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Leiden  
The Netherlands

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Fu, E.L.; Clase, C.M.; Evans, M.; Lindholm, B.; Rotmans, J.I.; Dekker, F.W.; ... ; Carrero, J.J.

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# Comparative Effectiveness of Renin-Angiotensin System Inhibitors and Calcium Channel Blockers in Individuals With Advanced CKD: A Nationwide Observational Cohort Study



Edouard L. Fu, Catherine M. Clase, Marie Evans, Bengt Lindholm, Joris I. Rotmans, Friedo W. Dekker, Merel van Diepen, and Juan-Jesus Carrero

**Rationale & Objective:** It is unknown whether initiating renin-angiotensin system (RAS) inhibitor therapy in patients with advanced chronic kidney disease (CKD) is superior to alternative antihypertensive agents such as calcium channel blockers (CCBs). We compared the risks for kidney replacement therapy (KRT), mortality, and major adverse cardiovascular events (MACE) in patients with advanced CKD in routine nephrology practice who were initiating either RAS inhibitor or CCB therapy.

**Study Design:** Observational study in the Swedish Renal Registry, 2007 to 2017.

**Settings & Participants:** 2,458 new users of RAS inhibitors and 2,345 CCB users with estimated glomerular filtration rates < 30 mL/min/1.73 m<sup>2</sup> (CKD G4-G5 without KRT) who were being followed up by a nephrologist. As a positive control cohort, new users of the same drugs with CKD G3 (estimated glomerular filtration rate, 30-60 mL/min/1.73 m<sup>2</sup>) were evaluated.

**Exposures:** RAS inhibitor versus CCB therapy initiation.

**Outcome:** Initiation of KRT (maintenance dialysis or transplantation), all-cause mortality, and MACE

(composite of cardiovascular death, myocardial infarction, or stroke).

**Analytical Approach:** HRs with 95% CIs were estimated using propensity score-weighted Cox proportional hazards regression adjusting for demographic, clinical, and laboratory covariates.

**Results:** Median age was 74 years, 38% were women, and median follow-up was 4.1 years. After propensity score weighting, there was significantly lower risk for KRT after new use of RAS inhibitors compared with new use of CCBs (adjusted HR, 0.79 [95% CI, 0.69-0.89]) but similar risks for mortality (adjusted HR, 0.97 [95% CI, 0.88-1.07]) and MACE (adjusted HR, 1.00 [95% CI, 0.88-1.15]). Results were consistent across subgroups and in as-treated analyses. The positive control cohort of patients with CKD G3 showed similar KRT risk reduction (adjusted HR, 0.67 [95% CI, 0.56-0.80]) with RAS inhibitor therapy compared with CCBs.

**Limitations:** Potential confounding by indication.

**Conclusions:** Our findings provide evidence from real-world clinical practice that initiation of RAS inhibitor therapy compared with CCBs may confer kidney benefits among patients with advanced CKD, with similar cardiovascular protection.

## Visual Abstract online

Complete author and article information provided before references.

Correspondence to E.L. Fu (e.l.fu@lumc.nl)

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Randomized trials of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), collectively renin-angiotensin system (RAS) inhibitors, have shown that these drugs are more effective in delaying the progression of chronic kidney disease (CKD) than placebo or alternative agents such as diuretics,  $\beta$ -blockers, or calcium channel blockers (CCBs).<sup>1-6</sup> Clinical guidelines recommend RAS inhibitors as the first-line pharmacologic antihypertensive treatment strategy in patients with CKD glomerular filtration rate (GFR) categories 1-3 (G1-G3) and proteinuria, with or without diabetes.<sup>7-9</sup>

However, there is less evidence on the benefits of RAS inhibitor therapy in patients with CKD G4-G5, a population that was underrepresented in pivotal trials.<sup>3,10-15</sup> A small randomized trial<sup>16</sup> and various observational studies<sup>17-20</sup> suggest that RAS inhibitors confer renoprotection compared with placebo or no use, but no data exist

to inform the choice of RAS inhibitor therapy over alternative antihypertensive agents. This, together with concerns about the persistent hemodynamic effects of RAS inhibition,<sup>21,22</sup> may lead to underuse of these medications in advanced CKD.<sup>23,24</sup> Recent studies indicate that a substantial proportion of individuals with CKD G3-G5 do not receive inhibitor therapy.<sup>23-25</sup> A recent National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) controversies report<sup>14</sup> identified the lack of comparative effectiveness data as a critical knowledge gap and emphasized the need for further studies to inform practice.

CCBs are also frequently prescribed to treat hypertension, especially in patients with CKD.<sup>26-28</sup> Although CCBs were used as an active comparator to RAS inhibitors in trials such as AASK (African American Study of Kidney Disease and Hypertension) or IDNT (Irbesartan Diabetic

### PLAIN-LANGUAGE SUMMARY

There is uncertainty regarding the best antihypertensive medications to use in patients with advanced chronic kidney disease (CKD) because they are often excluded from clinical trials. In a population-based Swedish database, we studied the clinical outcomes of starting renin-angiotensin system (RAS) inhibitor or calcium channel blocker (CCB) therapy in patients with advanced CKD who were using neither and were followed up by a nephrologist. Compared with CCBs, RAS inhibitor therapy initiation was associated with lower risk for kidney replacement therapy but similar risks for mortality and major adverse cardiovascular events. These findings suggest that RAS inhibitor therapy initiation might slow the progression of kidney disease compared with CCBs in patients with advanced CKD and offer similar cardiovascular protection.

Nephropathy Trial),<sup>4,11</sup> these trials included very few patients with advanced CKD to allow for stratification. In the absence of trial evidence, observational studies in patients cared for in routine clinical practice can provide insights into the relative efficacy of medications. To fill this knowledge gap, we studied kidney and cardiovascular outcomes in patients with advanced CKD who initiated RAS inhibitor or CCB therapy.

## Methods

### Data Sources

We conducted an observational cohort study using data from the Swedish Renal Registry (SRR), a nationwide registry including patients with CKD G3-G5 under nephrologist care.<sup>29,30</sup> The SRR includes information on outpatient visits, including laboratory tests and results from clinical examination. According to the guidelines of the registry, patients with estimated GFR (eGFR) < 30 mL/min/1.73 m<sup>2</sup> should be enrolled. Registrations of subsequent outpatient visits to nephrology care are thereafter performed until death, emigration from the country, or start of kidney replacement therapy (KRT). Nearly all nephrology clinics in Sweden (96%) report to the SRR-CKD and the estimated national coverage is 75% to 90% of nephrologist-referred patients with recognized CKD G4-G5.<sup>31</sup>

Using each citizen's unique personal identification number, the SRR-CKD was linked to other national registries. The Swedish Prescribed Drug Register provided complete information on all prescribed drugs dispensed at Swedish pharmacies.<sup>33,32</sup> The Swedish Patient Register added information on all outpatient specialist consultations and hospitalizations occurring in Swedish health care and was used to obtain information on comorbid conditions and outcomes.<sup>33</sup> The Swedish Cause of Death Register

added information on date and causes of death.<sup>34</sup> All these registers are run by the Swedish National Board of Welfare and are considered to have no or minimal loss to follow-up. We used deidentified data and the study was approved by the regional ethical review boards and the Swedish National Board of Welfare and was judged not to require informed consent.

### Patient Selection and Study Design

We created a cohort of all adult (aged ≥18 years) patients in the SRR-CKD newly initiating therapy with a RAS inhibitor or CCB between January 1, 2007, and December 31, 2016. New users were defined as individuals receiving a RAS inhibitor or CCB without dispensation of either drug in the previous 6 months. Prevalent users of these drugs were excluded to prevent prevalent user bias.<sup>35</sup> We further excluded all individuals with a history of kidney transplantation, eGFR > 30 mL/min/1.73 m<sup>2</sup>, or those initiating treatment with both drugs simultaneously.

The date of initiation was defined as the index date of the study and start of follow-up. Patients were followed up from index date to first occurrence of a study outcome or end of follow-up (June 1, 2017). eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation from routine plasma creatinine measurements performed using enzymatic or corrected Jaffé methods traceable to isotope-dilution mass spectroscopy standards. Information on race is not available in Sweden by law; we assumed that all patients were of European ancestry.

### Study Exposure and Covariates

The exposure of interest was RAS inhibitor therapy initiation compared with initiation of CCB therapy. Baseline covariates included age, sex, eGFR, comorbid conditions (diabetes mellitus, myocardial infarction, heart failure, arrhythmia, peripheral vascular disease, cerebrovascular disease, and ischemic heart disease), medications (β-blocker, thiazide diuretic, loop diuretic, potassium-sparing diuretic, potassium binder, nonsteroidal anti-inflammatory drug, and statin), systolic blood pressure, diastolic blood pressure, urinary albumin-creatinine ratio (UACR), and potassium level. In addition, we considered other covariates in an attempt to evaluate reasons that led to the use of either medication: the rate of eGFR decline before therapy initiation, occurrence of a cardiovascular-related hospitalization in the preceding 6 months, number of overall hospitalizations in the year prior, and history of hyperkalemia or acute kidney injury (AKI). Covariate definitions are detailed in [Table S1](#).

### Study Outcomes

The primary study outcome was initiation of KRT, defined as the date of start of maintenance dialysis or kidney transplantation as registered in the SRR. Secondary outcomes were all-cause mortality and major adverse cardiovascular events (MACE), defined as a composite of

cardiovascular death (International Classification of Diseases, Tenth Revision code of the I family as main cause of death), hospitalization due to stroke (I63), or myocardial infarction (I21-I23). For the analysis of mortality and MACE, KRT was not considered a censoring event. In addition, we reported information about hospitalizations for hyperkalemia and AKI after medication initiation.

### Statistical Analysis

We combined outcome regression with inverse probability of treatment weighting (IPTW) to control for confounding.<sup>36</sup> A multivariable logistic regression model was used to calculate the probability of receiving RAS inhibitor (vs CCB) therapy as a function of baseline covariates. Weighting was considered appropriate if the standardized mean difference between treatment groups was <0.1. Weights were stabilized to increase precision by adding the marginal probability of treatment to the numerator of the weights. Robust variance estimation was used to calculate CIs after weighting. We assessed the association between RAS inhibitor use compared with CCB use on outcomes using multivariable cause-specific Cox proportional hazards regression in the inverse probability-weighted sample, additionally adjusting for all baseline covariates.

In addition, we estimated adjusted cumulative incidence curves standardized to the distribution of the baseline variables in the study population. To do so, we fitted a weighted pooled logistic model including an indicator for treatment, month and its quadratic term, all baseline confounders, and interactions between treatment and time.<sup>37</sup> Interaction terms were included to allow for nonproportional hazards.<sup>38</sup> The predicted probabilities from this logistic model were used to estimate the adjusted absolute risks for KRT, mortality, and MACE, which were then standardized to the baseline distribution of confounders.

For calculation of the cumulative incidence of KRT and MACE, we took into account the competing risk for (noncardiovascular) death.<sup>39-41</sup> Pointwise 95% CIs for the cumulative incidence curves were calculated using nonparametric bootstrap based on 500 full samples. In primary analyses, we adopted an intention-to-treat approach and analyzed patients according to their initially assigned treatment group irrespective of discontinuation or treatment switch. Next, we examined whether there was an interaction between treatment effect and the following variables, according to a priori-defined strata: age ( $\geq 70$  vs  $< 70$  years), sex, diabetes, myocardial infarction, heart failure, systolic blood pressure ( $\geq 140$  vs  $< 140$  mm Hg), eGFR ( $\geq 15$  vs  $< 15$  mL/min/1.73 m<sup>2</sup>), and UACR ( $\geq 70$  vs  $< 70$  mg/mmol). To calculate subgroup hazard ratios (HRs), we separately estimated the propensity score model and Cox model in each subgroup.<sup>42</sup> Multiplicative interaction was tested by including interaction terms

between treatment and the variable of interest to the Cox model.

Multiple imputation by chained equations was used to impute missing data on systolic and diastolic blood pressure (missing for 2.3% of patients). Treatment, confounding variables, outcomes, and interaction terms between treatment and confounders were used in the imputation model to derive 50 imputed data sets.<sup>43</sup> eGFR was non-normally distributed and was log-transformed before imputation. Multiple imputation was combined with IPTW using the within method.<sup>44</sup> In the within method, effect estimates are obtained separately in each imputation using the propensity score, which are then combined to an overall estimate. The within method has been shown to produce unbiased estimates with appropriate CIs compared with the across approach.<sup>44</sup>

We performed several sensitivity analyses to test the robustness of our results. First, we additionally adjusted our analyses for plasma potassium and UACR values. These variables were missing for a large proportion of patients (32% and 41%, respectively) because it was not mandatory to report these measures. Those with missing UACR measurements had similar characteristics as those without missing UACR measurements and we assumed data to be missing at random (Table S2). We used multiple imputation with chained equations, a technique well suited to impute data that are missing at random.

Second, we redefined new users as those not using RAS inhibitors and CCBs for at least 12 months. Third, we replicated our analyses in a positive control cohort of patients with CKD G3, for which we expected a reduction in KRT initiation consistent with previously conducted randomized trials.<sup>3,45-47</sup> Fourth, we performed an as-treated analysis in which patients were censored at the time of therapy discontinuation (no dispensation for the index drug within 60 days after the estimated last day of pill supply from the previous drug dispensation), treatment switch (on the day RAS inhibitor was added to CCB or vice versa), or at the end of the study period. To account for potential informative censoring due to discontinuation or treatment switch, inverse probability of censoring weighting was applied (see Item S1 for details). Fifth, we used incident cancer diagnosis as a negative control outcome to study the influence of potential unmeasured confounders (such as smoking and alcohol use) on our effect estimates. Although unmeasured confounders may predict the risk for cancer, we did not expect initiation of RAS inhibitors or CCBs to cause or prevent cancer.<sup>48</sup> For this analysis, we excluded patients with a recent cancer diagnosis (within 2 years from index date). Last, we repeated our analysis adding heart failure-related hospitalization (I50) as an outcome in the composite of MACE. All analyses were performed using R, version 3.6.2 (R Foundation for Statistical Computing).

**Table 1.** Baseline Characteristics of Patients With Advanced CKD by RAS Inhibitor or CCB Treatment Before and After Inverse Probability Weighting

|   | Unweighted       |                 |                       | Weighted <sup>a</sup> |                 |                       |
|---|------------------|-----------------|-----------------------|-----------------------|-----------------|-----------------------|
|   | RASi (n = 2,458) | CCB (n = 2,345) | Std Diff <sup>b</sup> | RASi (n = 2,473)      | CCB (n = 2,330) | Std Diff <sup>b</sup> |
| Age, <sup>c</sup> y                           | 73 [62-80]       | 74 [66-81]      | 0.22                  | 74 [64-80]            | 73 [64-80]      | 0.00                  |
| Age category                                  |                  |                 |                       |                       |                 |                       |
| <50 y   | 303 (12.3%)      | 159 (6.8%)      | 0.19                  | 238 (9.6%)            | 210 (9.0%)      | 0.02                  |
| 50-59 y                                       | 226 (9.2%)       | 189 (8.1%)      | 0.04                  | 195 (7.9%)            | 217 (9.3%)      | 0.05                  |
| 60-69 y                                       | 461 (18.8%)      | 443 (18.9%)     | 0.00                  | 477 (19.3%)           | 454 (19.5%)     | 0.01                  |
| 70-79 y                                       | 826 (33.6%)      | 805 (34.3%)     | 0.01                  | 871 (35.2%)           | 800 (34.4%)     | 0.02                  |
| ≥80 y   | 642 (26.1%)      | 749 (31.9%)     | 0.13                  | 692 (28.0%)           | 649 (27.8%)     | 0.00                  |
| Female sex                                    | 909 (37.0%)      | 906 (38.6%)     | 0.03                  | 950 (38.4%)           | 898 (38.5%)     | 0.00                  |
| eGFR, <sup>c</sup> mL/min/1.73 m <sup>2</sup> | 22 [17-26]       | 18 [13-24]      | 0.41                  | 20 [15-25]            | 20 [15-25]      | 0.00                  |
| eGFR category                                 |                  |                 |                       |                       |                 |                       |
| <15 mL/min/1.73 m <sup>2</sup>                | 399 (16.2%)      | 727 (31.0%)     | 0.35                  | 657 (25.4%)           | 678 (27.0%)     | 0.04                  |
| 15-30 mL/min/1.73 m <sup>2</sup>              | 2059 (83.8%)     | 1614 (68.8%)    | 0.36                  | 1816 (74.6%)          | 1652 (73.0%)    | 0.04                  |
| SBP, <sup>c</sup> mm Hg                       | 133 [120-146]    | 144 [130-160]   | 0.51                  | 140 [125-155]         | 140 (125-154)   | 0.00                  |
| SBP category                                  |                  |                 |                       |                       |                 |                       |
| <120 mm Hg                                    | 486 (19.8%)      | 161 (6.9%)      | 0.39                  | 333 (13.5%)           | 304 (13.0%)     | 0.02                  |
| 120-139 mm Hg                                 | 934 (38.0%)      | 689 (29.4%)     | 0.18                  | 842 (34.1%)           | 801 (34.4%)     | 0.01                  |
| 140-159 mm Hg                                 | 661 (26.9%)      | 804 (34.3%)     | 0.16                  | 774 (31.3%)           | 740 (31.8%)     | 0.01                  |
| >160 mm Hg                                    | 323 (13.1%)      | 633 (27.0%)     | 0.35                  | 524 (21.2%)           | 485 (20.8%)     | 0.01                  |
| Missing                                       | 54 (2.2%)        | 58 (2.5%)       | 0.02                  | —                     | —               | —                     |
| DBP, <sup>c</sup> mm Hg                       | 78 [70-84]       | 80 [70-89]      | 0.28                  | 80 [70-85]            | 80 [70-85]      | 0.00                  |
| DBP category                                  |                  |                 |                       |                       |                 |                       |
| <80 mm Hg                                     | 1,264 (51.4%)    | 942 (40.2%)     | 0.23                  | 1,156 (46.7%)         | 1,077 (46.2%)   | 0.01                  |
| 80-89 mm Hg                                   | 776 (31.6%)      | 783 (33.4%)     | 0.04                  | 847 (34.3%)           | 772 (33.1%)     | 0.03                  |
| 90-99 mm Hg                                   | 260 (10.6%)      | 380 (16.2%)     | 0.16                  | 323 (13.1%)           | 330 (14.2%)     | 0.03                  |
| >100 mm Hg                                    | 104 (4.2%)       | 182 (7.8%)      | 0.15                  | 147 (6.0%)            | 151 (6.5%)      | 0.02                  |
| Missing                                       | 54 (2.2%)        | 58 (2.5%)       | 0.02                  | —                     | —               | —                     |
| UACR, <sup>c</sup> mg/mmol                    | 24 [5-95]        | 33 [9-116]      | 0.12                  | 29 [7-111]            | 29 [7-113]      | 0.00                  |
| UACR category                                 |                  |                 |                       |                       |                 |                       |
| A1: <3 mg/mmol                                | 276 (11.2%)      | 150 (6.4%)      | 0.17                  | 373 (15.1%)           | 342 (14.7%)     | 0.01                  |
| A2: 3-29 mg/mmol                              | 542 (22.1%)      | 483 (20.6%)     | 0.04                  | 880 (35.6%)           | 829 (35.6%)     | 0.00                  |
| A3: 30-69 mg/mmol                             | 240 (9.8%)       | 204 (8.7%)      | 0.04                  | 400 (16.2%)           | 383 (16.4%)     | 0.01                  |
| A3: ≥70 mg/mmol                               | 461 (18.8%)      | 472 (20.1%)     | 0.03                  | 820 (33.2%)           | 776 (33.3%)     | 0.00                  |
| Missing                                       | 939 (38.2%)      | 1,036 (44.2%)   | 0.12                  | —                     | —               | —                     |
| Potassium, <sup>a,c</sup> mmol/L              | 4.4 [4.1-4.8]    | 4.3 [4.0-4.7]   | 0.15                  | 4.4 [4.0-4.7]         | 4.4 [4.0-4.7]   | 0.00                  |
| Comorbid conditions                           |                  |                 |                       |                       |                 |                       |
| DM  | 916 (37.3%)      | 734 (31.3%)     | 0.13                  | 851 (34.4%)           | 833 (35.8%)     | 0.03                  |
| MI  | 423 (17.2%)      | 353 (15.1%)     | 0.06                  | 398 (16.1%)           | 361 (15.5%)     | 0.02                  |
| HF  | 580 (23.6%)      | 320 (13.6%)     | 0.26                  | 457 (18.5%)           | 420 (18.0%)     | 0.01                  |
| Arrhythmia                                    | 469 (19.1%)      | 316 (13.5%)     | 0.15                  | 416 (16.8%)           | 395 (17.0%)     | 0.00                  |
| PVD   | 313 (12.7%)      | 312 (13.3%)     | 0.02                  | 330 (13.3%)           | 313 (13.5%)     | 0.00                  |
| CBVD  | 294 (12.0%)      | 327 (13.9%)     | 0.06                  | 321 (13.0%)           | 311 (13.3%)     | 0.01                  |
| IHD   | 691 (28.1%)      | 574 (24.5%)     | 0.08                  | 657 (26.6%)           | 617 (26.5%)     | 0.00                  |
| Medication                                    |                  |                 |                       |                       |                 |                       |
| β-Blockers                                    | 1,443 (58.7%)    | 1,586 (67.6%)   | 0.19                  | 1,563 (63.2%)         | 1,486 (63.8%)   | 0.01                  |
| Thiazides                                     | 79 (3.2%)        | 66 (2.8%)       | 0.02                  | 71 (2.9%)             | 70 (3.0%)       | 0.01                  |
| Loop diuretics                                | 1,613 (65.6%)    | 1,395 (59.5%)   | 0.13                  | 1,551 (62.7%)         | 1,463 (62.8%)   | 0.00                  |
| Potassium-sparing diuretics                   | 167 (6.8%)       | 114 (4.9%)      | 0.08                  | 136 (5.5%)            | 121 (5.2%)      | 0.01                  |
| Potassium binders                             | 242 (9.8%)       | 240 (10.2%)     | 0.01                  | 254 (10.2%)           | 216 (9.3%)      | 0.03                  |
| NSAIDs  | 103 (4.2%)       | 90 (3.8%)       | 0.02                  | 101 (4.1%)            | 92 (4.0%)       | 0.01                  |
| Statins                                       | 1,270 (51.7%)    | 1,121 (47.8%)   | 0.08                  | 1,232 (49.8%)         | 1,167 (50.1%)   | 0.01                  |
| Hospitalizations                              |                  |                 |                       |                       |                 |                       |
| Any hospitalization in previous y             | 1,084 (44.1%)    | 1,254 (53.5%)   | 0.19                  | 1,210 (48.9%)         | 1,138 (48.8%)   | 0.00                  |

(Continued)

**Table 1 (Cont'd).** Baseline Characteristics of Patients With Advanced CKD by RAS Inhibitor or CCB Treatment Before and After Inverse Probability Weighting

|  | Unweighted       |                 |                       | Weighted <sup>a</sup> |                 |                       |
|--|------------------|-----------------|-----------------------|-----------------------|-----------------|-----------------------|
|  | RASi (n = 2,458) | CCB (n = 2,345) | Std Diff <sup>b</sup> | RASi (n = 2,473)      | CCB (n = 2,330) | Std Diff <sup>b</sup> |
| CV hospitalization in previous 6 mo                | 249 (10.1%)      | 231 (9.9%)      | 0.01                  | 251 (10.1%)           | 229 (9.8%)      | 0.01                  |
| Hyperkalemia hospitalization                       | 35 (1.4%)        | 39 (1.7%)       | 0.02                  | 38 (1.5%)             | 37 (1.6%)       | 0.00                  |
| AKI hospitalization                                | 125 (5.1%)       | 213 (9.1%)      | 0.16                  | 187 (7.6%)            | 169 (7.2%)      | 0.01                  |
| Previous eGFR decline, mL/min/1.73 m <sup>2d</sup> | -2.03 (0.08)     | -1.98 (0.08)    | 0.02                  | —                     | —               | —                     |

Unless otherwise indicated, values for continuous variables given as median [interquartile range]; for categorical variables, as count (percentage). Abbreviations: AKI, acute kidney injury; CBVD, cerebrovascular disease; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; IHD, ischemic heart disease; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PVD, peripheral vascular disease; RASi, renin-angiotensin system inhibitor; SBP, systolic blood pressure; Std Diff, standardized difference; UACR, urinary albumin-creatinine ratio.

<sup>a</sup>Inverse probability weighting was performed after imputation. Baseline characteristics are shown after imputation and weighting (marked with<sup>a</sup>).

<sup>b</sup>Std diff > 0.1 indicates meaningful imbalance between groups.

<sup>c</sup>Std diff for the mean was calculated for age, eGFR, blood pressure, UACR, and potassium.

<sup>d</sup>Calculated in the overall population on all previous eGFR assessments with a linear mixed model containing fixed effects for time, treatment, and time-treatment interaction and random intercept and slope. Value in parentheses is standard error.

## Results

### Cohort Characteristics

We identified 21,065 patients under nephrologist care with eGFR < 30 mL/min/1.73 m<sup>2</sup> and no history of KRT. Of these, 13,896 (66%) were prevalent users of RAS inhibitors or CCBs and were excluded. We further excluded 1,913 patients who received neither of these drugs during observation and 453 patients who were prescribed both medications simultaneously. The final study cohort consisted of 4,803 patients: 2,458 (51%) who initiated RAS inhibitor therapy and 2,345 (49%) who initiated CCB therapy (Fig S1). Of patients initiating RAS inhibitor therapy, most initiated enalapril (37.2%), candesartan (23.4%), losartan (21.4%), or ramipril (9.6%) therapy. In total, 249 of 2,458 (10.1%) individuals initiating RAS inhibitor therapy had a cardiovascular hospitalization in the 6 months before initiation, 129 (5.2%) due to heart failure and 37 (1.5%) due to myocardial infarction. Five people initiated dual RAS blockade with an ACE inhibitor and ARB. Most patients initiating CCB therapy used a dihydropyridine CCB (97.7%), mainly amlodipine (55.4% of total CCB initiators) or felodipine (36.9%). In total, 231 of 2,345 (9.9%) individuals initiating CCB therapy had a cardiovascular hospitalization in the 6 months before initiation, 49 (2.1%) due to heart failure and 32 (1.4%) due to myocardial infarction.

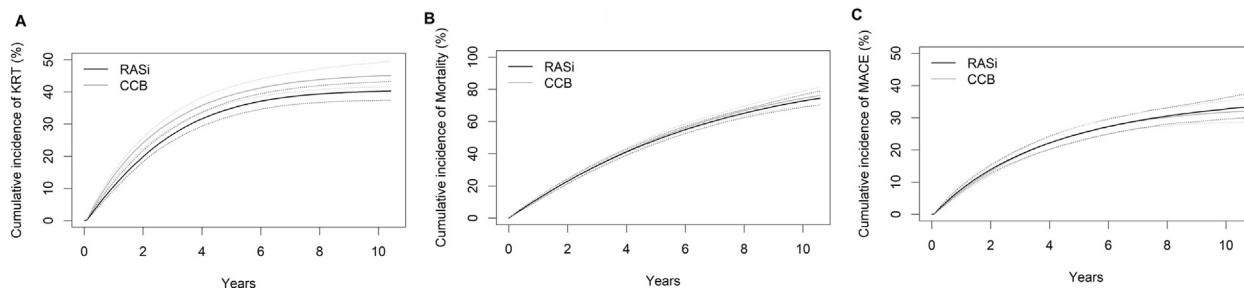
Overall, study participants had a median age of 74 (interquartile range [IQR], 64-81) years and 38% were women. Median eGFR was 20 (IQR, 15-21) mL/min/1.73 m<sup>2</sup>, median UACR was 28 (IQR, 7-108) mg/mmol, median systolic blood pressure was 140 (IQR, 125-153) mm Hg, and median diastolic blood pressure was 80 (IQR, 70-85) mm Hg. The most common comorbid conditions were diabetes (34%), ischemic heart disease (26%), and heart failure (19%). Concurrent use of  $\beta$ -blockers (63%), loop diuretics (63%), and statins (50%) was prevalent. At baseline, patients who initiated RAS inhibitor therapy,

compared with those initiating CCB therapy, had higher eGFR, lower systolic blood pressures and UACRs, and higher prevalence of comorbid conditions such as diabetes, heart failure, and arrhythmia. After weighting, all baseline covariates appeared well balanced between treatment groups (standardized differences < 0.1; Table 1).

### Comparative Effectiveness of RAS Inhibitor Versus CCB Initiation

Median follow-up was 4.1 (95% CI, 3.9-4.2) years, maximum follow-up was 10.4 years, and total follow-up time of the cohort was 14,682 person-years. During follow-up, 1,416 individuals initiated KRT. The absolute 5-year risk for KRT was 39.0% among CCB users and 34.8% among RAS inhibitor users, with a 5-year absolute risk difference of -4.3% (95% CI, -8.0% to -0.6%). The KRT risk was consistently lower in RAS inhibitor users compared with CCB users during the entire follow-up period. For instance, risk differences were -3.3% (95% CI, -4.9% to -1.6%) at 1 year and -4.4% (95% CI, -7.4% to -1.6%) at 3 years (Fig 1; Table S3). For patients initiating RAS inhibitor therapy compared with those initiating CCB therapy, we observed a weighted HR of 0.79 (95% CI, 0.69-0.89), in favor of RAS inhibitor therapy initiation (Table 2).

In total, 1,974 individuals died, with an absolute 5-year mortality risk of 49.5% among CCB users and 48.3% among RAS inhibitor users. The absolute risk difference at 5 years was -1.2% (95% CI, -4.1% to 1.7%), with a weighted mortality HR of 0.97 (95% CI, 0.88-1.07). During follow-up, 1,043 individuals experienced MACE, with a weighted HR of 1.00 (95% CI, 0.88-1.15). The absolute 5-year risk for MACE was 25.1% among CCB users and 25.0% among RAS inhibitor users, with a 5-year risk difference of -0.1% (95% CI, -3.4% to 3.0%). Among individuals initiating RAS inhibitor therapy, 18 (0.7%) experienced a hospitalization for hyperkalemia and 83 (3.4%) experienced a hospitalization for AKI. Among



**Figure 1.** Weighted standardized survival curves for (A) kidney replacement therapy (KRT), (B) mortality, and (C) major adverse cardiovascular events (MACE) stratified by renin-angiotensin system inhibitor (RASi) or calcium channel blocker (CCB) use.

those initiating CCB therapy, 18 (0.8%) experienced a hospitalization for hyperkalemia and 72 (3.1%) experienced a hospitalization for AKI.

**Subgroup and Sensitivity Analyses**

Results were robust in most subgroup analyses (Figs 2, S2, and S3; Table S4). Lower risk for KRT for RAS inhibitor users compared with CCB users was observed across strata of sex, diabetes, UACR, eGFR, heart failure, and systolic blood pressure, but a significant interaction was observed for age, with benefit for initiating RAS inhibitor therapy in younger but not older patients ( $P < 0.01$ ). Increased risk for mortality and MACE (interaction  $P < 0.01$ ) was observed for patients with baseline heart failure and CKD G4-G5 initiating RAS inhibitor therapy compared with CCB therapy, as well as a significant interaction for MACE according to sex ( $P < 0.01$ ). Other than this, risks for mortality and MACE did not differ by prespecified subgroups (all interaction  $P > 0.1$ ).

The positive control cohort included 2,608 nephrologist-referred patients with CKD G3, of whom

1,663 started RAS inhibitor therapy and 945 started CCB therapy (baseline characteristics in Table S5). After IPTW, the adjusted HR for RAS inhibitors compared with CCBs was 0.68 (95% CI, 0.48-0.98) for KRT, 0.97 (95% CI, 0.81-1.17) for mortality, and 1.09 (95% CI, 0.85-1.40) for MACE (Table S6).

In the as-treated analysis, an HR of 0.67 (95% CI, 0.56-0.80) was observed for KRT for RAS inhibitor therapy initiation compared with CCB therapy initiation. Adjusted HRs for mortality and MACE were 1.05 (95% CI, 0.87-1.26) and 1.03 (95% CI, 0.83-1.26), respectively (Table S7). Additional adjustment for UACR and potassium level or redefining new users as no recorded dispensation of either RAS inhibitor or CCB for at least 12 months, produced HRs consistent with results of our main analysis (Table S7). Individuals who initiated RAS inhibitor therapy had similar risks for cancer compared with CCB therapy initiators, with a weighted HR of 1.03 (95% CI, 0.87-1.22). Adding heart failure-related hospitalization to the MACE outcome did not alter our results (adjusted HR, 1.00 [95% CI, 0.89-1.13]; Table S8).

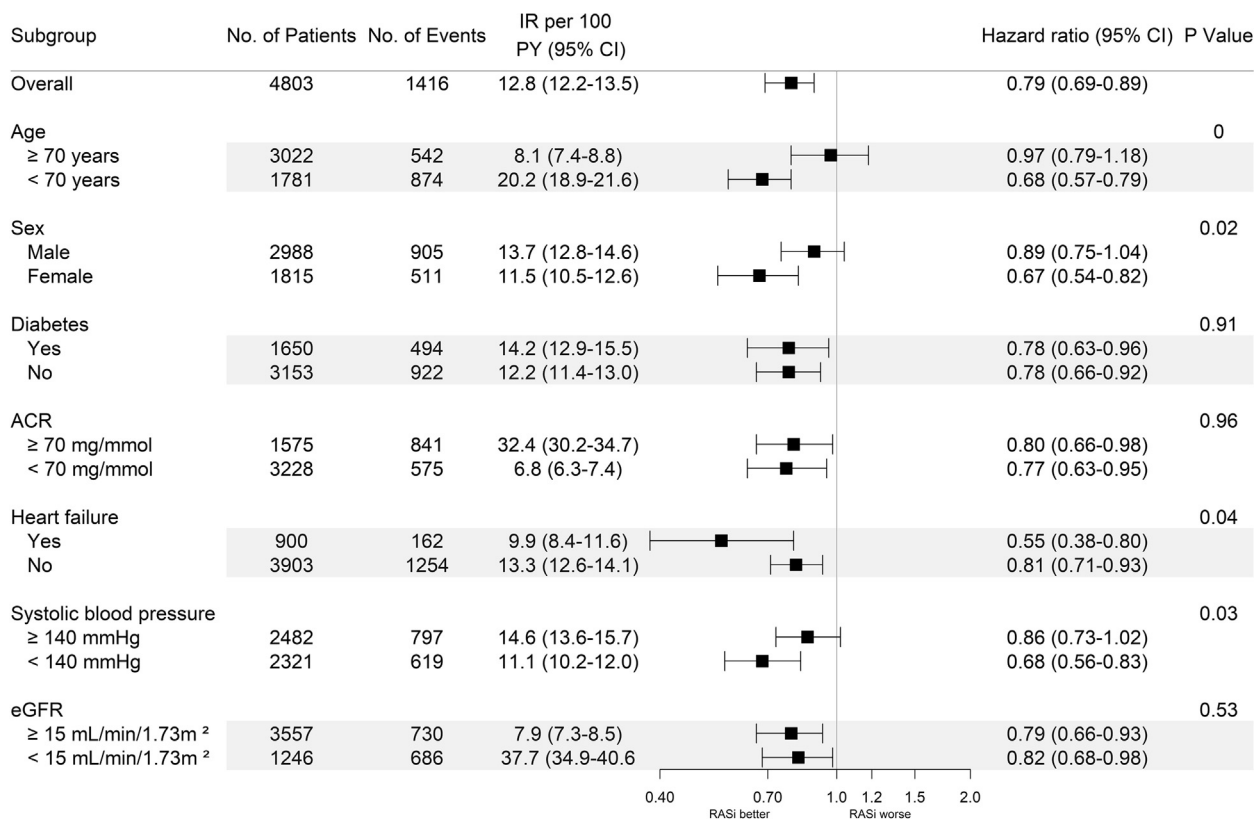
**Table 2.** Number of Events, Incidence Rates, and Crude and Adjusted HRs for the Association of RAS Inhibitor Versus CCB Initiation and KRT, All-Cause Mortality and MACE

|                            | No. of Events <sup>a</sup> | PY <sup>a</sup> | IR per 100 PY (95% CI) <sup>a</sup> | Crude HR (95% CI) | Adjusted HR (95% CI) <sup>b</sup> |
|----------------------------|----------------------------|-----------------|-------------------------------------|-------------------|-----------------------------------|
| <b>KRT</b>                 |                            |                 |                                     |                   |                                   |
| Overall                    | 1,416                      | 11,044          | 12.8 (12.2-13.5)                    |                   |                                   |
| CCB                        | 753                        | 4,872           | 15.5 (14.4-16.6)                    | 1.00 (reference)  | 1.00 (reference)                  |
| RASi                       | 663                        | 6,172           | 10.7 (9.9-11.6)                     | 0.70 (0.63- 0.78) | 0.79 (0.69-0.89)                  |
| <b>All-cause mortality</b> |                            |                 |                                     |                   |                                   |
| Overall                    | 1,974                      | 14,682          | 13.4 (12.9-14.1)                    |                   |                                   |
| CCB                        | 991                        | 6,769           | 14.6 (13.7-15.6)                    | 1.00 (reference)  | 1.00 (reference)                  |
| RASi                       | 983                        | 7,912           | 12.4 (11.7-13.2)                    | 0.85 (0.78-0.93)  | 0.97 (0.88-1.07)                  |
| <b>MACE</b>                |                            |                 |                                     |                   |                                   |
| Overall                    | 1,043                      | 13,814          | 7.6 (7.1-8.0)                       |                   |                                   |
| CCB                        | 510                        | 6,311           | 8.1 (7.4-8.8)                       | 1.00 (reference)  | 1.00 (reference)                  |
| RASi                       | 533                        | 7,503           | 7.1 (6.5-7.7)                       | 0.90 (0.80-1.02)  | 1.00 (0.88-1.15)                  |

Abbreviations: CCB, calcium channel blocker; HR, hazard ratio; IR, incidence rate; KRT, kidney replacement therapy; MACE, major adverse cardiovascular events; PY, person-years; RASi, renin-angiotensin system inhibitor.

<sup>a</sup>Number of events, PY, and IRs were calculated in the unweighted population.

<sup>b</sup>Analyses adjusted for age, sex, estimated glomerular filtration rate, heart failure, arrhythmia, peripheral vascular disease, cerebrovascular disease, ischemic heart disease, diabetes mellitus, systolic blood pressure, diastolic blood pressure, use of  $\beta$ -blocker, thiazide diuretic, potassium-sparing diuretic, statin, total number of hospitalizations in previous year, hospitalization in previous year (yes/no), history of hyperkalemia hospitalization, and history of acute kidney injury hospitalization using inverse probability of treatment weighting.



**Figure 2.** Number of events, incidence rates (IRs), and adjusted hazard ratios for kidney replacement therapy after renin-angiotensin system inhibitor (RASi) versus calcium channel blocker therapy initiation, according to subgroups of age, sex, diabetes, urinary albumin-creatinine ratio (ACR), heart failure, systolic blood pressure, and estimated glomerular filtration rate (eGFR). Abbreviation: PY, person-year.

## Discussion

Current clinical guidelines recommend the use of ACE inhibitors or ARBs as first-line therapy in patients with CKD and proteinuria, with or without diabetes<sup>7-9,49</sup> but provide no guidance regarding eGFR thresholds for which these recommendations are valid.<sup>14,15</sup> In our study of a large nationwide cohort of nephrologist-referred patients with advanced CKD, initiation of RAS inhibitor therapy compared with CCB therapy was associated with reduced risk for KRT but similar risk for mortality and MACE. These findings were robust across subgroups of patients and following an as-treated design.

Our study does not evaluate the health benefits of RAS inhibitor use versus no use in patients with CKD G4-G5. This has been investigated previously,<sup>17,18,24</sup> including the randomized trial by Hou et al<sup>16</sup> or the post hoc analysis of the REIN (Ramipril Efficacy in Nephropathy) trial.<sup>10</sup> Our goal was to inform on the choice of antihypertensive agents in the advanced CKD population by comparing outcomes associated with initiating RAS inhibitor or CCB therapy as the 2 most commonly used antihypertensive agents in clinical practice.<sup>28</sup>

A considerable proportion of patients reach CKD G4-G5 without having received these medications. In our register, this equaled 34% of the population, a figure that agrees with other contemporary reports: in the CRIC (Chronic Renal Insufficiency) cohort, ~30% of patients with CKD G4 and ~73% of patients with CKD G5 did not receive RAS inhibitors, and similar proportions of nonuse were reported for CCBs in CKD G4 (50%) and G5 (40%).<sup>24</sup> Recent data from CKDopps (Chronic Kidney Disease Outcomes and Practice Patterns Study) indicates that this pattern is followed globally: for instance, only 52% of DOPPS (Dialysis Outcomes & Practice Patterns Study) patients in the United States and 66% in Brazil were receiving RAS inhibitors.<sup>25</sup>

We observed that RAS inhibitor therapy may be superior to CCB therapy in delaying KRT in advanced CKD. This is consistent with a recent network meta-analysis of patients with CKD G3 showing that ACE inhibitors reduced the odds of KRT by 35% (odds ratio [OR], 0.65 [95% credibility interval, 0.51-0.80]), and ARBs reduced the odds of kidney failure by 25% (OR, 0.75 [95% credibility interval, 0.54-0.97]) compared with other antihypertensive drugs, which included CCBs, diuretics, and



$\beta$ -blockers.<sup>13</sup> Our positive control cohort of individuals with CKD G3 showed a reduction in KRT risk (HR, 0.68 [95% CI, 0.48-0.98]) of magnitude similar to that meta-analysis, which lends reassurance to our observations. We note that 98% of our patients used dihydropyridine CCBs, and the comparative effectiveness and safety of nondihydropyridine CCBs cannot be informed by our study.

We observed no differences in risk for MACE between both therapies in persons with advanced CKD, a finding that we believe is novel,<sup>7,14</sup> and in a magnitude similar to our control population of patients with CKD G3. Again, this agrees with and expands 2 large meta-analyses of randomized trials comparing antihypertensive agents in patients with CKD G3.<sup>13,50</sup> Compared with placebo, blood-pressure-lowering regimens were observed to significantly reduce the risk for MACE in individuals with CKD G3 (HR, 0.83 [95% CI, 0.76-0.90]), but results were similar whether the regimen was based on ACE inhibitors, CCBs, diuretics, or  $\beta$ -blockers.<sup>50</sup> Another Bayesian network meta-analysis found ORs of 0.94 (95% credibility interval, 0.75-1.12) for ACE inhibitors and 0.86 (95% credibility interval, 0.70-1.03) for ARBs versus active controls (either CCBs, diuretics, or  $\beta$ -blockers) on cardiovascular events.<sup>13</sup> Collectively these findings may suggest that there is little evidence to support a particular drug class for the prevention of cardiovascular outcomes in the general population with CKD.

Few studies have compared the mortality risk of RAS inhibitors versus alternative antihypertensive agents in advanced CKD. In the meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), both ACE inhibitors versus placebo and CCBs versus placebo were associated with similar reductions in all-cause mortality for patients with CKD (predominantly CKD G3a), with HRs of 0.86 (95% CI, 0.76-0.97) and 0.83 (95% CI 0.56-1.24), respectively.<sup>50</sup> Head-to-head comparisons of RAS inhibitors versus CCBs in patients with CKD yielded an HR of 1.00 (95% CI, 0.89-1.13),<sup>50</sup> which is again similar to what we observed in patients with CKD G4-G5 without KRT (HR, 0.97 [95% CI, 0.88-1.07]) and our control cohort of patients with CKD G3 (HR, 0.97 [95% CI, 0.81-1.17]).

Our study used a unique nationwide inception cohort design of patients referred to a nephrologist in a country with universal health care access, with long-term follow-up data of more than 10 years, assessment of multiple relevant end points, virtually no loss to follow-up, and low likelihood of misclassification for the outcomes KRT and mortality. Furthermore, results were robust in multiple subgroup and sensitivity analyses. Our positive control analysis of persons with CKD G3 aligned with findings from 2 meta-analyses of trials and the patients included are representative of routine clinical practice. In addition, the negative control analysis with cancer did not indicate that

the observed associations were due to different health status.

However, we recognize limitations. Despite adjustment for a wide range of potential confounders, selection of patients referred to nephrologists, and the use of an active comparator (CCB therapy initiation), residual confounding-by-indication bias cannot be excluded in observational designs, and the reasons for the initiation of these drugs in the patients of our study are unknown. Because only ~10% of individuals starting RAS inhibitor or CCB therapy in our study had a cardiovascular hospitalization in the 6 months before therapy start, we speculate that medications may have been initiated for renoprotection or as antihypertensive agents. Data were missing for UACR and potassium level but our results were similar regardless of whether these variables were included using multiple imputation, and those with missing measurements had similar characteristics to those without missing measurements. We recognize that it may be unusual to start RAS inhibitor or CCB therapy this late in the course of disease and that there may be special indications for it. Although we acknowledge that we do not have the precise reasons that prompted the use of these therapies, we went through a great deal of effort to identify and control for these potential indications. Our results are likely generalizable to Swedish clinical practice during the period 2007 to 2017. However, extrapolations to other ethnicities, countries, or periods should be done with caution. Finally, our conclusions remain observational in nature and do not substitute for randomized trials. However, until these trials are conducted, they may assist in informing clinical decisions.

In conclusion, in patients with CKD G4-G5 without KRT, RAS inhibitor therapy initiation, compared with CCB therapy initiation, was associated with lower risk for KRT but similar risks for MACE or mortality. These results suggest that use of RAS inhibitors may confer additional renal benefits compared with CCBs in patients with CKD G4-G5 without KRT. This evidence may potentially inform clinical decisions on the choice of antihypertensive therapy for this patient group, who have to date been minimally included in pivotal trials.

## Supplementary Material

### Supplementary File (PDF)

**Figure S1:** Assembly of the study cohort.

**Figure S2:** Number of events, incidence rates, and adjusted HRs for mortality following RAS inhibitor vs CCB initiation, by age, sex, diabetes, UACR, heart failure, systolic blood pressure, and eGFR subgroups.

**Figure S3:** Number of events, incidence rates, and adjusted HRs for MACE following RAS inhibitor vs CCB initiation, by age, sex, diabetes, UACR, heart failure, systolic blood pressure, and eGFR subgroups.

**Item S1:** Supplemental methods.

**Table S1:** Definition of medications and comorbid conditions.

**Table S2:** Comparison of baseline characteristics for individuals with and without baseline UACR measurements.

**Table S3:** Absolute risks and risk differences for KRT, mortality, and MACE after 1, 2, 3, 5, and 10 years of follow-up.

**Table S4:** Subgroup analyses for systolic blood pressure using 130 mm Hg as cutpoint.

**Table S5:** Baseline characteristics of patients in the positive control cohort (CKD G3), by RAS inhibitor or CCB treatment, before and after inverse probability weighting.

**Table S6:** Number of events, incidence rates, and crude and adjusted HRs for the association of RASi vs CCB initiation and all-cause mortality, MACE, and KRT in the positive control cohort (CKD G3).

**Table S7:** Adjusted HRs for the sensitivity analyses.

**Table S8:** Number of events, incidence rates, and crude and adjusted HRs for the association of RAS inhibitor vs CCB initiation and MACE plus (composite of cardiovascular death, hospitalization due to stroke, myocardial infarction, or heart failure).

## Article Information

**Authors' Full Names and Academic Degrees:** Edouard L. Fu, BSc, Catherine M. Clase, MB, MSc, Marie Evans, MD, PhD, Bengt Lindholm, MD, PhD, Joris I. Rotmans, MD, PhD, Friedo W. Dekker, PhD, Merel van Diepen, PhD, and Juan-Jesus Carrero, PharmD, PhD.

**Authors' Affiliations:** Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands (ELF, FWD, MvD); Department of Medicine and Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada (CMC); Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden (ME, BL); Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands (JIR); and Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden (J-JC).

**Address for Correspondence:** Edouard L. Fu, BSc, Department of Clinical Epidemiology, Leiden University Medical Center, Albinusdreef 2, Leiden, the Netherlands. Email: [e.l.fu@lumc.nl](mailto:e.l.fu@lumc.nl)

**Authors' Contributions:** Research idea and study design: ELF, CMC, ME, JJC; data acquisition: JJC, ME; data analysis/interpretation: ELF, CMC, BL, ME, JIR, JJC; statistical analysis: ELF; supervision or mentorship: MvD, FWD, JJC. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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## Comparative Effectiveness of RASi and CCB in Advanced CKD

| Setting & Participants  | Findings  |
|---|---|
|  Nationwide observational cohort study<br>Swedish Renal Registry, 2007-2017                          | <p style="text-align: center;"><b>RASi vs. CCB: Hazard ratio (95% CI)</b></p>   |
|  4,803 patients with<br>eGFR <30 mL/min/1.73 m <sup>2</sup>  |  <b>Dialysis/transplant</b> <span style="float: right;"><b>0.79</b><br/>(0.69-0.89)</span> |
|  New users of renin-angiotensin<br>system inhibitors (RASi) versus<br>calcium channel blockers (CCB) |  <b>Mortality</b> <span style="float: right;"><b>0.97</b><br/>(0.88-1.07)</span>           |
|  Median 4.1 years follow-up  |  <b>CV events</b> <span style="float: right;"><b>1.00</b><br/>(0.88-1.15)</span>           |

**CONCLUSION:** This real-world evidence indicates that initiation of RASi compared with CCB slows kidney disease progression in those with advanced CKD.

Edouard L. Fu, Catherine M. Clase, Marie Evans, et al (2020)

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