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# Longer predialysis ACEi/ARB utilization is associated with reduced postdialysis mortality

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## Abstract

**Background:** Angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEi/ARB) improve predialysis outcomes; however, ACEi/ARB are underutilized in patients transitioning to dialysis. We examined the association of different patterns of predialysis ACEi/ARB use with postdialysis survival, and whether potentially modifiable adverse events are associated with lower predialysis ACEi/ARB utilization.

**Methods:** This was a historic cohort study of 34,676 US veterans with, and 10,690 without ACEi/ARB exposure in the 3-year predialysis period who subsequently transitioned to dialysis between 2007–2014. Associations of different patterns of predialysis ACEi/ARB utilization with postdialysis all-cause mortality and with predialysis acute kidney injury and hyperkalemia events were examined using multivariable adjusted regression analyses.

**Results:** The mean age of the cohort was 70 years, 98% were males and 27% were African Americans. Compared to ACEi/ARB nonuse, continuous ACEi/ARB use was associated with lower postdialysis all-cause mortality (adjusted hazard ratio (aHR); 95% confidence interval [95% CI] 0.87; 0.83–0.92). In analyses modeling the duration of predialysis ACEi/ARB utilization, ACEi/ARB use of 50–74 and ≥75% were associated with lower mortality compared to nonuse (aHR, 95% CI 0.96, 0.92–0.99 and 0.91; 0.88–0.94, respectively), while no increase in postdialysis survival was observed with shorter predialysis ACEi/ARB use. Predialysis acute kidney injury was associated with shorter duration (<50%) of ACEi/ARB use and hyperkalemia was associated with interrupted and ACEi/ARB use of <75%.

**Conclusions:** Longer predialysis ACEi/ARB exposure was associated with lower postdialysis mortality. Prospective studies are needed to evaluate the benefits of strategies enabling uninterrupted predialysis ACEi/ARB utilization.

### Keywords

ACEi/ARB; mortality; ESKD; dialysis; veterans

## Introduction

Chronic kidney disease is one of the most common non-communicable diseases.[1] The cornerstones of its management include correction of underlying etiology, control of blood pressure, proteinuria, and cardiovascular disease risk factors to reduce disease progression and mortality. Beneficial effects of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are well established in predialysis chronic kidney disease. ACEi/ARB delay the development of end-stage kidney disease and reduce cardiovascular events and all-cause mortality in patients with chronic kidney disease.[2–9] Nonetheless, ACEi/ARB use is not without associated risks; e.g. higher rates of

hyperkalemia-related hospitalizations have been reported in patients receiving ACEi/ARB.[10–12]

Hypertension is highly prevalent in chronic kidney disease.[13] A large number of patients reaching dialysis would be expected to receive ACEi/ARB due to current guidelines.[14,15] Nonetheless, the rates of ACEi/ARB use at the time of dialysis initiation are around 40–50%.[16,17] The reasons for the lower than expected rates of ACEi/ARB use in advanced chronic kidney disease are not well studied. It is possible that ACEi/ARB are being actively stopped when kidney function declines due to increasing incidence of hyperkalemia and/or acute kidney injury. A small study showed that deliberate discontinuation of ACEi/ARB in advanced kidney disease led to a stabilization and even temporary improvement in kidney function with no increase in predialysis mortality, suggesting that ACEi/ARB withdrawal in the predialysis period may be beneficial.[18] However, it is unknown if discontinuation of ACEi/ARB could adversely affect long-term outcomes. We examined the association between different patterns of ACEi/ARB utilization in the 3-year period before dialysis initiation (predialysis) and postdialysis all-cause mortality. In addition, we evaluated the association between predialysis ACEi/ARB utilization patterns and potentially modifiable predialysis adverse events, such as acute kidney injury and hyperkalemia.

## Materials and Methods

### Study Participants

The study population was derived from the Transition of Care in Chronic Kidney Disease historic cohort, comprising US veterans with incident end-stage kidney disease.[19, 20] We identified 102,477 patients from the United States Renal Data System (USRDS) who initiated renal replacement therapy between October 1, 2007 and March 31, 2014. The predialysis period was defined as the 3-year period before the start of dialysis. Patients were excluded from analyses if they had no predialysis drug prescriptions in the Veterans Affairs (VA) or Centers for Medicare and Medicaid Services (CMS) (28,165 patients), predialysis follow-up of <3 years in the VA system (N=9,206), missing information on predialysis serum potassium and/or serum creatinine (N=17,069), or ACEi/ARB prescription of <30 days (N=2,771). The final analytic cohort consisted of 45,266 patients (Suppl. Figure 1). The study was approved by the Memphis and Long Beach VA Medical Centers Institutional Review Boards.

### Data Collection

The USRDS, VA and CMS databases were used to ascertain baseline patient characteristics. Information on preexisting comorbidities recorded up to dialysis transition were extracted from VA and CMS databases using inpatient and outpatient International Classification of Disease, Ninth Revision Diagnostic codes and Current Procedural Terminology codes as previously described.[21,22] The Charlson comorbidity index was calculated using the Deyo modification for administrative data sets excluding kidney disease.[23] Information about predialysis laboratory data were obtained from the VA Corporate Data Warehouse LabChem data files and the Decision Support System National Data Extracts Laboratory Results file of the VA database,[24,25] and the mean of all intraindividual values was used for descriptive

purposes. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[26] and slopes of eGFR decline were calculated from mixed-effect models. Predialysis medication dispensation was collected from both VA pharmacy and CMS Medicare Part D records.[27] Information about all-cause mortality was obtained from the VA Vital Status files.[28]

## Exposure Measurement and Outcome Assessment

Prescribing information for ACEi and ARB was extracted using specific drug class codes and names. Patients who received at least one ≥30-day supply for any ACEi or ARB during predialysis were defined as ACEi/ARB users (34,676 patients). Patients with any other predialysis medication prescription(s) but without ACEi/ARB prescriptions were categorized as ACEi/ARB nonusers (N=10,690) (Suppl. Figure 1). Our primary exposures were different patterns of ACEi/ARB utilization compared to ACEi/ARB nonuse during predialysis. We performed two analyses to describe ACEi/ARB utilization in more detail. First, we characterized ACEi/ARB use as percentages of exposure of <25% (N=7,588), 25–49% (N=7,811), 50–74% (N=9,475), and ≥75% (N=9,752) based on the duration of time ACEi/ARB were administered predialysis as determined from the proportion of days with an available prescription for ACEi or ARB of ≥30 days (numerator) to the total duration of the predialysis period (denominator). Second, we categorized ACEi/ARB utilization as (1) continuous ACEi/ARB use if a patient was using ACEi/ARB during all 12 quarters of predialysis (N=2,776) vs. (2) interrupted ACEi/ARB use if ACEi/ARB prescriptions were present during quarters 5–12 but not during the last year (quarters 1–4) before dialysis initiation (N=10,397).

The primary study outcome was all-cause mortality after transition to dialysis. Patients were followed until death, kidney transplantation, or the last date of documented contact (up to May 24, 2017) in the VA system, whichever occurred first. The distribution of kidney transplantation was similar in all groups (data not shown). Secondary study outcomes were (1) incidence of acute kidney injury defined as >50% increase in serum creatinine from the previous value, and (2) incidence of two levels of hyperkalemia, defined as at least one serum potassium value of >5.5 mmol/L or >6.0 mmol/L during predialysis.

## Statistical Analysis

Continuous variables were compared using *t* test or ANOVA for normally distributed data and Mann–Whitney U test or Kruskal-Wallis tests for non-parametric data, as appropriate. Categorical variables were compared with chi-square test. ACEi/ARB nonusers served as the reference group for all analyses. Cox proportional hazard models were applied to evaluate the relationship of different patterns of ACEi/ARB use with all-cause mortality adjusted incrementally for potential confounders, including demographic characteristics (age, gender, race, and ethnicity), comorbidities (diabetes, ischemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, mild and moderate/severe liver disease, chronic lung disease, malignancies, Charlson comorbidity index), use of potassium-sparing diuretics, predialysis nephrology care, mean predialysis eGFR, slopes of eGFR decline, systolic blood pressure, serum potassium, acute kidney injury events, hyperkalemia events, and the cause of end-stage kidney disease. We performed sensitivity analyses for all-cause

mortality by restricting follow-up to the initial 12 months of the postdialysis period and by restricting the cohort to patients who performed hemodialysis as renal replacement therapy (N=37,675). No data were missing for age, gender, predialysis eGFR, slopes of eGFR decline, blood pressure, serum potassium. Data were missing about ethnicity in <0.01% of patients, about comorbidities in 0.2% of patients, and about nephrology care in 2.8% of patients. Given these small numbers, no imputation analyses were done.

We also examined the associations of different patterns of ACEi/ARB utilization with acute kidney injury and hyperkalemia in logistic regression models adjusted for baseline case-mix.

Two-sided p-values of less than 0.05 were considered as significant. Analyses were conducted using SAS Enterprise Guide (7.1) (Cary, NC), or Stata 15 (College Station, TX).

## Results

### Baseline Patient Characteristics

In the total cohort, the mean age was 70 years, 98% were males, 27% were African Americans, 66% were seen by a nephrology specialist, and 76.4% had at least one ≥30-day predialysis ACEi/ARB prescription. Table 1 summarizes baseline characteristics of the study population by percentage of ACEi/ARB exposure and as interrupted/continuous predialysis ACEi/ARB use. Overall, regardless of ACEi/ARB utilization patterns, ACEi/ARB users were younger, had more diabetes, and higher prevalence of cardiovascular disease, but lower prevalence of malignancies, chronic liver and lung disease. The mean predialysis eGFR was not different between ACEi/ARB nonusers and ACEi/ARB users classified by increasing percentage of ACEi/ARB exposure but was lower in RAASi users classified as continuous/discontinuous use, as compared with ACEi/ARB nonusers. The mean predialysis serum potassium was clinically similar among study patients.

### Predialysis ACEi/ARB use and postdialysis all-cause mortality

The median (IQR) follow-up time after dialysis onset was 2.25 (0.81, 3.88) years. There were 31,365 deaths (mortality rate [95% confidence interval] 273.5 [270.5–276.5]/1000 patient-years (PY)). Incremental increases in the percentage of ACEi/ARB exposure (<25% to ≥75%) during predialysis were associated with reduced all-cause mortality in unadjusted analyses (Table 2). However, only ACEi/ARB exposure of 50–74 and ≥75% were associated with reduced multivariable-adjusted all-cause mortality (adjusted hazard ration (aHR); 95% confidence interval [95% CI] 0.96; 0.92–0.99 and 0.91; 95% CI 0.88–0.94, respectively), as compared with ACEi/ARB nonuse. Similarly, continuous predialysis ACEi/ARB use was associated with a 13% lower postdialysis all-cause mortality in the final multivariable adjusted model (aHR 0.87, 95% CI 0.83–0.92), while interrupted ACEi/ARB use showed no association (aHR 1.01, 95% CI 0.98–1.05), as compared with ACEi/ARB nonuse. The aforementioned associations were slightly more accentuated in the evaluations restricted to all-cause mortality in the initial 12 months after dialysis transition (Suppl. Table 1), and remained similar in analyses restricted to patients who received hemodialysis (Suppl. Table 2).

### Predialysis ACEi/ARB utilization patterns and predialysis acute kidney injury and hyperkalemia

Predialysis acute kidney injury and hyperkalemia events in patients with different patterns of predialysis ACEi/ARB use are shown in Table 3. Lower utilization of predialysis ACEi/ARB (categories of ACEi/ARB use <75% and interrupted ACEi/ARB use) was associated a higher unadjusted risk of acute kidney injury. In the multivariable adjusted analysis, ACEi/ARB utilization of <50% was associated with higher risk of acute kidney injury; while, higher ACEi/ARB utilization (≥75% and uninterrupted use) was associated with lower risk of acute kidney injury events, as compared with no ACEi/ARB use (Figure 1A).

During the 3-year predialysis period, 35% and 15% of the study population experienced at least one hyperkalemia event defined as serum potassium >5.5 mmol/L and >6.0 mmol/L, respectively. When considering the increasing percentage of ACEi/ARB utilization or interrupted/continuous ACEi/ARB use, the risk of mild hyperkalemia (serum potassium of >5.5 mmol/L) was higher across increasing ACEi/ARB exposure in unadjusted and adjusted analyses (Figure 1B). However, the risk of moderate-to-severe hyperkalemia (serum potassium of >6.0 mmol/L) was only higher in the interrupted ACEi/ARB use category and in the ACEi/ARB exposure of <75%, but not in the highest ACEi/ARB use group of ≥75% or in the continuous ACEi/ARB use category, comparing to ACEi/ARB nonuse in all analyses (Figure 1C).

## Discussion

We found that utilization of ACEi/ARB for a longer period and, especially, continuous ACEi/ARB utilization during the 3-year predialysis period was associated with reduced all-cause mortality after dialysis initiation. It is generally accepted that ACEi/ARB reduce mortality in predialysis patients based on evidence derived from subgroups of clinical trials that assessed composite rather than individual clinical outcomes.[8,29–31] Nonetheless, meta-analyses[9] and most[6,8,32,33] but not all[34] observational studies also corroborate the survival benefits of ACEi/ARB use in patients with predialysis kidney disease. Our group has previously shown that *de novo* initiation of ACEi/ARB in patients with chronic kidney disease was associated with reduced all-cause mortality irrespective of baseline eGFR, including in 2,535 patients with baseline eGFR <30%.[6] The survival benefit of ACEi/ARB was also demonstrated in end-stage kidney disease.[35–39] A smaller study from Thailand showed that predialysis ACEi/ARB exposure of ≥1-year was associated with reduction in the postdialysis all-cause mortality; however, possible reasons for low rates of predialysis ACEi/ARB use were not investigated.[32] Therefore, the current study further supports postdialysis benefits of predialysis ACEi/ARB use, while also providing insights into possible reasons for underutilization of ACEi/ARB.

Several potentially modifiable adverse associations with ACEi/ARB use emerged in this study. Interrupted and shorted duration of predialysis ACEi/ARB use were associated with a higher incidence of acute kidney injury and hyperkalemia. These are not unexpected findings, given the physiologic action of ACEi/ARB on potassium excretion and kidney adaptation to hemodynamic changes, and may be dissociated from their overall beneficial cardiovascular effects. The adverse events associated with ACEi/ARB use often lead to their

discontinuation and may explain why only 21.5 and 6.1% of patients transitioning to dialysis had predialysis ACEi/ARB exposure of ≥75% or continuous ACEi/ARB use, respectively. Previous studies also reported higher incidence of acute kidney injury[40], faster end-stage kidney disease onset[34] and an increased risk of hyperkalemia-associated hospitalizations[17,34] when ACEi/ARB are used in advanced kidney disease. Given these concerns, there has been interest to examine whether ACEi/ARB should be proactively discontinued in advanced kidney disease with the goal to preserve residual kidney function and to delay end-stage kidney disease onset.[41,42] The ongoing Multi-Centre Randomized Controlled Trial of ACEi/ARB Withdrawal in Advanced Renal Disease (STOP-ACEi) study is aimed to evaluate risks and benefits of withholding ACEi/ARB in predialysis diabetic patients; however, the trial was not designed to evaluate effects of ACEi/ARB discontinuation on postdialysis outcomes[43], and hence questions would remain about the risk-benefit balance of such interventions even if the study were to show a short-term benefit on kidney function. Although hyperkalemia was shown to be associated with higher risk of death in stage 3–4 chronic kidney disease,[44,45] there was no adverse effect on survival in patients with hyperkalemia-associated hospitalizations in a study including predominantly stage 5 patients.[17] However, it is unknown whether special measures were taken in these patients to reduce the mortality risk. In addition, Brar, et al, demonstrated that initiation of ACEi/ARB within 6 months after an acute kidney injury-related hospitalization was associated with 15% reduction in all-cause mortality and no effect on progression to end-stage kidney disease despite a 28% increase in the risk of recurrent acute kidney injury-associated hospitalizations.[46] Higher levels of ACEi/ARB exposure in the present study remained independently associated with improved survival after adjusting for baseline variables and whether or not predialysis slopes of eGFR decline, acute kidney injury and hyperkalemia events were included into adjusted models. Therefore, it can be argued that acute kidney injury and hyperkalemia episodes should not be considered as a contraindication for restarting ACEi/ARB. Instead, meticulous attention should be paid to kidney function changes and potassium levels in patients with advanced kidney disease using ACEi/ARB. Clinicians should evaluate individual risk of acute kidney injury and consider routine counselling about temporary discontinuation of ACEi/ARB during intercurrent illnesses to preserve kidney autoregulation.[42] Education about potassium intake and its moderation, as appropriate, should be provided. The introduction of novel potassium binders may further reduce the incidence of hyperkalemia and allow longer continuation of ACEi/ARB in predialysis period. The long-term benefits of such “ACEi/ARB -enabling” strategies will have to be tested in prospective trials.

## Limitations

Several limitations of the current investigation should be considered. This was an observational study; therefore, we can only describe associations and cannot make causal inferences. While we adjusted for many known confounders, unmeasured confounding (such as the lack of proteinuria measures or doses of ACEi/ARB) may affect the results. The reasons for ACEi/ARB use or nonuse were unknown and it is possible that patients who were perceived to be “sicker” were not prescribed ACEi/ARB, and, hence, would be at higher risk of postdialysis mortality. However, we included patients who survived for 3 years before dialysis start with no ACEi/ARB use and since RRT was instituted as a treatment

option in these patients, it is unlikely that ACEi/ARB nonusers were systematically more ill and were not candidates for ACEi/ARB. Cause-specific mortality was not examined in this analysis and it would be important to corroborate cardioprotective effect of ACEi/ARB in dialysis patients in future studies. Our analyses are based on predialysis data of patients with incident end-stage kidney disease, and hence these results may not apply to the overall population with chronic kidney disease, a large proportion of whom will not initiate renal replacement therapy. However, our design allowed the assessment of ACEi/ARB use patterns during a continuous 3-year follow-up in patients at highest risk for ACEi/ARB-associated complications, unaffected by predialysis deaths or other censoring events. Although, rates of potentially modifiable adverse events were higher in patients with lower levels of ACEi/ARB use, the observational design of this study cannot confirm that acute kidney injury and hyperkalemia were in fact the true reasons for ACEi/ARB interruption/discontinuation. Lastly, the study was limited to predominantly US male veterans and its results might not be generalizable to females or the general population. Nevertheless, this is largest study to date evaluating different patterns of predialysis ACEi/ARB utilization and their associations with important predialysis and postdialysis outcomes.

## Conclusions

The current study strengthens the supports for ACEi/ARB in predialysis chronic kidney disease by providing evidence that their use is associated with postdialysis survival in spite of increased risk of acute kidney injury and hyperkalemia. Further research is warranted to evaluate the risks and benefits of continuous ACEi/ARB use in predialysis patients, and the effects of proactive strategies aimed at enabling a higher proportion of patients with advanced kidney disease to maintain continuous ACEi/ARB therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References:

1. Centers for Disease Control and Preventon: Chronic Kidney Disease in the United States. http://www.cdc.gov/ckd. Last accessed: January 6, 2019.
2. Ahmed A, Love TE, Sui X, Rich MW. Effects of angiotensin-converting enzyme inhibitors in systolic heart failure patients with chronic kidney disease: a propensity score analysis. J Card Fail. 2006;12(7):499–506. [PubMed: 16952782]
3. Berger AK, Duval S, Manske C, Vazquez G, Barber C, Miller L, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. Am Heart J. 2007;153(6):1064–73. [PubMed: 17540211]

4. Gibney EM, Casebeer AW, Schooley LM, Cunningham F, Frover FL, Bell MR, et al. Cardiovascular medication use after coronary bypass surgery in patients with renal dysfunction: a national Veterans Administration study. Kidney Int. 2005;68(2):826–32. [PubMed: 16014062]
5. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109(8):1004–9. [PubMed: 14769700]
6. Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. J Am Coll Cardiol. 2014;63(7):650–8. [PubMed: 24269363]
7. Reinecke H, Matzkies F, Fobker M, Breithardt G, Schaefer RM. Diabetic nephropathy, percutaneous coronary interventions, and blockade of the renin-angiotensin system. Cardiology. 2005;104(1):24–30. [PubMed: 15942180]
8. Tokmakova MP, Skali H, Kenchaiah S, Braunwald E, Rouleau JL, Packer M, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival And Ventricular Enlargement (SAVE) study. Circulation. 2004;110(24):3667–73. [PubMed: 15569840]
9. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. Am J Kidney Dis. 2016;67(5):728–41. [PubMed: 26597926]
10. Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, et al. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. VAL-K Study Group. Kidney Int. 2000;58(5):2084–92. [PubMed: 11044229]
11. Kovesdy CP: Updates in hyperkalemia: Outcomes and therapeutic strategies. Rev Endocr Metab Disord. 2017;18(1):41–7. [PubMed: 27600582]
12. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. Clin J Am Soc Nephrol. 2010;5(3):531–48. [PubMed: 20150448]
13. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2017;69(3 Suppl 1):A7–A8. [PubMed: 28236831]
14. KDIGO Clinical Practice Guidelinefor the Management of Blood Pressure in Chronic Kidney Disease. Kidney International Supplement. 2012;2:372–6.
15. James PA, Oparil S, Carter BL, Cushman WC, Denneson-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20. [PubMed: 24352797]
16. Chang TI, Zheng Y, Montez-Rath ME, Winkelmayer WC. Antihypertensive Medication Use in Older Patients Transitioning from Chronic Kidney Disease to End-Stage Renal Disease on Dialysis. Clin J Am Soc Nephrol. 2016;11(8):1401–12. [PubMed: 27354656]
17. Hsu TW, Liu JS, Hung SC, Kuo KL, Chang YK, Chen YC, et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. JAMA Intern Med. 2014;174(3):347–54. [PubMed: 24343093]
18. Ahmed AK, Kamath NS, El Kossi M, El Nahas AM. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. Nephrol Dial Transplant. 2010;25(12):3977–82. [PubMed: 19820248]
19. Sumida K, Molnar MZ, Potukuchi PK, Thomas F, Lu JL, Ravel VA, et al. Blood pressure before initiation of maintenance dialysis and subsequent mortality. Am J Kidney Dis. 2017;70(2)207–17. [PubMed: 28291617]
20. Sumida K, Molnar MZ, Potukuchi PK, Thomas F, Lu JL, Ravel VA, et al. Association between vascular access creation and deceleratio of estimated glomerular filtration rate declne in late-stage chronic kidney disease patients transitioning to end-stage renal disease. Nephrol Dial Transplant. 2017;32(8):1330–37.
21. Streja E, Gosmanova EO, Molnar MZ, Soohoo M, Moradi H, Potukuchi PK, et al. Association of continuation of statin therapy initiated before transition to chronic dialysis therapy with mortality after dialysis initiation. JAMA Netw Open. 2018;1(6):e182311. [PubMed: 30646217]

22. Gaipov A, Molnar MZ, Potukuchi PK, Sumida K, Szabo Z, Akbigic O, et al. Acute kidney injury following coronary revascularization procedures in patients with advanced CKD. Nephrol Dial Transplant. 2018;34(11):1894–1901.
23. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613–9. [PubMed: 1607900]
24. US Deptartment of Veterans Affairs HSRaDS, VA Information Resource Center. VIReC Resource Guide: VA Corporate Data Warehouse, Hines, IL, VA Information Resource Center 2012
25. US Department of Veterans Affairs HSRaDS, VA Information Resource Center. VIReC Research User Guide: Veterans Health Administration Decision Support System Clinical National Data Extracts, 2nd Ed., Hines, IL, VA Information Resource Center 2009
26. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12. [PubMed: 19414839]
27. VIR. CC. VIReC Research User Guide: VHA Pharmacy Prescription Data, 2nd ed. Hines, IL: US Department of Veterans Affairs, Health Services Research and Development Service, VA Information Resource Center 2008
28. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr. 2006;4:2. [PubMed: 16606453]
29. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. Circulation. 2009;120(16):1577–84. [PubMed: 19805651]
30. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134(8):629–36. [PubMed: 11304102]
31. Perkovic V, Ninomiya T, Arima H, Gallagher M, Jardine M, Cass A, et al. Chronic kidney disease, cardiovascular events, and the effects of perindopril-based blood pressure lowering: data from the PROGRESS study. J Am Soc Nephrol. 2007;18(10):2766–72. [PubMed: 17804673]
32. Vejakama P, Ingsathit A, McKay GJ, Maxwell AP, McEvoy M, Attia J, et al. Treatment effects of renin-angiotensin aldosterone system blockade on kidney failure and mortality in chronic kidney disease patients. BMC Nephrol. 2017;18(1):342. [PubMed: 29187194]
33. Jovanovich AJ, Chonchol MB, Sobhi A, Kendrick JB, Cheung AK, Kaufman JS, et al. Mineral Metabolites, Angiotensin II Inhibition and Outcomes in Advanced Chronic Kidney Disease. Am J Nephrol. 2015;42(5):361–8. [PubMed: 26606453]
34. Oh YJ, Kim SM, Shin BC, Kim HL, Chung JH, Kim AJ, et al. The Impact of Renin-Angiotensin System Blockade on Renal Outcomes and Mortality in Pre-Dialysis Patients with Advanced Chronic Kidney Disease. PLoS One. 2017;12(1):e0170874. [PubMed: 28122064]
35. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. Nephrol Dial Transplant. 2014;29(3):672–81. [PubMed: 24398888]
36. Cice G, Di Benedetto A, D'Isa S, D'Andrea A, Marcelli D, Gatti E, et al. Effects of telmisartan added to Angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2010;56(21):1701–8. [PubMed: 21070920]
37. Suzuki H, Kanno Y, Sugahara S, Ikeda N, Shoda J, Takenaka T, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis. 2008;52(3):501–6. [PubMed: 18653268]
38. Takahashi A, Takase H, Toriyama T, Sugiura T, Kurita Y, Ueda R, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis--a randomized study. Nephrol Dial Transplant. 2006;21(9):2507–12. [PubMed: 16766543]
39. Zannad F, Kessler M, Lehert P, Grünfeld JP, Thuilliez C, Leizorovicz A, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int. 2006;70(7):1318–24. [PubMed: 16871247]

40. Mansfield KE, Nitsch D, Smeeth L, Bhaskaran K, Tomlinson LA. Prescription of renin-angiotensin system blockers and risk of acute kidney injury: a population-based cohort study. BMJ Open. 2016;6(12):e012690.

41. Ahmed A, Jorna T, Bhandari S. Should We STOP Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers in Advanced Kidney Disease? Nephron. 2016;133(3):147–58. [PubMed: 27336470]

42. Weir MR, Lakkis JI, Jaar B, Rocco MV, Choi MJ, Kramer HJ, et al. Use of Renin-Angiotensin System Blockade in Advanced CKD: An NKF-KDOQI Controversies Report. Am J Kidney Dis. 2018;72(6):873–84. [PubMed: 30201547]

43. Bhandari S, Ives N, Brettell EA, Valente M, Cockwell P, Topham PS, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. Nephrol Dial Transplant. 2016;31(2):255–61. [PubMed: 26429974]

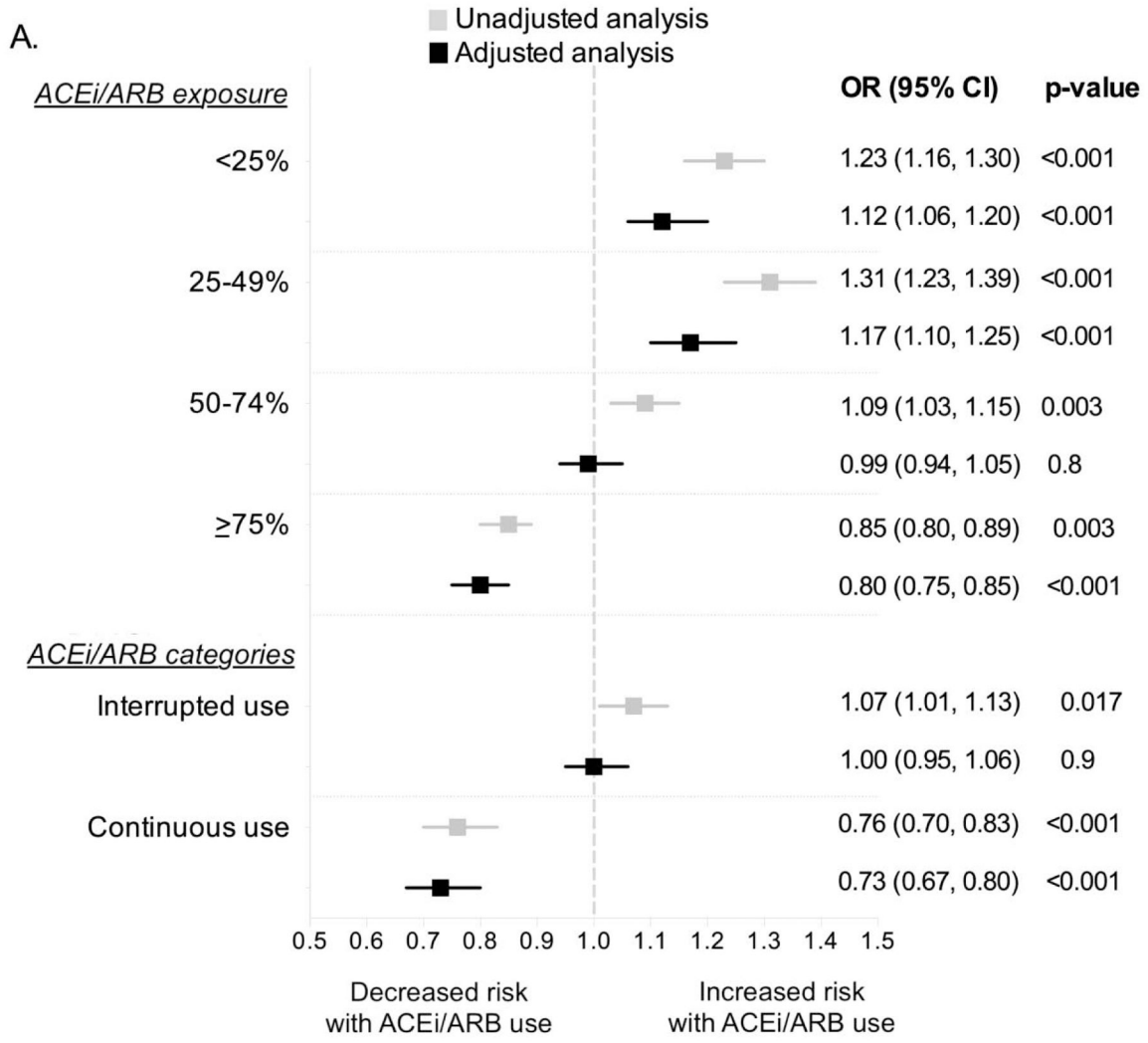
44. Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. Nephron Clin Pract. 2012;120(1):c8–16. [PubMed: 22156587]

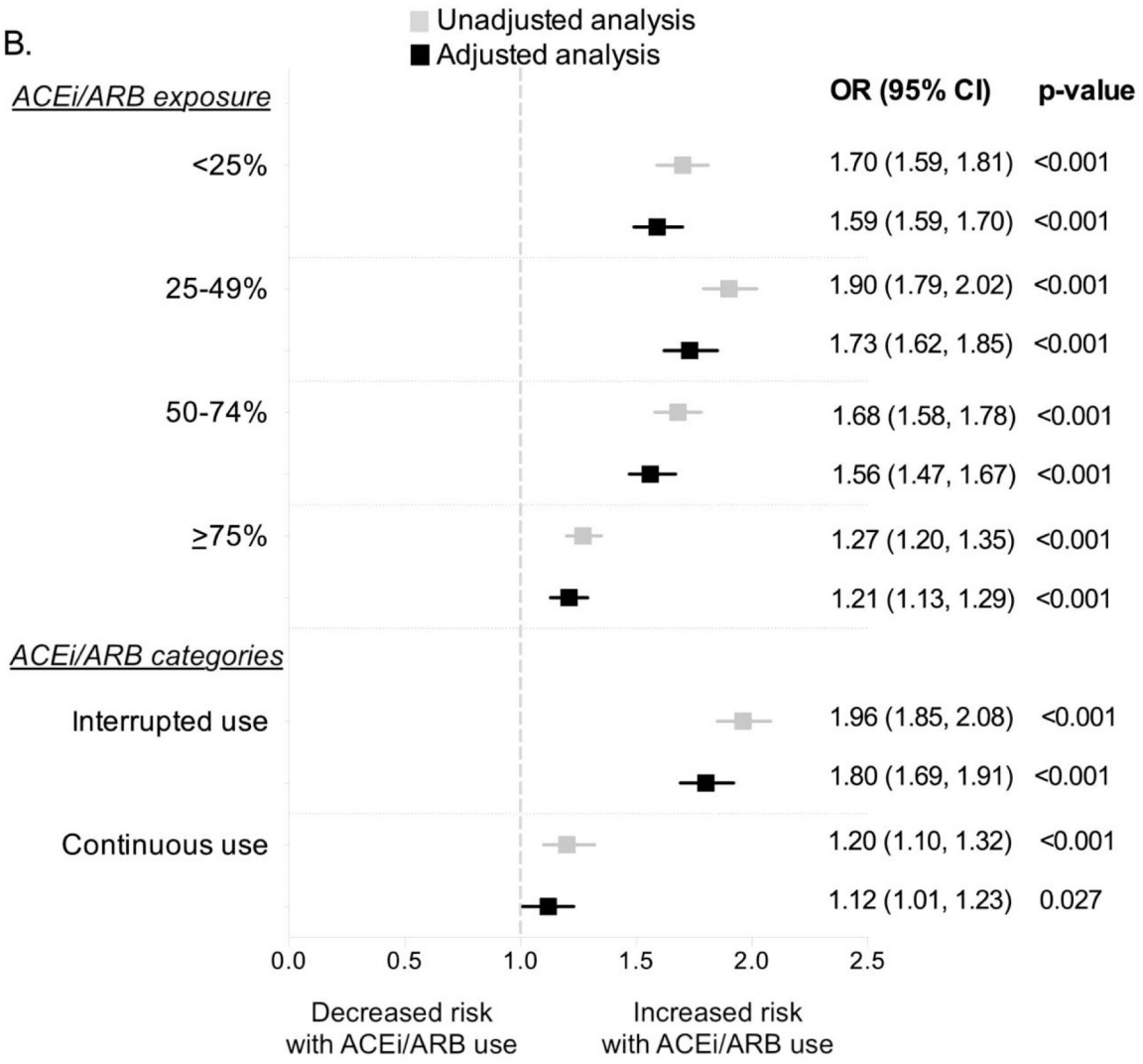
45. Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV Jr, et al. Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease. Am J Nephrol. 2015;41(6):456–63. [PubMed: 26228532]

46. Brar S, Ye F, James MT, Hemmelgarn B, Klarenbach S, Pannu N, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With Outcomes After Acute Kidney Injury. JAMA Intern Med. 2018;178(12):1681–90. [PubMed: 30422153]

### Clinical Significance

- ACEi/ARB utilization during the predialysis period was suboptimal: only 1 in 5 individuals used ACEi/ARB >75% of the time and only 1 in 16 individuals had uninterrupted ACEi/ARB use.
- Acute kidney injury and hyperkalemia events were associated with lower utilization of ACEi/ARB during the predialysis period.
- Patients with longer ACEi/ARB use and uninterrupted ACEi/ARB use during the predialysis period had lower all-cause mortality after dialysis initiation.





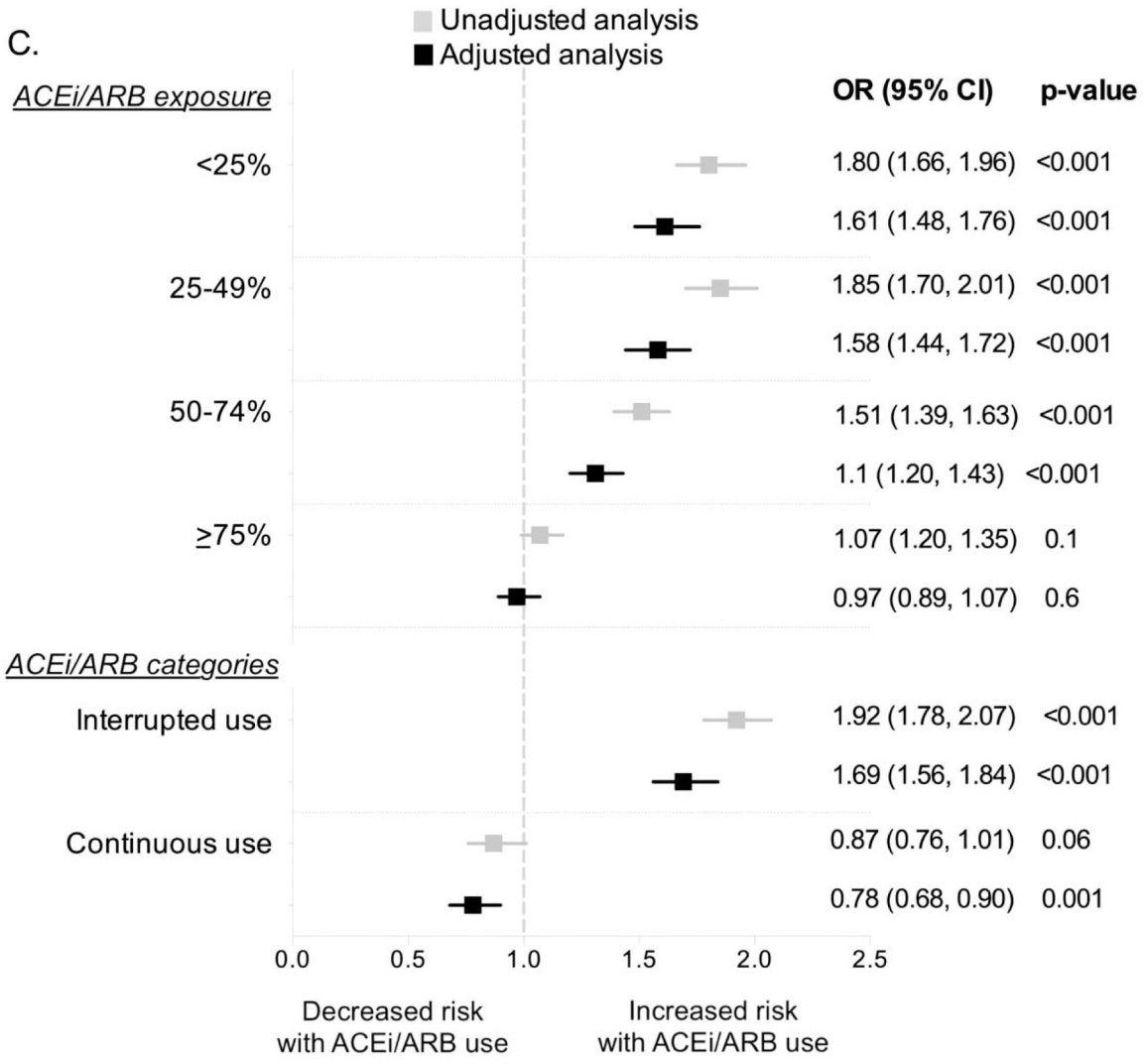



**Figure 1:**

Association between different patterns of ACEi/ARB utilization and adverse predialysis outcomes. A. Association between different patterns of ACEi/ARB utilization and predialysis acute kidney injury. B. Association between different patterns of ACEi/ARB utilization and mild hyperkalemia, defied as serum potassium of >5.5 mmol/L; C. Association between different patterns of ACEi/ARB utilization and moderately severe hyperkalemia, defied as serum potassium of >6.0 mmol/L.

ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; OR, odds ratio; CI, confidence interval; p-p-value; Interrupted ACEi/ARB use defined as ACEi/ARB prescription for more than 30 days in quarters 5–12 and no ACEi/ARB prescription in quarters 1–4 before dialysis onset; Continuous ACEi/ARB use, defined as continuous ACEi/ARB prescription in all 12 quarters of predialysis period; Adjusted analysis, Cox regression adjusted for age, sex, and race/ethnicity, diabetes, ischemic heart disease, congestive heart failure, Charlson comorbidity index, mild and moderate/severe liver disease, chronic lung disease, malignancies, use of potassium sparing diuretics, the cause of end-stage kidney disease, predialysis nephrology care, mean predialysis systolic

blood pressure, mean predialysis serum potassium (for predialysis acute kidney injury events analyses only), presence of hyperkalemia events (for predialysis acute kidney injury events analyses only) and mean predialysis estimated glomerular filtration rate.

**Table 1.**

Baseline cohort characteristics according to increasing percentage of ACEi/ARB use during prelude

| | All (*n* = 45,266) | ACEi/ARB nonuse (*n* = 10,690) | ACEi/ARB use <25% (n=7,588) | ACEi/ARB use 25–49% (n=7,811) | ACEi/ARB use 50–74% (n=9,475) | ACEi/ARB use≥75% (n=9,752) | Interrupted ACEi/ARB (n=10,397) | Continuous ACEi/ARB (n=2,776) |
|---|---|---|---|---|---|---|---|---|
| Age[¶], years | 70 (11) | 72 (12) | 70 (11) | 69 (11) | 69 (11) | 71 (10) | 70 (11) | 71 (10) |
| Sex (male)[*] | 44,358 (98) | 10,485 (98) | 7,414 (98) | 7,628 (98) | 9,240 (98) | 9,591 (98) | 10,174 (98) | 2,726 (98) |
| Race[*] | | | | | | | | |
| White | 31,702 (70) | 7.928 (74) | 5,264 (70) | 5,120 (66) | 6,426 (68) | 6,964 (71) | 7,264 (70) | 2,012 (72) |
| African-American | 12,265 (27) | 2,496 (23) | 2,082 (27) | 2,440 (31) | 2,715 (29) | 2,532 (26) | 2,833 (27) | 686 (25) |
| Other | 1,296 (3) | 263 (3) | 242 (3) | 251 (3) | 284 (3) | 256 (3) | 300 (3) | 78 (3) |
| Nephrology care[*] | | | | | | | | |
| Yes | 28,204 (66) | 6,529 (63) | 4,733 (64) | 4,940 (65) | 5,893 (64) | 6,109 (65) | 6,876 (68) | 1,783 (66) |
| No | 10,153 (23) | 2,511 (24) | 1,695 (23) | 1,655 (22) | 2,104 (23) | 2,188 (23) | 2,009 (20) | 613 (22) |
| Unknown | 5,568 (13) | 1,281 (12) | 948 (13) | 991 (13) | 1,189 (13) | 1,159 (12) | 1,248 (12) | 313 (12) |
| Comorbid conditions[*] | | | | | | | | |
| Ischemic heart disease | 31,016 (69) | 7,030 (66) | 5,195 (69) | 5,351 (69) | 6,634 (70) | 6,806 (70) | 7,297 (70) | 1,942 (70) |
| Congestive heart failure | 29,439 (65) | 6,412 (60) | 4,951 (65) | 5,281 (68) | 6,389 (68) | 6,406 (66) | 6,939 (67) | 1,787 (64) |
| Peripheral vascular disease | 24,718 (55) | 5,848 (55) | 4,178 (55) | 4,237 (54) | 5,080 (54) | 5,375 (55) | 5,808 (56) | 1,526 (55) |
| Cerebrovascular disease | 20,948 (46) | 5,052 (47) | 3,608 (48) | 3,652 (48) | 4,293 (46) | 4,342 (45) | 4,948 (48) | 1,218 (44) |
| Diabetes mellitus | 34,622 (77) | 6,616 (62) | 5,763 (76) | 6,305 (81) | 7,861 (83) | 8,077 (83) | 8,282 (80) | 2,282 (82) |
| Dementia | 2,414 (5) | 698 (7) | 420 (6) | 449 (6) | 459 (5) | 388 (4) | 599 (6) | 104 (4) |
| Chronic lung disease | 25,927 (57) | 6,235 (58) | 4,327 (57) | 4,94 (57) | 5,415 (58) | 5,456 (56) | 6,040 (58) | 1,511 (54) |
| Liver disease, mild | 7,471 (17) | 1,864 (17) | 1,290 (17) | 1,302 (17) | 1,565 (17) | 1,450 (15)) | 1,706 (16) | 380 (16) |
| Liver disease, moderate/severe | 1,668 (4) | 501 (5) | 314 (4) | 277 (4) | 324 (3) | 252 (3) | 401 (4) | 66 (2) |
| Malignancy | 14,759 (33) | 4,190 (39) | 2,405 (32) | 2,384 (31) | 2,773 (29) | 3,007 (31) | 3,387 (33) | 861 (31) |
| Charlson comorbidity index[¶] | 5.5 (3) | 5.5 (3) | 5.6 (3) | 5.6 (3) | 5.6 (3) | 5.4 (3) | 5.7 (3) | 5.4 (3) |
| Predialysis systolic BP[¶] | 142.3 (15) | 139.3 (15) | 143.5 (15) | 144.3 (15) | 143.5 (14) | 142.1(14) | 143.5 (15) | 141.8 (14) |
| Predialysis maximal systolic BP[¶] | 180.0 (29) | 170.5 (27) | 181.7 (29) | 185.6 (29) | 184.3 (20) | 180.5 (28) | 182.3 (29) | 179.5 (27) |

| | All (*n* = 45,266) | ACEi/ARB nonuse (*n* = 10,690) | ACEi/ARB use <25% (n=7,588) | ACEi/ARB use 25–49% (n=7,811) | ACEi/ARB use 50–74% (n=9,475) | ACEi/ARB use≥75% (n=9,752) | Interrupted ACEi/ARB (n=10,397) | Continuous ACEi/ARB (n=2,776) |
|---|---|---|---|---|---|---|---|---|
| Predialysis lowest systolic BP[¶] | 108.6 (18) | 111.5 (19) | 109.2 (19) | 107.0 (18) | 106.9 (17) | 107.7 (17) | 108.6 (18) | 108.1 (17) |
| Predialysis eGFR, ml/min1.73m$^2$[¶] | 27.9 (17) | 28.0 (20) | 27.6 (16) | 27.3 (15) | 28.3 (15) | 28.4 (16) | 25.8 (14) | 27.4 (16) |
| Predialysis potassium, mmol/L[¶] | 4.5 (0.5) | 4.5 (0.5) | 4.5 (0.5) | 4.5 (0.5) | 4.5 (0.5) | 4.5 (0.4) | 4.5 (0.5) | 4.5 (0.5) |
| Predialysis eGFR slope, ml/min1.73m$^2$[¶] | −8.4 (7.0) | −7.3 (7.1) | −8.4 (7.3) | −9.4 (7.4) | −9.1 (7.0) | −8.1 (6.4) | −8.0 (6.2) | −7.5 (6.0) |
| Potassium-sparing diuretic use[¶,#] | 6,453 (14) | 1,002 (9) | 1,018 (13) | 1,247 (16) | 1,618 (17) | 1,568 (16) | 1,466 (14) | 430 (18) |
| Percentage of MRA among PSD, % | 84 | 78 | 83 | 86 | 84 | 85 | 86 | 82 |
| Cause of end-stage kidney disease[¶] | | | | | | | | |
| Diabetes | 20,788 (46) | 3,201 (30) | 3,496 (46) | 4,030 (52) | 4,968 (53) | 5,093 (52) | 5,163 (50) | 1,459 (53) |
| Hypertension | 13,351 (30) | 3,919 (37) | 2,329 (31) | 2,155 (27) | 2,541 (27) | 2,417 (25) | 3,083 (30) | 659 (24) |
| Glomerulonephritis | 2,471 (5) | 619 (6) | 418 (5) | 403 (5) | 443 (5) | 588 (6) | 511 (5) | 182 (6) |
| Other | 5,792 (13) | 2,122 (20) | 908 (12) | 765 (10) | 956 (10) | 1,050 (11) | 1,078 (10) | 325 (12) |
| Unknown | 2,864 (6) | 829 (7) | 437 (6) | 467 (6) | 527 (5) | 604 (6) | 562 (5) | 151 (5) |
| Mode of renal replacement therapy[¶] | | | | | | | | |
| Hemodialysis | 37,675 (84) | 8,703 (82) | 6,323 (84) | 6,642 (85) | 7,951 (85) | 8,056 (83) | 8,747 (84) | 2,282 (82) |
| Peritoneal dialysis | 2,264 (5) | 509 (5) | 387 (5) | 383 (5) | 497 (5) | 488 (5) | 594 (6) | 144 (5) |
| Preemptive kidney transplant | 422 (1) | 123 (1) | 53 (1) | 60 (1) | 79 (1) | 107 (1) | 84 (1) | 40 (2) |
| Unknown | 4,751 (10) | 1,303 (12) | 805 (10) | 704 (9) | 867 (9) | 1,072 (11) | 943 (9) | 303 (11) |

[¶], Mean (Standard deviation);

[*], Number (%);

[#], dispensation of at least one prescription for potassium-sparing diuretics of more than 30-days in predialysis period; ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; BP, blood pressure in mmHg, MRA, mineralocorticoid receptor antagonists; PSD, potassium sparing diuretics. Interrupted ACEi/ARB use defined as ACEi/ARB prescription for ≥30 days in quarters 5–12 and no ACEi/ARB prescription in quarters 1–4 before dialysis onset; Continuous ACEi/ARB use, defined as continuous ACEi/ARB prescription in all 12 quarters of prelude.

**Table 2:**

Association of different patterns of predialysis ACEi/ARB utilization and postdialysis all-cause mortality

| *Groups* | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|---|---|---|---|---|---|---|---|---|
| | **HR (95%CI)** | ***p*** | **HR (95%CI)** | ***p*** | **HR (95%CI)** | ***p*** | **HR (95%CI)** | ***p*** |
| ***Percentage of ACEi/ARB use during predialysis period*** | | | | | | | | |
| | N=44,124 Event number=31,365 | | N=44,124 Event number=31,365 | | N=43,004 Event number=30,670 | | N=43,004 Event number=30,670 | |
| *ACEi/ARB nonuse* 301 [294–308]/ 1000 PY¶ | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| *ACEi/ARB use <25%* 287 [280–295]/1000 PY¶ | 0.96 (0.92–0.99) | 0.013 | 1.08 (1.05, 1.12) | <0.001 | 1.05 (1.01, 1.09) | 0.008 | 1.06 (1.02, 1.10) | 0.003 |
| *ACEi/ARB use 25–49%* 266 [259–273]/1000PY¶ | 0.89 (0.86–0.92) | <0.001 | 1.05 (1.01, 1.09) | 0.008 | 1.00 (0.97, 1.04) | 0.8 | 1.01 (0.97, 1.05) | 0.7 |
| *ACEi/ARB use 50–74%* 262 [255–268]/1000 PY¶ | 0.88 (0.85–0.91) | <0.001 | 1.00 (0.97, 1.04) | 0.8 | 0.96 (0.93, 0.99) | 0.018 | 0.96 (0.92, 0.99) | 0.016 |
| *ACEi/ARB use ≥ 75%* 255 [249–261]/1000PY¶ | 0.86 (0.83–0.88) | <0.001 | 0.93 (0.90, 0.96) | <0.001 | 0.92 (0.89, 0.95) | <0.001 | 0.91 (0.88–0.94) | <0.001 |
| ***Categories of ACEi/ARB use during predialysis period*** | | | | | | | | |
| | N=23,178 Event number=16,575 | | N=23,178 Event umber=16,575 | | N=22,610 Event number=16,232 | | N=22,610 Event number=16,232 | |
| *ACEi/ARB nonuse* 300 [293–307]/ 1000 PY¶ | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| *Interrupted ACEi/ARB* 279 [273–285]/1000 PY¶ | 0.93 (0.90, 0.96) | <0.001 | 1.04 (1.00, 1.07) | 0.02 | 1.00 (0.97, 1.04) | 0.9 | 1.01 (0.98, 1.05) | 0.5 |
| *Continuous ACEi/ARB* 244 [233–255]/1000 PY¶ | 0.82 (0.78, 0.86) | <0.001 | 0.88 (0.84–0.93) | <0.001 | 0.88 (0.83, 0.93) | <0.001 | 0.87 (0.83, 0.92) | <0.001 |

ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; N, number, HR, hazard ratio; CI, confidence interval; p-p-value;

¶, Death Rate and 95% CI; PY, person-years; ACEi/ARB nonusers served as a reference group for ACEi/ARB utilization patterns characterized by increasing percentage of exposure and interrupted/continuous use during 3-year predialysis period, Interrupted ACEi/ARB use defined as ACEi/ARB prescription for ≥30 days in quarters 5–12 and no ACEi/ARB prescription in quarters 1–4 before dialysis onset; Continuous ACEi/ARB use, defined as continuous ACEi/ARB prescription in all 12 quarters of prelude; Model 1, unadjusted analysis; Model 2, adjusted for age, sex, and race/ethnicity; Model 3, Model 2 and also adjusted for ischemic heart disease, congestive heart failure, Charlson comorbidity index, diabetes, mild and moderately-severe liver disease, chronic lung disease, malignancies, use of potassium sparing diuretics, predialysis nephrology care and the cause of end-stage kidney disease; Model 4, Model 3 also adjusted for mean predialysis systolic blood pressure, mean predialysis estimated glomerular filtration rate (eGFR) and potassium, acute kidney injury events, hyperkalemia events, and slopes of predialysis eGFR decline.

**Table 3:**

Predialysis period acute kidney injury, hyperkalemia according to different levels of ACEi/ARB exposure

| Outcomes | ACEi/ARB use | | | | | | |
|---|---|---|---|---|---|---|---|
| | **nonuse (*n* = 10690)** | **<25% (n=7,588)** | **25–49% (n=7,811)** | **50–74% (n=9,475)** | **≥75% (n=9,752)** | **Interrupted (n=10,397)** | **Continuous (n=2,776)** |
| Acute kidney injury events | | | | | | | |
| Total N (%) of patients with event | 5,265 (49) | 4,128 (54) | 4,370 (56) | 4,843 (51) | 4,398 (45) | 5,291 (51) | 1,177 (42) |
| Mean (SD) N of events per patient with event | 0.8 (1.0) | 0.7 (1.0) | 0.9 (1.0) | 0.9 (1.0) | 0.8 (1.0) | 0.9 (1.0) | 0.8 (1.0) |
| Potassium >5.5 mmol/L | | | | | | | |
| Total N (%) of patients with event | 2,882 (27) | 2,921 (39) | 3,224 (41) | 3,604 (38) | 3,112 (32) | 4,365 (42) | 853 (31) |
| Mean (SD) N of events per patient with event | 1.2 (2.7) | 0.9 (2.7) | 1.5 (3.3) | 1.5 (3.0) | 1.2 (2.6) | 1.5 (3.2) | 0.8 (1.8) |
| Potassium K>6.0 mmol/L | | | | | | | |
| Total N (%) of patients with event | 1,192 (11) | 1,399 (18) | 1,471 (19) | 1,499 (16) | 1,159 (12) | 2.019 (19) | 275 (10) |
| Mean (SD) N of events per patient with event | 0.3 (1.0) | 0.2 (0.9) | 0.4 (1.2) | 0.4 (1.1) | 0.3 (0.9) | 0.4 (1.2) | 0.2 (0.6) |

AKI, acute kidney injury, defined as a 50% increase in serum creatinine compared to the last value in the preceding period; eGFR, estimated glomerular filtration rate; K, serum potassium expressed in mmol/L; ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; N, number; Predialysis period was defined as a 3-year period before dialysis initiation. Interrupted ACEi/ARB use was defined as ACEi/ARB prescription for ≥30 days in quarters 5–12 and no ACEi/ARB prescription in quarters 1–4 before dialysis onset; Continuous ACEi/ARB use, defined as continuous ACEi/ARB prescription in all 12 quarters of prelude.