)	0.31	0.73 (0.41, 1.30)	0.29
Ventilator support: events (n)	**57 (459)**		**71 (1,047)**	
Model 1	1.31 (0.78, 2.21)	0.30	0.64 (0.36, 1.15)	0.14
Model 2	1.33 (0.77, 2.28)	0.31	0.71 (0.38, 1.31)	0.27
Model 3	1.47 (0.85, 2.53)	0.17	0.65 (0.34, 1.25)	0.20
Model 4	1.41 (0.81, 2.46)	0.22	0.77 (0.40, 1.51)	0.45

ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; ICU, Intensive care unit
*Non-use as reference group
Model 1=Crude
Model 2=Model 1 + age, sex and frailty
Model 3=Model 2 + systolic blood pressure, diabetes, heart failure
Model 4=Model 3 + anti-inflammatory therapy, anti-viral therapy

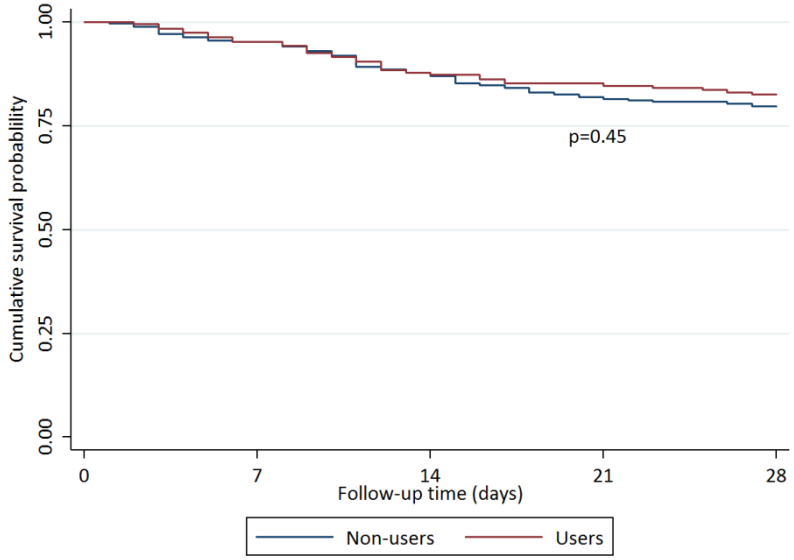
Table 4: Association of ACEi/ARB discontinuation with 28-day mortality in ACEi/ARB users. Presented are hazard ratios (95% confidence interval) in transplant and dialysis patients, separately*

	Transplant recipients		Dialysis patients	
Events (n)	**31 (160)**	**p-value**	**45 (188)**	**p-value**
Model 1	3.05 (1.40, 6.62)	0.005	1.16 (0.64, 2.08)	0.63
Model 2	4.48 (1.87, 10.71)	0.001	1.41 (0.69, 2.88)	0.34
Model 3	5.23 (1.99, 13.73)	0.001	1.68 (0.77, 3.66)	0.19
Model 4	5.03 (1.84, 13.76)	0.002	2.01 (0.91, 4.45)	0.09
Model 5	1.36 (0.40, 4.58)	0.616	1.52 (0.51, 4.56)	0.45

*continuation as reference group
Model 1=Crude
Model 2=Model 1 + age, sex and frailty
Model 3=Model 2 + systolic blood pressure, diabetes, heart failure
Model 4=Model 3 + start of anti-inflammatory therapy, anti-viral therapy
Model 5=Model 4 + cough, shortness of breath, fever, pulse rate, respiration rate, lymphocyte count, C-reactive protein, >25% serum creatinine increase (only in transplant population)

Figure 1: Cumulative survival probability in: A) transplant patients (left panel) and B) dialysis patients (right panel)
among ACEi/ARB users and non-users

A)



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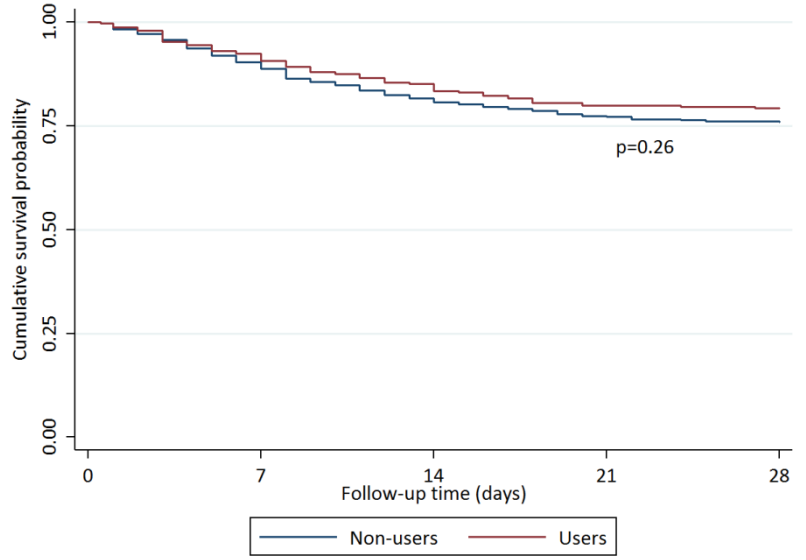
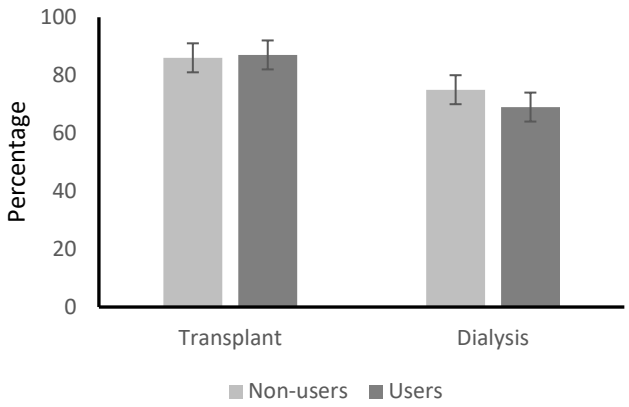


Figure 2: Distribution of: A) hospitalization; B) ICU admission and C) ventilator support in dialysis and transplant patients by ACEi/ARB use

A)



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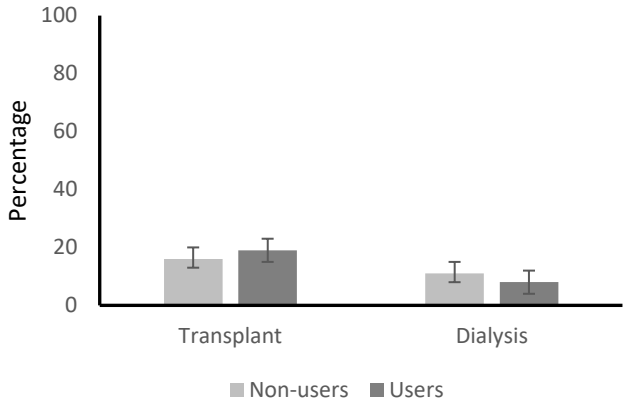
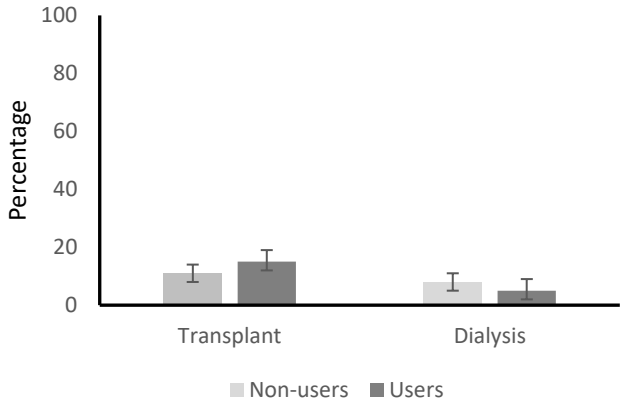

100
80
60
40
20
0
Percentage
Transplant
Dialysis
Non-users
Users

C)


100
80
60
40
20
0
Percentage
Transplant
Dialysis
Non-users
Users

Supplementary Material

Title: Renin–Angiotensin System Blockers and risk of COVID-19 related mortality in patients with kidney failure.

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Supplementary table 2: Distribution of 28-day mortality, hospitalization, ICU admission and ventilator support in ACEi/ARB users and non-users in transplant and dialysis patients (presented are proportions with 95% confidence interval)

Outcome	ACEi/ARB	Kidney replacement therapy	
		Transplant	Dialysis
Mortality	Non-users	20 (16 - 26)	24 (21 - 27)
	Users	17 (13 - 24)	21 (17 - 26)
Hospitalization	Non-users	86 (81 - 90)	75 (72 - 78)
	Users	87 (82 - 91)	69 (63 - 74)
Intensive Care Unit	Non-users	16 (12 - 20)	11 (9 - 13)
	Users	19 (14 - 25)	8 (6 - 12)
Ventilator support	Non-users	11 (8 - 15)	8 (6 - 10)
	Users	15 (10 - 20)	5 (3 - 9)

Supplementary table 3: Association of ACEi/ARB use with 28-day mortality with primary and secondary outcomes in model 5*

	Transplant patients		Dialysis patients	
	HR (95% CI)	p-value	HR (95% CI)	p-value
28 day Mortality				
Model 5	1.26 (0.75, 2.13)	0.38	0.97 (0.67, 1.40)	0.86
Hospitalization				
Model 5	1.03 (0.82, 1.31)	0.76	0.91 (0.74, 1.12)	0.36
ICU admission				
Model 5	1.67 (0.98, 2.86)	0.06	0.75 (0.42, 1.36)	0.34
Ventilator support				
Model 5	1.84 (0.98, 3.45)	0.06	0.81 (0.41, 1.60)	0.54

*Model 5 = age, sex, frailty, systolic blood pressure, diabetes, heart failure, anti-inflammatory therapy, anti-viral therapy and variables statistically different in users and non-users in transplant and dialysis patients

Supplementary Table 4: Characteristics of kidney transplant and dialysis patients with COVID-19, overall and according to ACEi/ARB use status (continue/discontinue)

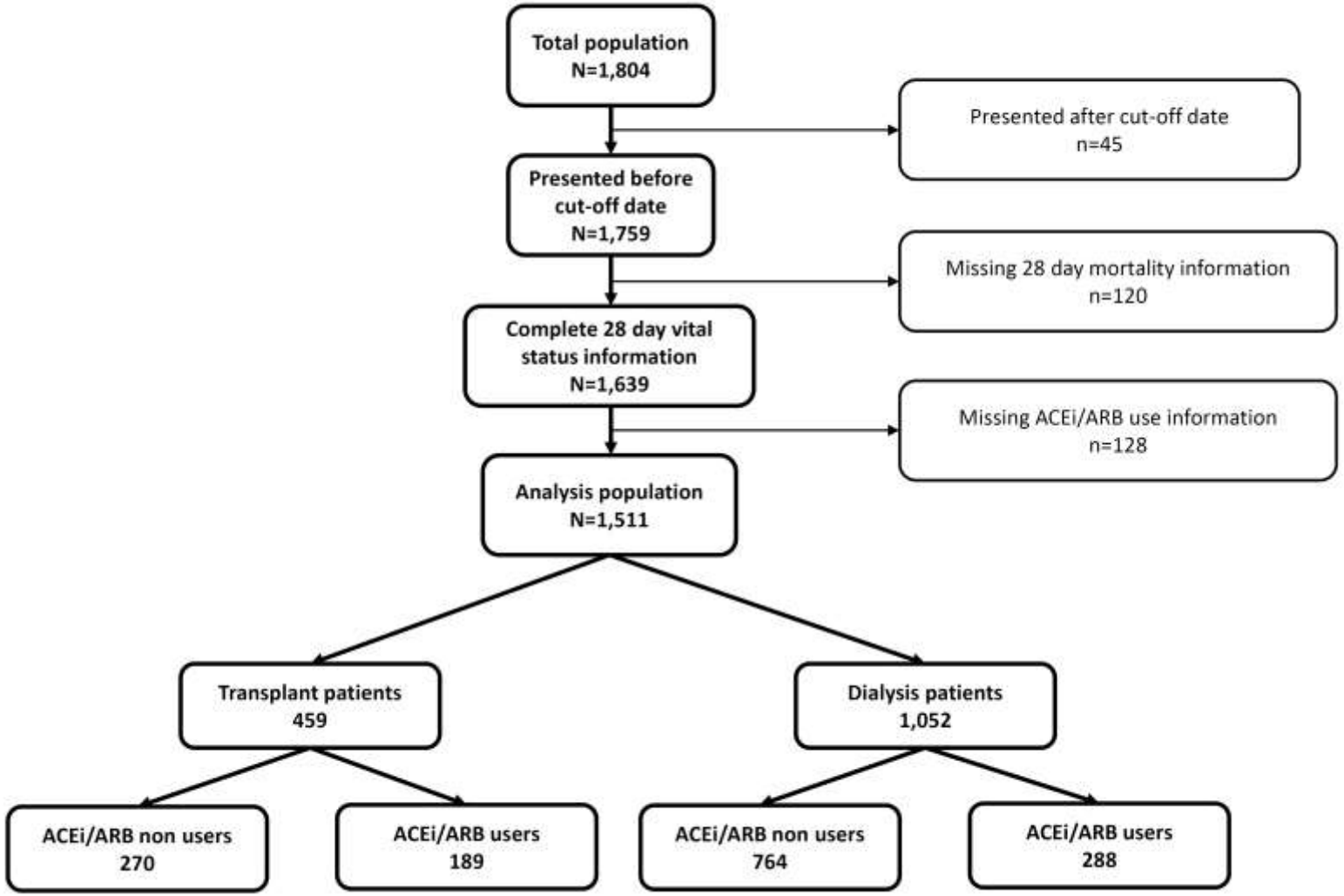
	Kidney transplant recipients				Dialysis patients			
		ACEi/ARB use				ACEi/ARB use		
	All N=184	Continue N=77	Discontinue N=107	p-value	All N=264	Continue N=183	Discontinue N=81	p-value
Patient characteristics								
Male sex, %	65	62	69	0.32	70	70	70	0.95
Age, year	58 ±12	57 ± 12	60 ± 12	0.10	63 ±16	62 ± 15	65 ± 16	0.30
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5	0.41	27 ± 5	26 ± 5	27 ± 5	0.20
Race				0.80				0.10
Asian, %	5	6	3		6	9	1	
Black or African descent, %	5	6	4		10	10	10	
White or Caucasian, %	87	86	90		78	75	85	
Other or unknown, %	3	3	3		6	8	3	
Tobacco use				0.21				0.05
Current, %	2	3	0		12	13	11	
Prior, %	23	19	29		24	22	27	
Never, %	54	57	49		46	43	53	
Unknown, %	22	22	22		18	22	9	
Clinical frailty scale, AU	2.8 ± 1.5	2.9 ± 1.5	2.6 ± 1.5	0.18	3.7 ± 1.8	3.7 ± 1.9	3.8 ± 1.6	0.60
Patient identification				0.56				0.02
Symptoms only	89	86	93		69	73	62	
Symptoms and contact	10	11	7		15	11	22	
No symptoms but contact	-	-	-		9	7	14	
Routine screening	1	2	0		7	9	3	
Comorbidities								
Obesity, %	24	25	23	0.69	23	18	34	0.01
Hypertension, %	95	95	95	0.87	91	92	90	0.66
Diabetes Mellitus, %	27	26	29	0.72	48	46	52	0.37
Coronary artery disease, %	16	15	18	0.56	33	33	32	0.84
Heart failure, %	5	4	8	0.23	26	25	28	0.51
Chronic lung disease, %	6	4	9	0.13	11	9	16	0.08
Active malignancy, %	7	7	6	0.99	5	4	9	0.11
Auto-immune disease, %	5	5	5	0.87	5	5	4	0.66
Primary kidney disease								
Prim. glomerulonephritis, %	18	22	13	0.15	11	10	15	0.23
Pyelonephritis, %	4	7	0	0.02	1	1	1	0.55

Interstitial nephritis, %	3	1	7	0.03	3	3	4	0.66
Hereditary kidney disease, %	17	15	19	0.52	8	7	10	0.43
Congenital diseases, %	5	5	5	0.85	2	2	1	0.81
Vascular diseases, %	9	7	13	0.13	12	13	10	0.47
Sec. glomerular disease, %	6	5	8	0.36	6	8	3	0.11
Diabetic kidney disease, %	11	11	9	0.67	32	30	36	0.34
Other, %	13	10	16	0.26	17	19	11	0.11
Unknown, %	14	18	9	0.11	8	8	8	0.77
Hemodialysis, %	NA	NA	NA		92	93	90	0.44
Peritoneal dialysis, %	NA	NA	NA		8	7	10	
Residual diuresis ≥200 ml/day, %	NA	NA	NA		45	44	47	0.44
Transplant waiting list status								0.02
Active on waiting list, %	NA	NA	NA		14	18	5	
In preparation, %	NA	NA	NA		17	18	14	
Temporarily not on list, %	NA	NA	NA		13	11	19	
Not transplantable, %	NA	NA	NA		54	51	62	
Unknown, %	NA	NA	NA		2	3	0	
Time since transplantation				0.28				
<1 year, %	1	0	1		NA	NA	NA	
1-5 years, %	28	31	23		NA	NA	NA	
>5 years, %	72	69	75		NA	NA	NA	
Medication use								
Use of immunosuppressive medication								
Prednisone, %	82	80	83	0.64	NA	NA	NA	
Tacrolimus, %	76	78	74	0.58	NA	NA	NA	
Cyclosporine, %	11	14	8	0.19	NA	NA	NA	
Mycophenolate, %	68	71	64	0.29	NA	NA	NA	
Azathioprine, %	3	4	3	0.67	NA	NA	NA	
mTOR inhibitor, %	19	16	23	0.20	NA	NA	NA	
Disease characteristics								
Presenting symptoms								
Sore throat, %	13	12	13	0.98	15	13	19	0.51
Cough, %	71	70	71	0.69	52	46	65	0.01
Shortness of breath, %	45	34	61	0.001	31	27	38	0.20
Fever, %	77	72	83	0.08	62	59	69	0.19
Headache, %	21	21	21	0.69	16	13	22	0.17
Nausea or vomiting, %	16	13	19	0.09	13	11	16	0.58
Diarrhea, %	30	31	29	0.66	11	11	11	0.47
Myalgia or arthralgia, %	29	30	29	0.70	24	21	30	0.26

Vital signs								
Temperature, °C	37.7 ± 1.1	37.6 ± 1.1	37.7 ± 1.1	0.50	37.5 ± 1.1	37.4 ±1.1	37.8 ± 1.1	0.03
Respiration rate, /min	21 ± 7	19 ± 5	23 ± 9	<0.001	20 ± 5	19 ±5	21 ± 5	0.02
O2 saturation room air, %	93 ± 10	94 ± 9	92 ± 10	0.12	94 ± 5	95 ± 5	94 ± 4	0.63
SBP, mm Hg	132 ± 19	132 ± 19	132 ± 20	0.99	143 ± 28	143 ±28	143 ± 27	0.99
DBP, mm Hg	77 ± 13	78 ± 13	76 ± 13	0.30	77 ± 16	77 ± 16	79 ± 17	0.51
Pulse rate, BPM	86 ± 15	85 ± 14	87 ± 16	0.49	82 ± 15	79 ±14	88 ± 16	<0.001
Laboratory test results								
Creatinine increase (>25%)	31	18	49	<0.001	-	-	-	
Lymphocytes, x1000/µL	0.8 (0.5, 1.2)	0.8 (0.6, 1.2)	0.7 (0.5, 1.2)	0.17	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	0.9 (0.5, 1.3)	0.49
CRP, mg/L	48 (14, 97)	47 (17, 94)	49 (9, 97)	0.55	27 (6, 73)	33 (8, 93)	18 (4, 45)	0.01

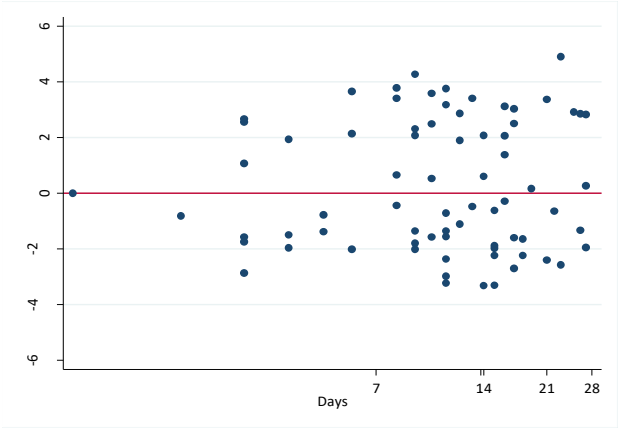
Continuous variables are reported as mean ± SD or median (IQR). Continuation/discontinuation groups were compared using Student-t, Wilcoxon or Chi-square test as appropriate. Obesity is defined as BMI >30 kg/m^2. *Abbreviations are:* ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; BMI, body mass index; °C, degree Celsius; CRP, C-reactive protein; DBP, diastolic blood pressure; O2, oxygen; prim., primary; SBP, systolic blood pressure.

Supplementary figure 1: Flow chart of study participants selection.



Supplementary figure 2: Test of proportionality in 28-day mortality analysis for A) ACEi/ARB users vs. non-users in transplant patients B) ACEi/ARB users vs. non users in dialysis patients

A)



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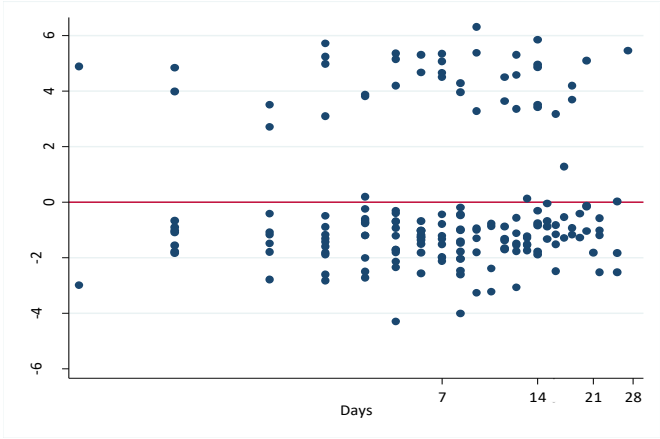
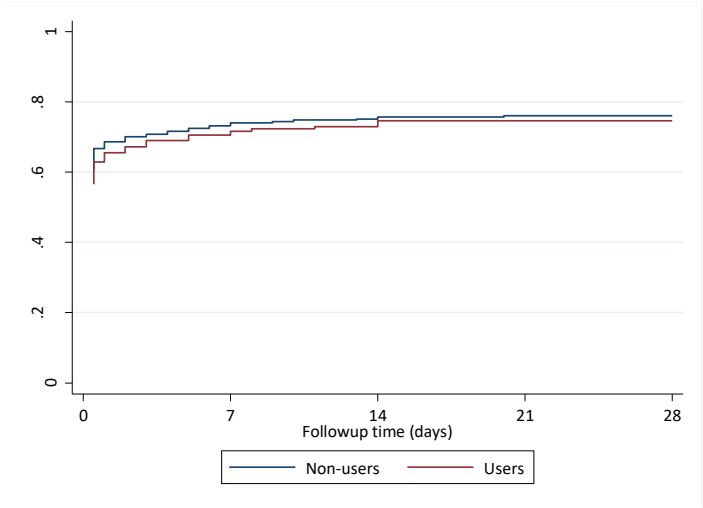
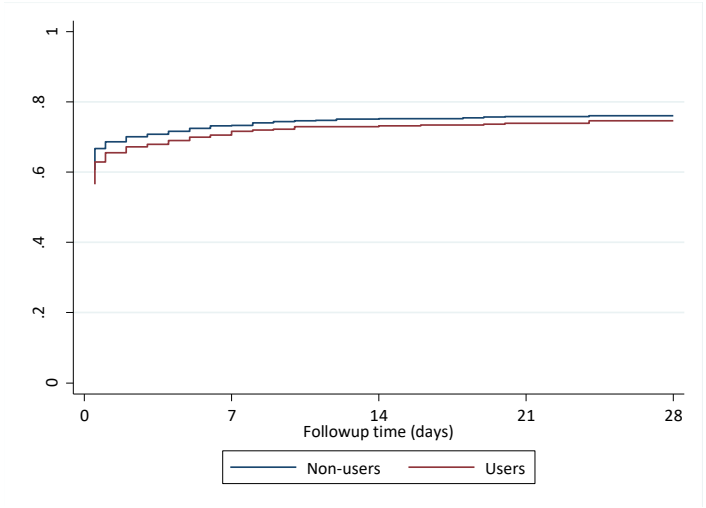


Supplementary Figure 3: Cumulative hospitalization incidence in: A) transplant patients and B) dialysis patients by ACEi/ARB use

A)

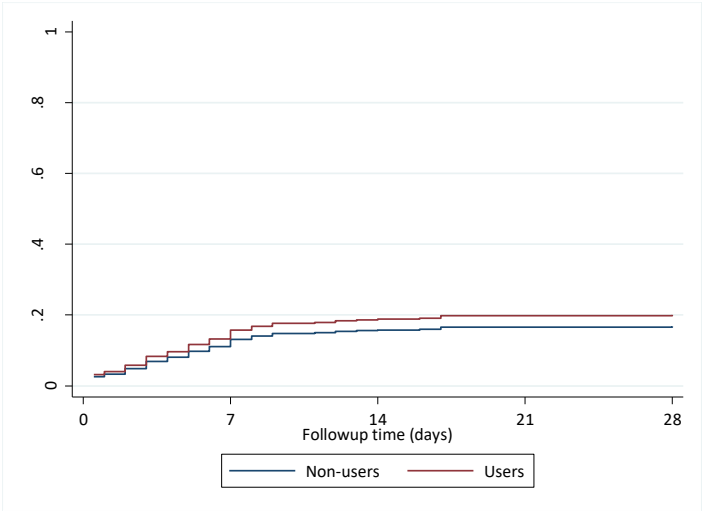


B)



Supplementary Figure 4: Cumulative ICU admission incidence in: A) transplant patients and B) dialysis patients by ACEi/ARB use

A)



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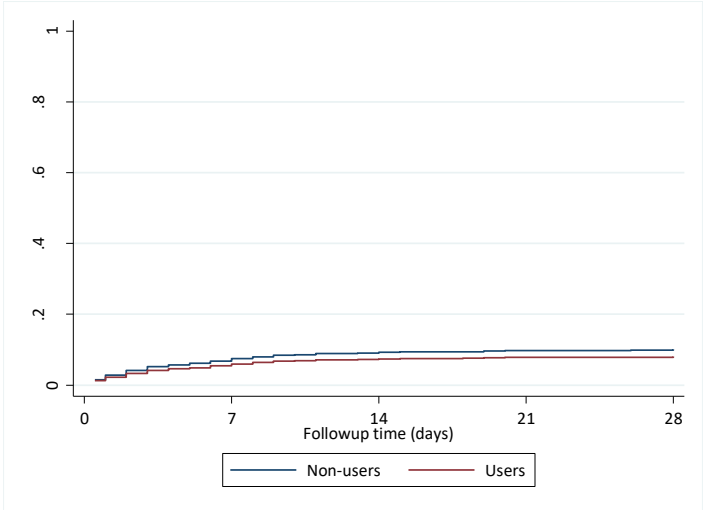
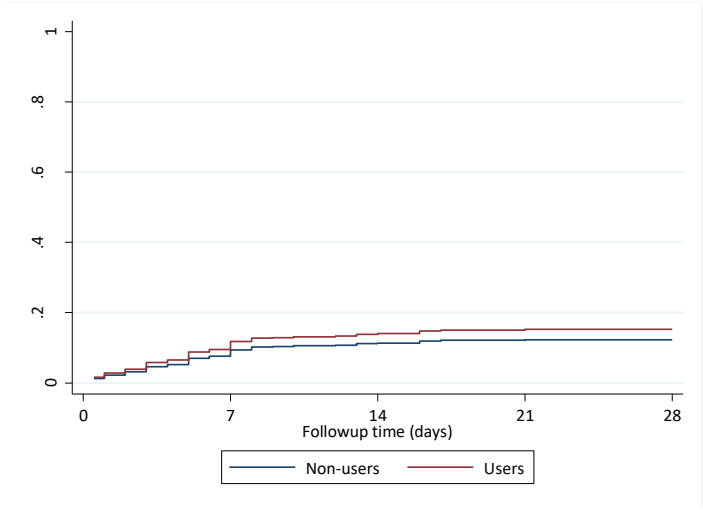


Supplementary Figure 5: Cumulative ventilator support incidence in: A) transplant patients and B) dialysis patients by ACEi/ARB use

A)



B)