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**Research Article**

# Dose and Time Effects of Renin–Angiotensin Inhibitors on Patients With Advanced Stages 4 to 5 of Diabetic Kidney Disease

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## Abstract

**Context:** Limited evidence exists regarding the cumulative dosing and duration impact of renin–angiotensin system inhibitors (RASis) on cardiorenal and mortality outcomes in patients with advanced stages (predominantly in stage 5 and a minority in stage 4) of diabetic kidney disease (DKD).

**Objective:** To retrospectively investigate whether there are dose- and time-dependent relationships between RASis and cardiorenal and mortality outcomes in this population.

**Methods:** Using Taiwan's national health insurance data in 2000-2017, we analyzed 2196 RASi users and 2196 propensity-matched nonusers among 8738 patients living with diabetes and newly diagnosed with advanced chronic kidney disease (23% stage 4, 77% stage 5). Cox proportional hazards regression models were used to estimate adjusted hazard ratios (aHRs) and 95% CI.

**Results:** RASi use was significantly associated with reduced risks of all-cause mortality (aHR, 0.53; 95% CI 0.47-0.60) and cardiovascular mortality (0.68; 0.56-0.83) with the degree of benefit depending on therapeutic dosage and duration, despite a nonsignificant increase in acute kidney injury risk (1.16; 0.98-1.38) and a significant increase in hyperkalemia risk (1.45; 1.19-1.77). Significant differences in proteinuria risk (1.32; 1.21-1.43) were observed, while there were no significant differences in end-stage renal disease risk (1.01; 0.88-1.15) and no dose– or time–response relationships for either end-stage renal disease or proteinuria risks. Sensitivity analyses confirmed cardiovascular and survival benefits, even in patients with stage 5 DKD.

**Conclusion:** This real-world study suggests that RASi use in advanced stages 4 to 5 DKD may provide dose- and time-dependent cardioprotection and improved survival, without excess renal harms.

**Key Words:** advanced stages 4 to 5 of diabetic kidney disease, renin–aldosterone system inhibitors, dose- and time-response relationships, end-stage renal disease, mortality

**Abbreviations:** aHR, adjusted hazard ratio; AKI, acute kidney injury; cDDD, cumulative defined daily dose; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; LGTD2005, 2005 Longitudinal Generation Tracking Database; NHI, National Health Insurance; RAS, renin–angiotensin system; RASi, renin–angiotensin system inhibitor; SMD, standardized mean difference; TGF-β, transforming growth factor-β.

In the early stages of diabetes, an overactive renin–angiotensin system (RAS) emerges, affecting both systemic and local processes, with angiotensin II playing a central role as its primary effector [1]. In addition to its blood pressure–dependent hemodynamic actions, angiotensin II binding to angiotensin type 1 receptor exerts blood pressure–independent nonhemodynamic effects, fostering a harmful interplay between heightened oxidative inflammatory stress and subsequent fibrosis [1-4]. These processes mutually reinforce each other, contributing to endothelial dysfunction and the onset and progression of diabetic kidney disease (DKD), cardiovascular disease, and atherosclerosis [1, 3, 5]. These conditions collectively fall under the category of noncommunicable diseases, which are the leading causes of death, accounting for 74% of all worldwide fatalities [6]. The well-established strategy of initiating high-dose, long-term treatment with RAS inhibitors (RASis), including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, at an early stage of diabetes is recognized for its capacity to decelerate the progression of DKD, mitigate cardiovascular and vascular remodeling, and reduce overall mortality [7]. This is achieved by the effective and thorough suppression of long-term tissue

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(including blood vessels, heart, and kidneys) RAS activation, along with circulating RAS activation, to alleviate oxidative stress, inflammation, and fibrosis [5].

Considering the intrinsic progressive nature of chronic kidney disease (CKD), individuals with DKD frequently progress to the advanced stages 4 to 5 of CKD (ie, advanced DKD) [8] after surviving diabetic macrovascular and microvascular complications [9]. In this context, oxidative inflammatory stress significantly intensifies owing to heightened activation of the RAS resulting from the concurrent presence of diabetes and advanced CKD. This, in turn, leads to an exponential increase in both cardiovascular and all-cause mortality rates [10]. Four large-scale retrospective studies with varying percentages of diabetes and different distributions of stages 4 and 5 CKD demonstrated improved cardiovascular [11-13] and survival [11, 12, 14] benefits in patients with advanced CKD who were prescribed RASis. However, the renal benefits observed in these studies ranged from low [12] to neutral [11] to improved [13, 14]. One of these studies focused on stage 5 CKD with 53% diabetes [14], another on stage 4 CKD (estimated glomerular filtration rate [eGFR] of 29 mL/min/1.73 $m^2$) with 100% diabetes [13], and the remaining 2 [11, 12] on a majority in stage 4 and a minority in stage 5, with diabetes prevalence ranging from 28% to 48%. However, these studies did not address the knowledge gap concerning the dose–response and time–response relationships of RASi treatment on cardiorenal and survival outcomes in patients with advanced stages 4 to 5 DKD because underutilization (discontinuation or dose reduction) of RASis becomes increasingly prevalent as CKD advances to stages 4 and 5 [11].

Considering the proinflammatory, oxidant, and fibrotic properties of angiotensin II in DKD progression, we hypothesized that RASi treatment could exhibit dose- and time-dependent mitigation of these effects in patients with advanced stages 4 to 5 DKD. To investigate this hypothesis, we leveraged extensive national health insurance claims data from 2000 to 2017. This dataset includes a large representative sample and provides the ability for long-term tracking, allowing us to effectively bridge the existing knowledge gap.

## Material and Methods

### Data Source and Study Design

This national cohort study retrospectively analyzed claims data from Taiwan's 2005 Longitudinal Generation Tracking Database (LGTD2005) from 2000 to 2017, which is derived from Taiwan's National Health Insurance (NHI) claims database. A detailed introduction regarding LGTD2005, a compulsory universal of Taiwan's NHI program, and the claims database have been presented in our previous research [15-19]. Briefly, LGTD2005 is a deidentified database comprising 2 million individuals randomly selected from all beneficiaries in Taiwan's NHI program, which has shown no discernible differences between LGTD2005 and the NHI program. It contains comprehensive medical information and lacks information on laboratory and lifestyle data. Therefore, this study did not require informed consent and was exempt from full review by the institutional review board of the Dalin Tzu Chi Hospital (B10804001). LGTD2005 uses ICD-9-CM (before 2016) and ICD-10-CM (after 2016) diagnosis codes and anatomical therapeutic chemical codes to define diseases and drugs, respectively.

### Study Population: Patients With Advanced Stages 4 to 5 DKD

The study cohort included 13 330 patients living with diabetes and newly diagnosed with advanced CKD (stages 4 and 5) between January 1, 2000, and December 31, 2017 (Fig. 1). Diabetes was defined using the ICD-CM-9/10 codes for diabetes or antihyperglycemic drugs [17, 19]. Advanced CKD indicates CKD stages 4 and 5. Before 2016, the NHI program used ICD-9-CM codes for disease identification. Consequently, CKD stages in the NHI claims database were categorized only as stage 5 CKD (identified by concurrent use of erythropoiesis-stimulating agent) and non–stage 5 CKD (ie, stages 1-4). Following the transition to ICD-10-CM codes in 2016, CKD stages could be identified accordingly in the NHI claims database: CKD stage 4 by ICD-10-CM, and CKD stage 5 by ICD-10-CM with or without erythropoiesis-stimulating agent use [14, 17]. After excluding 4111 patients due to factors such as being under 18 years of age, dropping out, having renal transplantation, or developing end-stage of renal disease (ESRD) before the onset of advanced CKD, we initially identified 9219 eligible patients with advanced stages 4 to 5 DKD. Among them, 482 (5%) had never been prescribed RASi before the onset of advanced CKD, whereas 8737 (95%) had received RASi prescriptions before the onset of advanced CKD. Notably, 7840 (85%) of these patients consistently received RASis for at least 6 months before the onset of advanced CKD.

### Exposure to RASis

RASi use was defined as the presence of at least 1 prescription claim for an RASi after the onset of advanced CKD during the study period. Individuals who did not meet this criterion were categorized as RASi nonusers. In Taiwan, the utilization of angiotensin receptor blockers exceeded that of angiotensin-converting enzyme inhibitors in advanced CKD [14]. Given evidence suggesting that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers exhibit similar mechanisms, advantages, and risks, we permitted the interchangeability between these 2 classes of medications [11]. Moreover, 1 randomized controlled trial [20] and several significant retrospective cohort studies in this field [10-14, 21] also did not separately investigate angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in advanced CKD, with or without diabetes. After excluding 481 patients due to factors such as ESRD development, dropout, or predetection mortality of RASi prescription, we identified 5970 (68.3%) RASi users and 2768 (31.7%) nonusers. This study included 8738 eligible patients with advanced stages 4 to 5 DKD entering propensity score matching, with 2045 (23%) in stage 4 CKD and 6693 (77%) in stage 5 CKD.

### Covariates

We considered several variables, including age, sex, Charlson comorbidity index (indicating overall disease burden) [16, 17, 19], the number of medical visits (to reduce detection bias) [16, 17, 19], baseline comorbidities such as hypertension (defined by ICD-9/10-CM codes or antihypertensives), coronary heart disease (defined by ICD-9/10-CM codes), hyperlipidemia (defined by ICD 9/10-CM codes or antilipidemic drugs), and chronic liver disease (defined by ICD 9/10-CM codes) [17, 19] in the 1-year period prior to the index date. Additionally, we considered 3 potentially confounding drugs (nonsteroidal

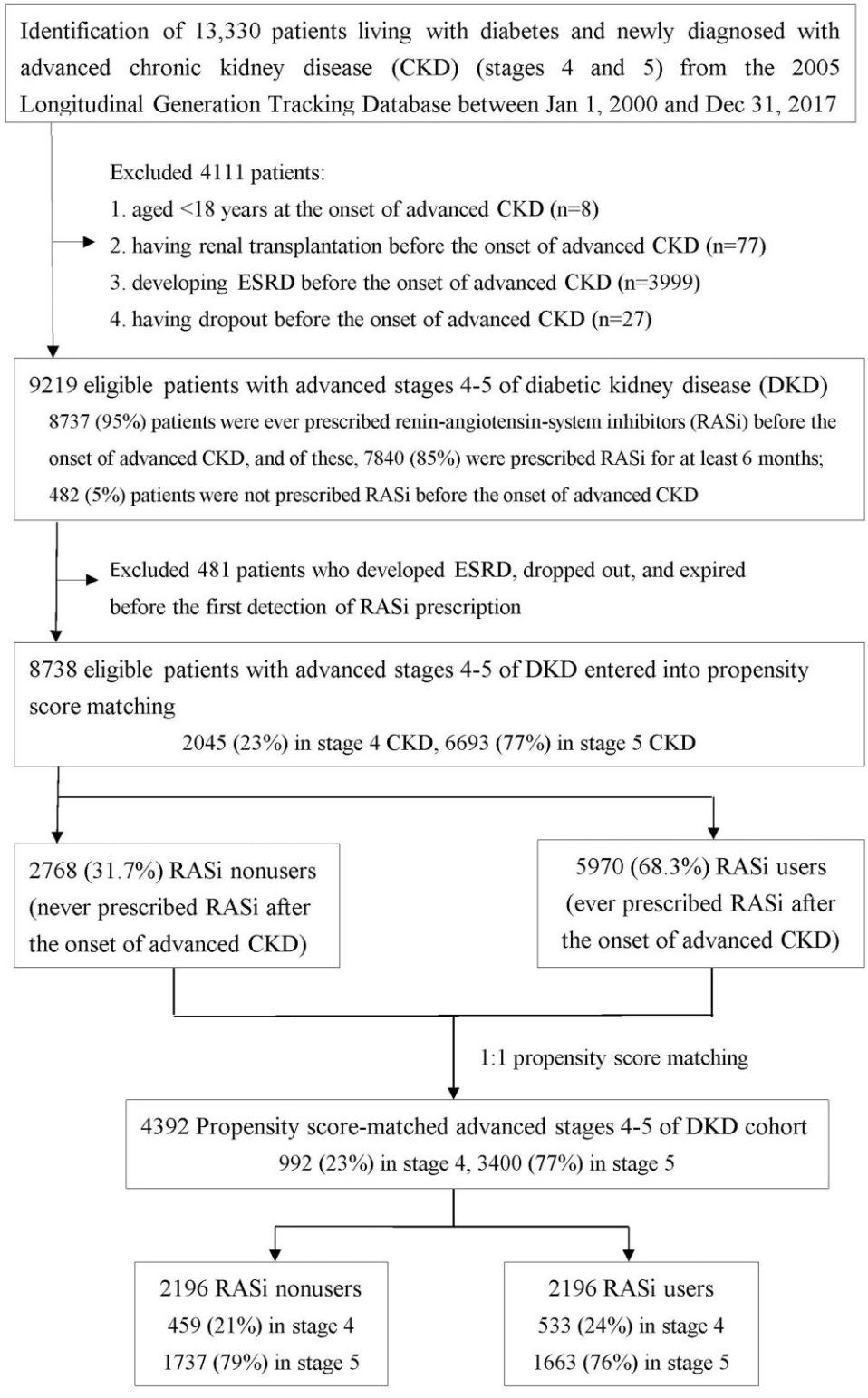


**Figure 1.** Flowchart of selecting patients with advanced stages 4 to 5 DKD.

anti-inflammatory drugs, antihypertensives, and antihyperglycemic drugs) administrated 1 year prior to the index date.

## Propensity Score Matching

For each RASi user, we selected a matched nonuser with a propensity score. To avoid immortal bias [17, 19], each matched nonuser had to be alive at the start of RASi use. The index date for RASi users was set as the precise day on which RASi therapy began, ensuring their survival from the onset of advanced CKD until this index date. Likewise, for nonusers, the index date was synchronized with the corresponding day of the RASi user's initiation. The propensity score, which captures the association between RASi usage and nonusage based on

various baseline characteristics (Table 1), was obtained using logistic regression analysis. Propensity score matching employed the nearest-neighbor approach without replacement, using a narrow caliper value of 0.0001 to ensure precise matching. The reliability of the propensity score model was confirmed by a Hosmer–Lemeshow test $P$ value of .42, and it exhibited reasonable discrimination between the matched cohorts, with a c-index of 0.62.

### Study Outcomes

The primary study outcomes were ESRD, all-cause mortality, and cardiovascular mortality. In Taiwan, ESRD was defined as having a catastrophic illness certificate for long-term dialysis. Before 2016, CKD and ESRD shared the same ICD-9-CM code 585. Thus, before confirming patients with CKD, it is essential to link them to the Registry for Catastrophic Illness Patient Database, a subsection of the NHI claims database, to verify if they possess registration cards for ESRD [16]. Mortality was determined by withdrawal from the NHI program [16, 17, 19]. Cardiovascular mortality included deaths attributed to primary diagnoses such as coronary heart disease, stroke, peripheral vascular disease, and heart failure, as classified by ICD 9/10-CM codes [15]. Patients were followed-up from their index date until the occurrence of ESRD, mortality, or the end of the study on December 31, 2017, whichever occurred first. The last 2 were considered censoring events. In the analysis of mortality outcomes, patients were tracked until the occurrence of the death event, with ESRD occurrences not acting as censoring points if they happened earlier [22]. The secondary study outcome involved the risk of proteinuria and the occurrence of RASi-related complications, such as hyperkalemia and acute kidney injury (AKI), during the study period. Hyperkalemia was identified through outpatient and inpatient records throughout the study and defined by ICD-9/10-CM codes for hyperkalemia, use of potassium-lowering agents, or procedure codes indicating immediate hemodialysis, alongside ICD-9/10-CM codes for hyperkalemia [17]. AKI was defined using ICD-9/10-CM codes [11].

### Assessments of Dose and Time Effects of RASi

To assess the dose–response relationship between RASi usage and both primary study outcomes and the secondary study outcome of proteinuria, we calculated each patient's cumulative defined daily dose (cDDD) of RASi according to the World Health Organization guidelines [15, 18]. We then categorized the cDDDs into 3 or 4 levels based on their respective median and mean doses. To address the time-dependent association between the duration of RASi exposure and primary study outcomes, we evaluated the duration of RASi prescription for participants with follow-up periods exceeding 1 and 2 months, respectively. Additionally, for the secondary study outcome of proteinuria, we examined RASi prescription duration for participants with follow-up periods exceeding 1 month to address the time-dependent association. Duration was measured in cumulative days of RASi use and categorized into 3 levels (1-100, 101-250, and ≥251 days) and 4 levels (1-63, 64-186, 187-271, and ≥272 days), with nonuse as the reference category.

### Supplemental Analyses

We conducted 2 supplemental analyses: 1 assessing the association between RASi and the primary study outcomes in patients with stage 5 DKD, and another involving subgroup analyses based on baseline characteristics.

### Statistical Analyses

Before propensity score matching, we assessed the disparities in baseline characteristics between RASi users and nonusers using a 2-sided t-test for continuous variables and a chi-square test for categorical variables. After propensity score matching, we used the standardized mean difference (SMD) to check the balance of each covariate in the between-group comparisons, where a SMD value <0.1 indicated a negligible distinction [17]. For both groups, we calculated the incidence rates per 100 person-years for the study outcomes and checked the assumption of proportional hazards through a log(-log(survival)) graph against the log of survival time, which showed no violation of the assumption. We estimated the adjusted hazard ratios (aHRs) with their corresponding 95% CIs by comparing RASi users to nonusers. These estimates considered all covariates and accounted for competing mortality when evaluating the ESRD risk [16]. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $P < .05$.

### Sensitivity Analyses

We conducted several sensitivity analyses to enhance the robustness of our main findings. First, we redefined the RASi usage group based on cumulative usage days as >30, >60, >90, and >180 days. Second, we re-evaluated the risk of study outcomes by excluding patients with CKD who either died or progressed to ESRD within 30, 60, 90, or 180 days after the index date. Third, we recalculated the association of a RASi with the main study outcomes if excluding individuals who had not been prescribed any RASi before the onset of advanced CKD, or only including individuals who had been prescribed a RASi for at least 6 months or within 6 months before the onset of advanced CKD. Additionally, we considered 4 confounding drugs (antiplatelets, statins, beta-blockers, and sodium–glucose cotransporter 2 inhibitors) and 1 comorbidity (chronic obstructive pulmonary disease) serving as a proxy for lifestyle factor smoking [23], which are known to positively influence cardiorenal and mortality outcomes, in the regression models. In order to validate our results, considering the higher number of RASi users compared with nonusers, we additionally propensity-matched 2 RASi users with 1 nonuser. Finally, we employed incident cancer occurrence as a negative control outcome to assess the impact of potential unmeasured confounders on our effect estimates [12].

## Results

### Patient Characteristics

Before propensity score matching (Table 1), RASi users had a higher prevalence of hypertension and hyperlipidemia, and a greater use of nonsteroidal anti-inflammatory drugs, antihypertensives, and antihyperglycemic drugs. After the propensity score matching, we successfully balanced all baseline characteristics between the 2 groups, resulting in 2196 matched RASi users (24% in stage 4% and 76% in stage 5) and 2196 nonusers (21% in stage 4% and 79% in stage 5). This constituted a total of 4392 individuals in the propensity score–matched advanced stages 4 to 5 of the DKD cohort, with a mean age of 73 years, a mean Charlson comorbidity

**Table 1. Baseline characteristics of patients with advanced stages 4-5 DKD by use of RASis**

| Variables | All eligible patients with advanced stages 4-5 DKD (n = 8738) | | | Propensity-matched patients with advanced stages 4-5 DKD (n = 4392) | | |
|---|---|---|---|---|---|---|
| | Use (n = 5970) | Nonuse (n = 2768) | *P* value | Use (n = 2196) | Nonuse (n = 2196) | SMD |
| Sex, n (%) | | | .10 | | | 0.01 |
| Men | 3168 (53.1) | 1521 (55.0) | | 1215 (55.3) | 1204 (54.8) | |
| Women | 2802 (46.9) | 1247 (45.0) | | 981 (44.7) | 992 (45.2) | |
| Age (year), n (%) | | | <.0001 | | | 0.007 |
| 18-60 | 1107 (18.5) | 432 (15.6) | | 329 (15.0) | 343 (15.6) | |
| 61-70 | 1517 (25.4) | 609 (22.0) | | 510 (23.2) | 500 (22.8) | |
| 71-80 | 1800 (30.1) | 802 (29.0) | | 667 (30.4) | 658 (30.0) | |
| >80 | 1546 (26.0) | 925 (33.4) | | 690 (31.4) | 695 (31.6) | |
| Mean (SD) | 71.6 (12.4) | 73.6 (12.7) | | 73.3 (12.3) | 73.3 (12.4) | |
| Comorbidities, n (%) | | | | | | |
| Hypertension | 5740 (96.2) | 2493 (90.1) | <.0001 | 2116 (96.4) | 2118 (96.5) | 0.005 |
| Coronary heart disease | 1909 (32.0) | 922 (33.3) | .22 | 763 (34.7) | 754 (34.3) | 0.008 |
| Hyperlipidemia | 4098 (68.6) | 1617 (58.4) | <.0001 | 1427 (64.9) | 1418 (64.6) | 0.009 |
| Chronic liver disease | 685 (11.5) | 399 (14.4) | .0001 | 225 (10.3) | 258 (11.8) | 0.048 |
| Charlson comorbidity index, n (%) | | | <.0001 | | | 0.013 |
| ≤2 | 373 (6.3) | 222 (8.0) | | 134 (6.1) | 132 (6.0) | |
| 3 | 999 (16.7) | 470 (17.0) | | 325 (14.8) | 345 (15.7) | |
| 4 | 1952 (32.7) | 742 (26.8) | | 629 (28.6) | 627 (28.6) | |
| 5 | 1358 (22.7) | 624 (22.5) | | 500 (22.8) | 525 (23.9) | |
| ≥6 | 1288 (21.6) | 710 (25.7) | | 608 (27.7) | 567 (25.8) | |
| Mean (SD) | 4.5 (1.5) | 4.6 (1.6) | | 4.7 (1.5) | 4.7 (1.6) | |
| Number of medical visits, n (%) | | | .18 | | | 0.007 |
| ≤12 | 723 (12.1) | 330 (11.9) | | 234 (10.7) | 245 (11.2) | |
| 12-24 | 1846 (30.9) | 829 (30.0) | | 677 (30.8) | 675 (30.7) | |
| 24-36 | 1469 (24.6) | 742 (26.8) | | 590 (26.9) | 569 (25.9) | |
| >36 | 1932 (32.4) | 867 (31.3) | | 695 (31.6) | 707 (32.2) | |
| Mean (SD) | 31.8 (19.6) | 31.6 (19.2) | | 31.9 (19.2) | 31.9 (19.2) | |
| Confounding drugs, n (%) | | | | | | |
| NSAID | 4087 (68.5) | 1786 (64.5) | .0003 | 1492 (67.9) | 1456 (66.3) | 0.035 |
| Antihyperglycemic drugs | 5249 (88.0) | 2297 (83.0) | <.0001 | 1952 (88.9) | 1934 (88.1) | 0.026 |
| Antihypertensive drugs | 5207 (87.2) | 2344 (84.7) | .0013 | 2024 (92.2) | 2014 (91.7) | 0.017 |

Categorical variables given as number (percentage); continuous variable, as mean ± SD.
Abbreviations: DKD, diabetic kidney disease; NSAID, nonsteroidal anti-inflammatory drugs; RASi, renin–angiotensin–system inhibitor; SMD, standardized mean difference.

index of 4.7, 55% being male, 95% hypertension, 34% coronary heart disease, 65% hyperlipidemia, 88% antihyperglycemic drugs, and 92% antihypertensives. Among them, 992 (23%) had stage 4 CKD and 3400 (77%) had stage 5 CKD (Fig. 1).

## Advantages of RASi for Patients With Advanced Stages 4 to 5 DKD

During the study period, 845 individuals (19.2%) progressed to ESRD, and 777 (17.7%) died before ESRD progression. Additionally, 1101 (25.1%) patients had all-cause mortality, and 403 (9.2%) had cardiovascular mortality, accounting for 36.6% of all-cause mortality. The incidence rates of ESRD (20.3 vs 24.2/100 patient-years), all-cause mortality (14.2 vs 27.9/100 patient-years), and cardiovascular mortality (6.1 vs 9.0/100 patient-years) were significantly lower ($P < .0001$) in RASi users than in nonusers (Table 2). After accounting for all covariates, RASi use in patients with advanced stages 4 to 5 DKD was significantly associated with reduced risks of all-cause mortality (aHR 0.53; 95% CI 0.47-0.60) and cardiovascular mortality (aHR 0.68; 95% CI 0.56-0.83). However, the association with ESRD risk (aHR 1.01; 95% CI 0.88-1.15) was not statistically significant. With a type I error α of 0.05, an event rate per year of 0.22 for the nonuser group, a median follow-up of 1.07 years, a censoring rate of 0.8, and a user to nonuser ratio of 1:1, a sample size of 2196 in each group with an aHR of 0.53 suggests a test power exceeding 90%. Consistent cardiovascular and survival benefits, along with a neutral renal impact, were observed in patients with stage 5 DKD when using RASis compared with nonusers (Table 3).

**Table 2. Hazard ratios of study outcomes among propensity score–matched patients with advanced stages 4-5 of DKD by use of RASi**

| Outcomes | Events (%) | | Estimated event rate (events/100 person-years) | | HR (95% CI) | |
|---|---|---|---|---|---|---|
| | Use | Nonuse | Use | Nonuse | Crude | Adjusted |
| Primary outcomes | | | | | | |
| ESRD | 439 (20%) | 406 (18.5%) | 20.3 (18.5, 22.3) | 24.2 (21.9, 26.7) | 0.92 (0.80, 1.05) | 1.01 (0.88, 1.15)[a] |
| All-cause mortality | 462 (21%) | 639 (29.1%) | 14.2 (12.9, 15.6) | 27.9 (25.8, 30.2) | 0.53 (0.47, 0.60) | 0.53 (0.47, 0.60) |
| Cardiovascular mortality | 197 (9%) | 206 (9.4%) | 6.1 (5.2, 7.0) | 9.0 (7.8, 10.3) | 0.70 (0.57, 0.85) | 0.68 (0.56, 0.83) |
| Secondary outcome | | | | | | |
| Proteinuria | 1272 (58.0%) | 1016 (46.0%) | 109.5 (103.5, 115.7) | 91.6 (86.1, 97.4) | 1.31 (1.21, 1.42) | 1.32 (1.21, 1.43)[b] |

Abbreviations: DKD, diabetic kidney disease; ESRD, end-stage renal disease; RASi, renin–angiotensin–system inhibitor.
[a]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs and competing risk for ESRD).
[b]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, and competing risk for death and ESRD).

**Table 3. Hazard ratios of study outcomes among propensity score-matched patients with stage 5 of DKD by use of RASi**

| Outcomes | Events (%) | | Estimated event rate (events/100 person-years) | | HR (95% CI) | |
|---|---|---|---|---|---|---|
| | Use | Nonuse | Use | Nonuse | Crude | Adjusted |
| Primary outcomes | | | | | | |
| ESRD | 389 (23.4%) | 394 (22.7%) | 22.6 (20.4, 24.9) | 28.5 (25.8, 31.5) | 0.87 (0.76, 1.00) | 0.95 (0.83, 1.10)[a] |
| All-cause mortality | 374 (22.5%) | 528 (30.4%) | 14 (12.6, 15.5) | 26.8 (24.6, 29.2) | 0.54 (0.48, 0.62) | 0.55 (0.48, 0.63) |
| Cardiovascular mortality | 163 (9.8%) | 168 (9.7%) | 6.1 (5.2, 7.1) | 8.5 (7.3, 9.9) | 0.74 (0.60, 0.93) | 0.74 (0.59, 0.92) |
| Secondary outcome | | | | | | |
| Proteinuria | 964 (58.0%) | 808 (46.5%) | 104.9 (98.4, 111.8) | 88.6 (82.6, 94.9) | 1.21 (1.10, 1.33) | 1.33 (1.21, 1.46)[b] |

Abbreviations: aHR, adjusted hazard ratio; DKD, diabetic kidney disease; ESRD, end-stage renal disease; RASi, renin–angiotensin–system inhibitor.
[a]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, (and competing risk for ESRD).
[b]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, (and competing risk for death and ESRD).

## Impact of RASi Dosage and Duration on Primary Study Outcomes

We observed a dose–response relationship between RASi usage and the risks of all-cause and cardiovascular mortality when categorizing the median and mean cDDDs of RASis into 3 or 4 tiers (Table 4 and Figs. 2 and 3). However, this relationship was not evident with respect to ESRD risk. Additionally, a time–response relationship was identified between RASi use and the risks of all-cause and cardiovascular mortality when categorizing cumulative exposure to RASis in days into 3 or 4 tiers (Table 5 and Fig. 4). Conversely, no time–response relationship was observed between RASi use and ESRD risk. These consistent findings persisted in patients with advanced stages 4 to 5 DKD who were followed up for a minimum of 2 months (Supplementary Table S1 [24]).

## Impact of RASi and its Dosage and Duration on Proteinuria Outcome in Patients With Advanced Stages 4 to 5 DKD

A total of 2288 (52.1%) patients with advanced stages 4 to 5 DKD exhibited proteinuria. The incidence rate of proteinuria (109.5 vs 91.6/100 patient-years) was significantly higher ($P < .0001$) among RASi users than nonusers (Table 2). After accounting for all covariates and considering competing risks for death and ESRD, RASi use did not significantly mitigate the risk of proteinuria (aHR 1.32; 95% CI 1.21-1.43) in patients with advanced stages 4 to 5 DKD. These findings were consistent (aHR 1.33; 95% CI 1.21-1.46) among patients with stage 5 DKD (Table 3). Moreover, there were no observed dose–response (Table 4) or time–response (Table 5) relationships between RASi use and proteinuria risk in patients with advanced stages 4 to 5 DKD.

## Complications Associated With RASi Use in Patients With Advanced Stages 4- to 5 DKD

Compared to nonuse, RASi use in patients with advanced stages 4 to 5 DKD exhibited a significant association with an increased risk of hyperkalemia (aHR 1.45; 95% CI 1.19-1.77). However, no significant change in the risk of AKI (aHR 1.16; 95% CI 0.98-1.38) was observed over the follow-up period (Supplementary Table S2 [24]).

## Subgroup Analyses

In the subgroup analyses of all-cause and cardiovascular mortality, the results were consistently favorable across almost all strata, supporting the use of RASi over nonuse. However, in the subgroup analyses for ESRD, a neutral risk was observed across almost all strata between RASi use and nonuse (Supplementary Table S3 [24]).

**Table 4. Association between cDDDs of RASi use and study outcomes among propensity score-matched patients with advanced stages 4-5 DKD**

| Taking nonuse as the reference | ESRD | | All-cause mortality | | Cardiovascular mortality | | Proteinuria | |
|---|---|---|---|---|---|---|---|---|
| | Events/N | aHR[a] (95% CI) | Events/N | aHR (95% CI) | Events/N | aHR (95% CI) | Events/N | aHR[b] (95% CI) |
| Median cDDD | | | | | | | | |
| ~by 3 layers | | | | | | | | |
| 1-150 | 170/972 | 1.08 (0.91, 1.30) | 286/972 | 0.99 (0.86, 1.14) | 122/972 | 1.27 (1.01, 1.59) | 514/972 | 1.31 (1.18, 1.46) |
| 151-400 | 109/731 | 0.69 (0.56, 0.85) | 92/731 | 0.31 (0.25, 0.38) | 34/731 | 0.34 (0.24, 0.49) | 457/731 | 1.35 (1.22, 1.51) |
| ≥401 | 160/493 | 1.31 (1.10, 1.57) | 84/493 | 0.28 (0.22, 0.35) | 41/493 | 0.40 (0.28, 0.58) | 301/493 | 1.27 (1.12, 1.44) |
| ~by 4 layers | | | | | | | | |
| 1-120 | 150/838 | 1.13 (0.94, 1.36) | 255/838 | 1.09 (0.94, 1.26) | 110/838 | 1.42 (1.12, 1.79) | 440/838 | 1.30 (1.16, 1.46) |
| 121-292 | 88/657 | 0.66 (0.53, 0.84) | 98/657 | 0.37 (0.30, 0.45) | 38/657 | 0.43 (0.30, 0.60) | 397/657 | 1.38 (1.23, 1.55) |
| 293-550 | 84/405 | 0.84 (0.66, 1.06) | 47/405 | 0.25 (0.18, 0.34) | 19/405 | 0.30 (0.18, 0.49) | 261/405 | 1.32 (1.16, 1.50) |
| ≥551 | 117/296 | 1.64 (1.34, 2.00) | 62/296 | 0.31 (0.24, 0.40) | 30/296 | 0.45 (0.30, 0.67) | 174/296 | 1.23 (1.05, 1.43) |
| Mean cDDD | | | | | | | | |
| ~by 3 layers | | | | | | | | |
| 1-100 | 132/708 | 1.22 (1.00, 1.48) | 229/708 | 1.18 (1.01, 1.37) | 103/708 | 1.58 (1.24, 2.00) | 362/708 | 1.28 (1.13, 1.45) |
| 101-250 | 85/640 | 0.69 (0.55, 0.87) | 108/640 | 0.44 (0.36, 0.54) | 39/640 | 0.47 (0.33, 0.66) | 386/640 | 1.39 (1.24, 1.56) |
| ≥251 | 222/848 | 1.08 (0.92, 1.27) | 125/848 | 0.28 (0.23, 0.34) | 55/848 | 0.37 (0.27, 0.50) | 524/848 | 1.29 (1.16, 1.43) |
| ~by 4 layers | | | | | | | | |
| 1-63 | 98/550 | 1.25 (1.00, 1.56) | 198/550 | 1.41 (1.20, 1.65) | 91/550 | 1.95 (1.52, 2.51) | 272/550 | 1.26 (1.10, 1.45) |
| 64-186 | 90/547 | 0.89 (0.71, 1.11) | 113/547 | 0.57 (0.47, 0.70) | 40/547 | 0.60 (0.43, 0.84) | 319/547 | 1.39 (1.23, 1.58) |
| 187-365 | 83/552 | 0.67 (0.53, 0.85) | 57/552 | 0.25 (0.19, 0.33) | 21/552 | 0.28 (0.18, 0.44) | 346/552 | 1.34 (1.19, 1.52) |
| ≥366 | 168/547 | 1.26 (1.05, 1.50) | 94/547 | 0.29 (0.23, 0.36) | 45/547 | 0.41 (0.29, 0.58) | 335/547 | 1.27 (1.12, 1.43) |

Abbreviations: aHR, adjusted hazard ratio; cDDD, cumulative define daily dose; ESRD, end-stage renal disease; RASi, renin–angiotensin–system inhibitor.
[a]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, (and competing risk for ESRD).
[b]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, (and competing risk for death and ESRD).

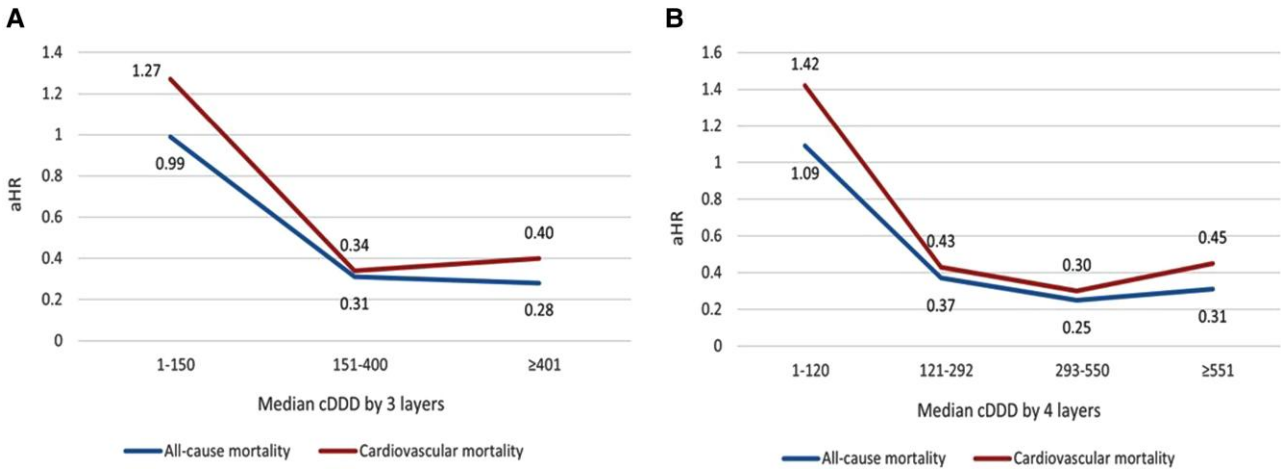


**Figure 2.** Dose–response relationship between the median dose of RASi, divided into (A) 3 layers and (B) 4 layers, and all-cause and cardiovascular mortality in propensity score-matched patients with advanced stages 4 to 5 diabetic kidney disease.

## Sensitivity Analyses

We performed various sensitivity analyses to ensure the robustness of the findings. Consistent associations between RASi use and reduced risks of all-cause and cardiovascular mortality, as well as a neutral risk of ESRD, were observed across different definitions of RASi use (Supplementary Table S4) [24]. Furthermore, these associations remained when excluding patients with advanced stages 4 to 5 DKD who died or developed ESRD within 30, 60, 90, and 180 days after the index date (Supplementary Table S5 [24]), excluding patients who had not been prescribed any RASi before the onset of advanced CKD (Supplementary Table S6 [24]), including only patients prescribed a RASi for at least 6 months (Supplementary Table S7 [24]) or within 6 months (Supplementary Table S8 [24]) before the onset of advanced CKD, accounting for 4 additional confounding drugs (antiplatelets, statins, beta-blockers,

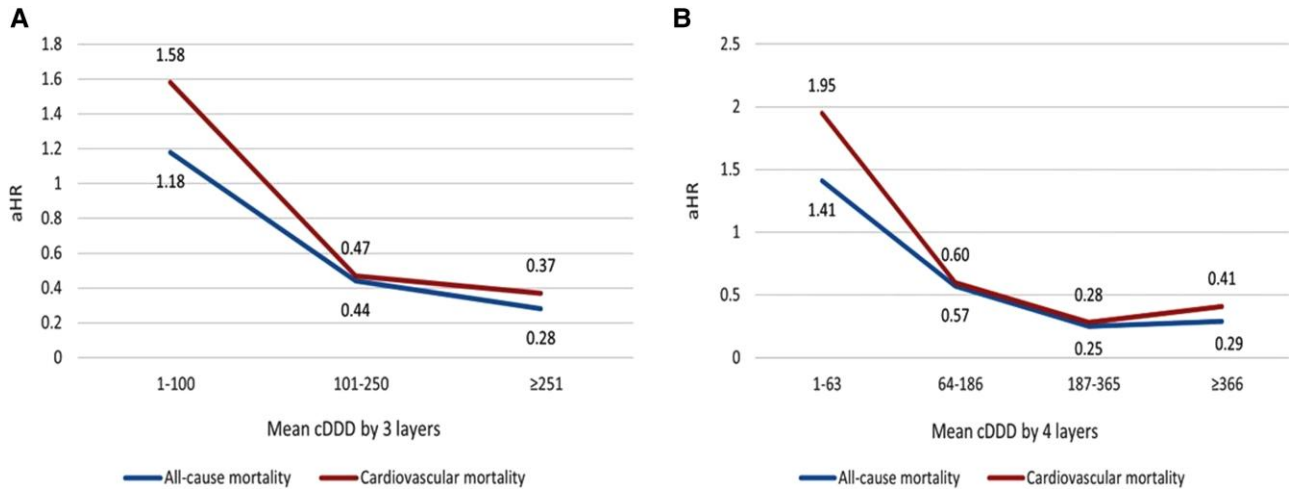


**Figure 3.** Dose–response relationship between the mean dose of RASi, divided into (A) 3 layers and (B) 4 layers, and all-cause and cardiovascular mortality in propensity score-matched patients with advanced stages 4 to 5 diabetic kidney disease.

**Table 5. Association between cumulative exposure duration of RASi use and risks of study outcomes at least >1 month of follow-up among propensity score-matched patients with advanced stages 4-5 DKD**

| Cumulative exposure in days | ESRD | | All-cause mortality | | Cardiovascular mortality | | Proteinuria | |
|---|---|---|---|---|---|---|---|---|
| | Events/N | aHR[a] (95% CI) | Events/N | aHR (95% CI) | Events/N | aHR (95% CI) | Events/N | aHR[b] (95% CI) |
| Nonuse | 267/1807 | 1.00 (reference) | 490/1938 | 1.00 (reference) | 163/1938 | 1.00 (reference) | 545/1425 | 1.00 (reference) |
| Use | | | | | | | | |
| ~by 3 layers | | | | | | | | |
| 1-100 | 83/576 | 1.23 (0.95, 1.57) | 200/623 | 1.38 (1.17, 1.63) | 94/623 | 1.87 (1.45, 2.42) | 174/437 | 1.24 (1.04, 1.48) |
| 101-250 | 62/614 | 0.70 (0.53, 0.92) | 108/637 | 0.55 (0.45, 0.68) | 39/637 | 0.58 (0.41, 0.82) | 215/452 | 1.31 (1.12, 1.54) |
| ≥251 | 168/794 | 1.09 (0.90, 1.32) | 125/848 | 0.33 (0.27, 0.40) | 55/848 | 0.44 (0.32, 0.60) | 319/597 | 1.32 (1.15, 1.51) |
| ~by 4 layers | | | | | | | | |
| 1-63 | 57/427 | 1.20 (0.90, 1.61) | 169/466 | 1.65 (1.39, 1.98) | 82/466 | 2.34 (1.78, 3.06) | 122/323 | 1.18 (0.97, 1.45) |
| 64-186 | 67/520 | 0.95 (0.73, 1.24) | 113/543 | 0.73 (0.59, 0.89) | 40/543 | 0.74 (0.52, 1.05) | 180/392 | 1.37 (1.16, 1.63) |
| 187-271 | 30/310 | 0.57 (0.39, 0.83) | 29/322 | 0.27 (0.19, 0.40) | 12/322 | 0.33 (0.19, 0.60) | 112/228 | 1.21 (0.99, 1.48) |
| ≥272 | 159/727 | 1.14 (0.93, 1.38) | 122/777 | 0.34 (0.28, 0.42) | 54/777 | 0.46 (0.33, 0.63) | 294/543 | 1.34 (1.17, 1.55) |

Abbreviations: aHR, adjusted hazard ratio; DKD, diabetic kidney disease; ESRD, end-stage renal disease; RASi, renin–angiotensin–system inhibitor.
[a]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, (and competing risk for ESRD).
[b]Adjusted for all covariates (age per year, sex, comorbidities, number of medical visits, Charlson comorbidity index, confounding drugs, (and competing risk for death and ESRD).

and sodium–glucose cotransporter 2 inhibitors) (Supplementary Tables S9 and 10 [24]) and 1 comorbidity chronic obstructive pulmonary disease (Supplementary Table S11 [24]), and conducting propensity matching of RASi users compared to nonusers at a ratio of 2:1 (Supplementary Tables S12-1, S12-2, S12-3, and S12-4 [24]). Finally, our investigation did not reveal any statistical association between RASi use and cancer occurrence, which served as a negative outcome in the assessment (Supplementary Fig. S1) [24].

## Discussion

To the best of our knowledge, this is the first extensive, long-term, retrospective cohort study to address the dose and time effects of RASi treatment on cardiorenal and survival outcomes in patients with advanced stages 4 to 5 DKD, with 23% in stage 4% and 77% in stage 5. This study demonstrated, with sufficient statistical power, that the use of RASi was associated with a 47% reduction in all-cause mortality and a 32% reduction in cardiovascular mortality, even in patients with stage 5 DKD. These cardiovascular and survival benefits were dose- and time-dependent, consistent across sensitivity and subgroup analyses, despite a nonsignificant increase in AKI risk and a significant increase in hyperkalemia risk. Additionally, RASis failed to reduce proteinuria and ESRD risks in these patients, regardless of treatment dose or duration. These results fill the current knowledge gap and provide insights into the cumulative dose and duration of RAS blockade in patients with advanced stages 4 to 5 DKD to strike a balance between hyperkalemia risk and cardiovascular and survival benefits.

Our patients with advanced stages 4 to 5 DKD, most of whom had stage 5 CKD, demonstrated a neutral risk of ESRD associated with the use of RASi, even in stage 5 CKD.

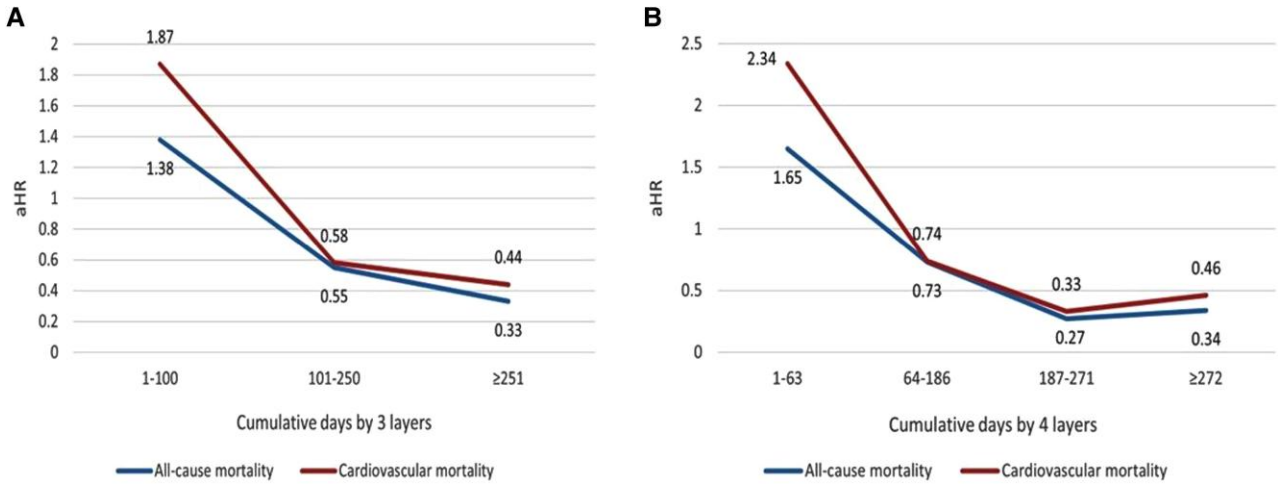


**Figure 4.** Time–response relationship between the cumulative days of RASi, divided into (A) 3 layers and (B) 4 layers, and all-cause and cardiovascular mortality in propensity score-matched patients with advanced stages 4 to 5 diabetic kidney disease.

This finding was in line with the results of 2 previous retrospective studies [10, 11] conducted in individuals with advanced CKD, where the mean eGFR was 24 to 25 mL/min/1.73 $m^2$, and 48% to 54% of participants had diabetes. Importantly, our analysis was the first to reveal that this neutral risk of ESRD was not influenced by the dosage or duration of RASi use over time in patients with advanced CKD, which is consistent with the experimental evidence [25]. Angiotensin II induces oxidative stress and possess pro-inflammatory, profibrotic, and proapoptotic properties [1, 2]. As advanced CKD progresses, overactivity of the RAS intensifies. Consequently, angiotensin II induction increases oxidative stress and inflammation, leading to a significant upregulation of angiotensin type 1 receptors within the inflamed interstitial areas [26]. This, in turn, triggers an enhanced production of angiotensin II by inflammatory cells, creating a self-propagating feedback loop that not only exacerbates oxidative stress but also perpetuates chronic inflammation and further upregulates transforming growth factor β-1 (TGF-β1) overexpression, culminating in irreversible interstitial fibrosis [26]. While a RASi can mitigate renal inflammation and suppress TGF-β1 overexpression, its maximum efficacy, even at maximal doses, achieves only a 45% reduction and falls short of normalizing the overproduction of TGF-β1 [25]. Furthermore, a RASi may not entirely suppress oxidative stress as renal injury progresses. Consequently, a RASi does not completely halt advanced CKD progression [25]. This can be further illustrated by our findings that RASis failed to significantly reduce proteinuria risk in advanced DKD. In advanced DKD, substantial proteinuria, often reaching nephrotic levels, underscores the pivotal role of podocytes in the progression of DKD [27] and significantly increases the risks of all-cause mortality and cardiovascular mortality [8]. Advanced DKD intensifies oxidative stress [28] and is marked by podocyte loss, as podocytes are particularly vulnerable to oxidative damage [29]. When podocyte loss exceeds 20%, it represents an irreversible stage in the pathogenesis of DKD, leading to glomerular scarring and eventual development of ESRD [27]. This suggests that a RASi does not halt the progression of proteinuria in advanced DKD and that the progression to ESRD is best mitigated when RASis are used before the onset of advanced stages 4 to 5 DKD. This progression occurs if patients with advanced DKD survive the high risks of all-cause mortality and cardiovascular mortality [8]. This could explain our non-significantly increased risk of ESRD after adjusting for competing mortality. Our sensitivity analyses (Supplementary tables 6-8) also revealed enhanced renal benefits among patients with advanced stages 4 to 5 DKD who were prescribed RASis for a minimum of 6 months or initiated RASi treatment within 6 months before the onset of advanced CKD, compared with those who began RASi treatment after the onset of advanced CKD. This finding indicates that the greatest benefits of RASis are achieved when administered early in the CKD course, in accordance with current treatment guidelines [7]. Our suggestion was augmented by a meta-analysis [30] involving 46 studies, with 44 focusing on patients with stages 1 to 3 DKD, 1 on patients with stages 1 to 4 DKD, and 1 on patients with stages 1 to 5 DKD. This report focusing on the majority of patients with stages 1 to 3 DKD indicated that compared with placebo, RASis reduced the continuous changes in serum creatinine and albuminuria levels and did not elevate the risks of kidney failure or doubling of serum creatinine.

Our patients with advanced stages 4 to 5 DKD, with the majority at stage 5 CKD, exhibited a reduction in all-cause and cardiovascular mortality risks associated with RASi use, even at stage 5 CKD. These findings are consistent with those of previous research [11, 12] that focused on patients with stage 4 CKD with 28% to 48% having diabetes. Notably, these cardiovascular and survival benefits were observed in a dose- and time-dependent manner, which was consistent with cumulative experimental evidence that RASi dose dependently improved survival in dogs with cardiac disease [31], suppressed the progression of cardiac hypertrophy and fibrosis [32], reduced aortic collagen content in the heart and aorta [33], decreased vascular oxidative stress [34], and prevented the time-dependent deterioration in left ventricular systolic function [35]. Diabetes, CKD, cardiovascular disease, and hypertension have been closely linked to upregulated systemic and local RAS [1, 3, 36], resulting in an increased production of angiotensin II. This may directly contribute to oxidative inflammatory stress and exacerbate endothelial dysfunction. Additionally, it leads to dose-dependent and time-dependent vascular remodeling [37], atherosclerosis, and

myocardial fibrosis through the dose-dependent and time-dependent upregulation of TGF-β1 [38, 39]. RASis, as demonstrated in experimental studies on DKD [3], diabetic atherosclerosis [3], human coronary artery endothelial cells [40], myocardial infarction rats [34], and human hypertension [41], have been shown to reduce oxidative stress. Therefore, this might contribute to a reduction in all-cause and cardiovascular mortality risk [42]. Diabetes and advanced CKD independently confer unfavorable cardiovascular mortality; however, this risk is significantly magnified when diabetes is coupled with advanced CKD [1]. Hence, patients with advanced stages 4 to 5 DKD have the potential to benefit from the cardioprotective effects of a more comprehensive RAS blockade using RASis through titration to the optimal dose. Our sensitivity analyses (Supplementary tables 6-8) further demonstrated that patients with advanced stages 4 to 5 DKD who initiated RASi treatment within 6 months before the onset of advanced CKD experienced the greatest cardiovascular and survival benefits. This was followed by those who were prescribed a RASi for a minimum of 6 months before the onset of advanced CKD, and finally, those who began RASi treatment after the onset of advanced CKD.

Studies [21, 43, 44] investigating the dose–response relationship of RASis with cardiorenal and survival outcomes have primarily focused on mild to moderate CKD. These studies, characterized by 8% to 63% diabetes prevalence and varying sample sizes, consistently indicated dose–dependent benefits in cardiovascular events [21, 43] and mortality [21], proteinuria reduction [44], ESRD [21], and all-cause mortality [21, 43]. However, evidence specifically targeting advanced DKD to ascertain the dose and time effects of RASi on cardiorenal and survival outcomes is lacking. This may be attributed to an increase in RASi-related adverse events, notably hyperkalemia [11, 14] and AKI, as DKD advances to stages 4 and 5 CKD, which subsequently leads to the underuse of RASi and necessitates the establishment of a sick-day plan [7]. However, it is important to note that this side effect is not the reason for discontinuing the use of RASis, as hyperkalemia does not increase mortality rates [7, 14] and can be mitigated by use of potassium-binding agents along with the concomitant administration of sodium bicarbonate and diuretics. Therefore, evaluating the cumulative dose and duration of RASi treatment rather than adhering to a fixed dose and duration in patients with advanced stages 4 to 5 DKD appears to be a reasonable approach. While there are currently no published guidelines specifically addressing RASi dosing for patients with advanced stages 4 to 5 DKD [43], our findings underscore the significance of appropriately implementing optimization and flexibility in RASi dosing to strike a balance between the potential for hyperkalemia and the advantages of mitigating cardiovascular and all-cause mortality. Customizing treatment plans through meticulous evaluation of hyperkalemia risk and cardiovascular benefits, coupled with regular monitoring of serum potassium levels, is imperative when employing RASis in the context of advanced stages 4 to 5 DKD.

The strengths of the study encompass several aspects: a nationally representative sample, providing strong statistical power and reliability of the findings; a comprehensive approach including study events and prescriptions to minimize potential information bias; the implementation of various sensitivity analyses to confirm result robustness; the use of propensity score matching to address confounding by indication; the incorporation of competing risk analysis to reduce the risk of overestimating ESRD risk; and an added layer of validity enhancement through the inclusion of a negative control outcome.

This study had some limitations. First, we failed to verify the actual intake of the RASi medications. Second, the NHI claims data did not include information on family history or the precise etiology of the primary kidney diseases. Moreover, crucial information concerning lifestyle factors (such as smoking, alcohol consumption, diet, and physical activity), body weight, blood pressure, glucose levels, and laboratory data (including serum creatinine, potassium, and proteinuria levels) was unavailable. The absence of these details may have contributed to the elevated risk of ESRD and mortality. The association between the dosage and duration of RASis and the severity of proteinuria outcome in advanced DKD could not be further explored. The risk of AKI may be underestimated as AKI was coded using ICD-9/10-CM. Nevertheless, when considering chronic obstructive pulmonary disease as a proxy for smoking [23], our main findings remained unchanged. A meta-analysis [45] on patients with nondialysis CKD showed that the effects of exercise, whether center-based, home-based, or combined, on all-cause mortality and eGFR did not differ significantly from usual care. Hence, it seemed that our main findings were minimally affected when smoking and exercise were not considered. High-protein diet increases intraglomerular pressure and glomerular hyperfiltration, resulting in increased release of TGF-β and subsequent progression of renal fibrosis and damage [46]. The protein source also plays a crucial role in DKD. There was a strong dose-dependent relationship with red meat intake and increased risk of ESRD [47]. Therefore, our main findings might be influenced when the amount and source of protein intake was not considered. Although several significant retrospective cohort studies in this field also did not incorporate blood pressure levels [14, 21] into their propensity score matching, we took into account hypertension (defined by ICD-9/10-CM codes or antihypertensives) and antihypertensive drugs in our propensity score matching. Following the propensity score matching, we successfully achieved balance between the 2 groups in terms of hypertension and antihypertensive drugs. Despite this limitation, the NHI claims data offers valuable reference for clinical physicians, especially in terms of dose and time effects, regarding the use of RASi in patients with advanced stages 4 to 5 DKD. Physicians are uncertain about the value of increasing the RASi dosage in patients with advanced stages 4 to 5 DKD, especially those in stage 5, and they struggle with the pivotal decision of determining the appropriate RASi dosage for this patient population. This important question appears to be currently unresolvable through 1 randomized controlled trial [20] on patients with advanced CKD due to an inadequate sample size and the need for longer-term follow-up. Therefore, the NHI claims data holds an advantage in evaluating the renal and survival effects of RASis in patients with advanced CKD [14] and in further extending the analysis of their cumulative dosage and time effects in patients with advanced stages 4 to 5 DKD in the current study. Finally, our study, being observational in nature, cannot establish causality and may have been influenced by unmeasured confounding variables. Therefore, they should not be regarded as a substitute for randomized trials.

## Conclusion

This study provides important real-world data and advocates for the ongoing use of RASis in patients with advanced stage 4 to 5 DKD, including those who were stage 5 DKD. This support is based on the observed dose- and time-dependent reduction in the risk of cardiovascular and all-cause mortality, notwithstanding a nonsignificant increase in the risks of ESRD and AKI and a significant rise in the risks of hyperkalemia and proteinuria. Frequent monitoring of serum potassium and consideration of potassium-binding agents should be implemented to continue RASi treatment for the preservation of cardiovascular health and survival benefits. Adopting a flexible approach to RASi treatment, rather than strictly adhering to a fixed dose and duration, seems to be a reasonable strategy for patients with advanced stages 4 to 5 DKD.

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## Author Contributions

Y.-C.C. and C.-H.T. designed the research; Y.-C.C. and B.-H.Y. performed the statistical analysis; Y.-C.C. wrote the paper; Y.-C.C., C.-H.T., and B.-H.Y. analyzed the data; Y.-C.C. supervised the study. All authors have read and agreed to the published version of the manuscript.

## Disclosures

The authors declare no conflict of interest.

## Data Availability

Restrictions apply to the availability of these data. Data were obtained from the National Health Insurance database and are available from the authors with the permission of the National Health Insurance Administration of Taiwan.

## Institutional Review Board Statement

Ethical review and approval were waived for this study and was exempt from full review by the Institutional Review Board of the Dalin Tzu Chi Hospital (B10804001).

## Informed Consent Statement

Patient consent was waived by both the National Health Insurance Administration and the Institutional Review Board of Buddhist Dalin Tzu Chi Hospital due to the deidentified database.

## References

1. Lim HS, MacFadyen RJ, Lip GY. Diabetes mellitus, the renin-angiotensin-aldosterone system, and the heart. *Arch Intern Med*. 2004;164(16):1737-1748.
2. Forbes JM, Coughlan MT, Cooper ME. Oxidative stress as a major culprit in kidney disease in diabetes. *Diabetes*. 2008;57(6):1446-1454.
3. Jha JC, Ho F, Dan C, Jandeleit-Dahm K. A causal link between oxidative stress and inflammation in cardiovascular and renal complications of diabetes. *Clin Sci (Lond)*. 2018;132(16):1811-1836.
4. Ravarotto V, Bertoldi G, Stefanelli LF, Nalesso F, Calò LA. Pathomechanism of oxidative stress in cardiovascularrenal remodeling and therapeutic strategies. *Kidney Res Clin Pract*. 2022;41(5):533-544.
5. Weinberg MS, Weinberg AJ, Zappe DH. Effectively targetting the renin-angiotensin-aldosterone system in cardiovascular and renal disease: rationale for using angiotensin II receptor blockers in combination with angiotensin-converting enzyme inhibitors. *J Renin Angiotensin Aldosterone Syst*. 2000;1(3):217-233.
6. Ouyang F, Cheng X, Zhou W, He J, Xiao S. Increased mortality trends in patients with chronic non-communicable diseases and comorbid hypertension in the United States, 2000-2019. *Front Public Health*. 2022;10:753861.
7. Morris S, Manickavasagam V. Advanced chronic kidney disease: considerations for renin-angiotensin system inhibitor use as disease processes. *Aust J Gen Pract*. 2023;52(4):209-213.
8. Cho S, Huh H, Park S, *et al.* Impact of albuminuria on the various causes of death in diabetic patients: a nationwide population-based study. *Sci Rep*. 2023;13(1):295.
9. Goldstein-Fuchs J, Kalantar-Zadeh K. Nutrition intervention for advanced stages of diabetic kidney disease. *Diabetes Spectr*. 2015;28(3):181-186.
10. Arora N, Katz R, Bansal N. ACE inhibitor/angiotensin receptor blocker use patterns in advanced CKD and risk of kidney failure and death. *Kidney Med*. 2020;2(3):248-257.
11. Qiao Y, Shin JI, Chen TK, *et al.* Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. *JAMA Intern Med*. 2020;180(5):718-726.
12. Fu EL, Evans M, Clase CM, *et al.* Stopping renin-angiotensin system inhibitors in patients with advanced CKD and risk of adverse outcomes: a nationwide study. *J Am Soc Nephrol*. 2021;32(2):424-435.
13. Yang A, Shi M, Lau ESH, *et al.* Clinical outcomes following discontinuation of renin-angiotensin-system inhibitors in patients with type 2 diabetes and advanced chronic kidney disease: a prospective cohort study. *EClinicalMedicine*. 2023;55:101751.
14. Hsu TW, Liu JS, Hung SC, *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):347-354.
15. Yu BH, Chen YC, Li YD, Chiou WY, Chen YC. No dose-response relationship of clarithromycin utilization on cardiovascular outcomes in patients with stable coronary heart disease: analysis of Taiwan's national health insurance claims data. *Front Cardiovasc Med*. 2022;9:1018194.
16. Chen YC, Su YC, Li CY, Wu CP, Lee MS. A nationwide cohort study suggests chronic hepatitis B virus infection increases the risk of end-stage renal disease among patients in Taiwan. *Kidney Int*. 2015;87(5):1030-1038.
17. Chen YC, Chen HT, Yeh CC, Hung SK, Yu BH. Four prescribed Chinese herbal medicines provide renoprotection and survival benefit without hyperkalemia risk in patients with advanced chronic kidney disease: a nationwide cohort study. *Phytomedicine*. 2022;95:153873.
18. Chen YC, Chiou WY, Yu BH. Impact of acid suppression therapy on renal and survival outcomes in patients with chronic kidney disease: a Taiwanese nationwide cohort study. *J Clin Med*. 2022;11(19):5612.
19. Chen HT, Yu BH, Yeh MH, Hung SK, Chen YC. Dose- and time-dependent renoprotection of *Angelica sinensis* in patients with chronic kidney disease: a longitudinal cohort study. *Front Pharmacol*. 2023;14:1153583.
20. Bhandari S, Mehta S, Khwaja A, *et al.* Renin-Angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med*. 2022;387(22):2021-2032.
21. Leon SJ, Whitlock R, Rigatto C, *et al.* Hyperkalemia-related discontinuation of renin-angiotensin-aldosterone system inhibitors and

clinical outcomes in CKD: a population-based cohort study. *Am J Kidney Dis*. 2022;80(2):164-173.e1.
22. Huang HK, Liu PPS, Lin SM, *et al*. Diabetes-related complications and mortality in patients with atrial fibrillation receiving different oral anticoagulants: a nationwide analysis. *Ann Intern Med*. 2022;175(4):490-498.
23. Stolt P, Bengtsson C, Nordmark B, *et al*. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis*. 2003;62(9):835-841.
24. Chen YC, Tung CH, Yu BH. data_repository/supplemental material.docx at depositar. Accessed May 23, 2024. https://demo.depositar.io/dataset/jes_data_repository_supplemental-material
25. Peters H, Border WA, Noble NA. Targeting TGF-beta overexpression in renal disease: maximizing the antifibrotic action of angiotensin II blockade. *Kidney Int*. 1998;54(5):1570-1580.
26. Fujihara CK, Velho M, Malheiros DMAC, Zatz R. An extremely high dose of losartan affords superior renoprotection in the remnant model. *Kidney Int*. 2005;67(5):1913-1924.
27. Mohandes S, Doke T, Hu H, Mukhi D, Dhillon P, Susztak K. Molecular pathways that drive diabetic kidney disease. *J Clin Invest*. 2023;133(4):e165654.
28. Wang N, Zhang C. Oxidative stress: a culprit in the progression of diabetic kidney disease. *Antioxidants (Basel)*. 2024;13(4):455.
29. Duni A, Liakopoulos V, Roumeliotis S, Peschos D, Dounousi E. Oxidative stress in the pathogenesis and evolution of chronic kidney disease: untangling Ariadne's thread. *Int J Mol Sci*. 2019;20(15):3711.
30. Alsalemi N, Sadowski CA, Elftouh N, *et al*. The effect of renin-angiotensin-aldosterone system inhibitors on continuous and binary kidney outcomes in subgroups of patients with diabetes: a meta-analysis of randomized clinical trials. *BMC Nephrol*. 2022;23(1):161.
31. Ward JL, Chou YY, Yuan L, Dorman KS, Mochel JP. Retrospective evaluation of a dose-dependent effect of angiotensin-converting enzyme inhibitors on long-term outcome in dogs with cardiac disease. *J Vet Intern Med*. 2021;35(5):2102-2111.
32. Nagai M, Horikoshi K, Izumi T, *et al*. Cardioprotective action of perindopril versus candesartan in renovascular hypertensive rats. *Cardiovasc Drugs Ther*. 2004;18(5):353-362.
33. Porteri E, Rodella L, Rizzoni D, *et al*. Effects of olmesartan and enalapril at low or high doses on cardiac, renal and vascular interstitial matrix in spontaneously hypertensive rats. *Blood Press*. 2005;14(3):184-192.
34. Khaper N, Singal PK. Modulation of oxidative stress by a selective inhibition of angiotensin II type 1 receptors in MI rats. *J Am Coll Cardiol*. 2001;37(5):1461-1466.
35. Runge MS, Patterson C. *Principles of Molecular Cardiology*. 1st ed. Humana; 2005:395.
36. Fanelli C, Zatz R. Linking oxidative stress, the renin-angiotensin system, and hypertension. *Hypertension*. 2011;57(3):373-374.
37. Imanishi T, Hano T, Nishio I. Angiotensin II potentiates vascular endothelial growth factor-induced proliferation and network formation of endothelial progenitor cells. *Hypertens Res*. 2004;27(2):101-108.
38. Chua CC, Diglio CA, Siu BB, Chua BH. Angiotensin II induces TGF-beta 1 production in rat heart endothelial cells. *Biochim Biophys Acta*. 1994;1223(1):141-147.
39. Lijnen PJ, Petrov VV, Fagard RH. Induction of cardiac fibrosis by angiotensin II. *Methods Find Exp Clin Pharmacol*. 2000;22(10):709-723.
40. Shi X, Guan Y, Jiang S, Li T, Sun B, Cheng H. Renin-angiotensin system inhibitor attenuates oxidative stress induced human coronary artery endothelial cell dysfunction via the PI3K/AKT/mTOR pathway. *Arch Med Sci*. 2019;15(1):152-164.
41. Dohi Y, Ohashi M, Sugiyama M, Takase H, Sato K, Ueda R. Candesartan reduces oxidative stress and inflammation in patients with essential hypertension. *Hypertens Res*. 2003;26(9):691-697.
42. Ahmed A, Jorna T, Bhandari S. Should we STOP angiotensin converting enzyme inhibitors/angiotensin receptor blockers in advanced kidney disease? *Nephron*. 2016;133(3):147-158.
43. Linde C, Bakhai A, Furuland H, *et al*. Real-world associations of renin-angiotensin-aldosterone system inhibitor dose, hyperkalemia, and adverse clinical outcomes in a cohort of patients with new-onset chronic kidney disease or heart failure in the United Kingdom. *J Am Heart Assoc*. 2019;8(22):e012655.
44. Kitamura M, Arai H, Abe S, *et al*. Renal outcomes of treatment with telmisartan in patients with stage 3-4 chronic kidney disease: a prospective, randomized, controlled trial (JINNAGA). *SAGE Open Med*. 2020;8:2050312120973502.
45. Nakamura K, Sasaki T, Yamamoto S, Hayashi H, Ako S, Tanaka Y. Effects of exercise on kidney and physical function in patients with non-dialysis chronic kidney disease: a systematic review and meta-analysis. *Sci Rep*. 2020;10(1):18195.
46. Kitada M, Ogura Y, Monno I, Koya D. A low-protein diet for diabetic kidney disease: its effect and molecular mechanism, an approach from animal studies. *Nutrients*. 2018;10(5):544.
47. Lew QJ, Jafar TH, Koh HW, *et al*. Red meat intake and risk of ESRD. *J Am Soc Nephrol*. 2017;28(1):304-312.