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EFFECT OF DUAL COMPARED TO NO OR SINGLE RENIN–ANGIOTENSIN SYSTEM BLOCKADE ON RISK OF RENAL REPLACEMENT THERAPY OR DEATH IN PRE–DIALYSIS PATIENTS: PREPARE–2 STUDY

Pauline WM Voskamp, Friedo W Dekker, Merel van Diepen, Ellen K Hoogeveen, for the PREPARE-2 Study Group

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Abstract

Introduction: Current guidelines on hypertension treatment in chronic kidney disease (CKD) patients discourage combined angiotensin converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) use due to the risk of an increased kidney function decline. However, dual compared to single renin-angiotensin system (RAS) blockade may have more efficacy with regard to hypertension and proteinuria. Among incident pre-dialysis patients (CKD 4-5) we compared dual with no or single RAS blockade regarding kidney function decline, and risk of renal replacement therapy (RRT) or death.

Methods: In a multi-center cohort study, 495 incident pre-dialysis patients (>18y) were included between 2004-2011 and followed until RRT, death or October 2016. At baseline, patients were divided into four categories: non-user, single or dual user of ACEi and/or ARB. Cox models were used to estimate the hazard ratio (HR) for the combined endpoint RRT or death. Differences in decline of kidney function among the four drug groups were compared with a linear mixed model.

Results: 119 patients were non-users, 164 ACEi-users, 133 ARB-users, and 79 dual RAS users. Compared to non-users, the multivariable adjusted HR (95% CI) for the combined endpoint was 0.75 (0.65-0.86) for ACEi-users, 0.87 (0.76-1.00) for ARB-users, and 0.79 (0.67-0.94) for dual RAS users. The average annual decline in kidney function did not differ among the four groups.

Conclusions: We observed in pre-dialysis patients that compared to no RAS blockade both dual RAS blockade and single ACEi-use were associated with about 20-25% lower risk of RRT or death, without difference in kidney function decline.

Introduction

Hypertension is one of the major risk factors of accelerated loss of kidney function in chronic kidney disease (CKD). CKD is a leading cause of death due to premature cardiovascular disease.[1] Therefore, prevention of kidney function decline is important to improve life expectancy. Globally, the prevalence rates of CKD are >20% among men and women aged 65-74 year and >30% among those aged 75-84 year.[2, 3] Current therapies in CKD patients aim at improving modifiable cardiovascular risk factors, such as hypertension, to slow down kidney function decline, and prevent or postpone end stage renal disease (ESRD).

To manage hypertension in patients with CKD, the use of renin–angiotensin system (RAS) inhibitors to a goal of <140/90 mmHg is recommended by international guidelines such as the Joint National Committee 8 guidelines (JNC8) and the Kidney Disease Improving Global Outcomes 2012 (KDIGO).[4, 5] RAS inhibitors, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), both lower systolic and diastolic blood pressure, without cardiac dysfunction, and have extensively been proven to be renoprotective agents.[6-11] ACEi down regulate the level of angiotensin II and aldosterone by blocking ACE, ARBs mainly block the angiotensin I receptor.

Cellular effects in the kidney and alterations in glomerular hemodynamics due to RAS inhibitors, probably prevent the development or reduce proteinuria, and delay the progression of CKD to ESRD.[12] Possible negative consequences of ACEi and ARBs include hypotension, decline in kidney function, and hyperkalemia. In patients with severe impaired renal perfusion, ACEi and ARBs can compromise glomerular perfusion pressure and glomerular filtration rate (GFR).[12]

Since ACEi or ARBs alone do not block the entire RAS and work via different pathways, it has been hypothesized that dual RAS blockade can improve renoprotective and antihypertensive effects.[13, 14] However, until now trials, such as the ONTARGET (Ongoing Telmisartan alone an in combination with Ramipril Global Endpoint Trial) trial, have not been able to prove this hypothesis and only found negative consequences, such as an increased risk of kidney function decline and hyperkalemia for which dialysis is required in dual RAS compared to single users.[6-11] Unfortunately, due to a lack of power to detect differences in renal outcome and small number of included patients with CKD (ONTARGET: mean eGFR 74 ml/min/1.73m^2), so far these trials have not been able to provide a definite conclusion for patients with CKD.[15, 16] Therefore, current guidelines discourage combined ACEi and ARB usage in CKD patients, based on expert opinion. When using a single RAS inhibitor both ACEi and ARBs are equally valued.[4] The aim of our prospective cohort study is to investigate in incident pre-dialysis patients whether dual compared to single use and non-use of ACEi and ARBs is associated with an increased risk of RRT or death, or an accelerated kidney function decline. These data reflect specialized nephrological care and allow us to evaluate real-world effectiveness and safety of ACEi and ARB in pre-dialysis patients often under-represented or excluded from clinical trials.

Methods

Study design and population

The PRE-dialysis Patient Record-2 (PREPARE-2) study is a prospective cohort study of incident pre-dialysis care patients (≥18 y) who had an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m^2 and progressive renal function loss. Patients with a failing kidney transplant who were transplanted at least one year ago were also eligible for inclusion. The PREPARE-2 study has been described in detail elsewhere.[17] In brief, patients were recruited in one of 25 nephrology specialized pre-dialysis outpatient clinics in the Netherlands between July 2004 and June 2011. All patients were treated by their nephrologist in accordance with the treatment guidelines of the Dutch Federation of Nephrology, guidelines partly based on the K/DOQI and EBPG guidelines.[18-21] Patients were followed from the start of pre-dialysis care until start of dialysis, kidney transplantation, death or censoring. Censoring was defined as: refusal for further participation, recovery of kidney function, moving to an outpatient clinic not participating in the PREPARE-2 study, loss to follow up or October, 2016 (end of follow up), whichever came first. This study was approved by the medical ethics committee or institutional review boards (as appropriate) of all participating centers. Written informed consent was obtained from all patients.

Demographic and clinical data

Data on demography, primary kidney disease, comorbidities, medication use, and laboratory values were collected at baseline and during routine visits to pre-dialysis outpatient clinics. These visits took place at the start of specialized pre-dialysis care, at the moment of reaching one of the study endpoints as described previously, and every intermediate 6-month interval. Laboratory data were extracted from the electronic hospital information systems or medical records. The closest laboratory measurement performed within 90 days before or after the date of a visit was appointed to that visit. Patients were categorized as non-users or users (single or dual) of ACEi and/or ARB medication based on medication use at baseline. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula from 2009, taking into account age, sex, race, and serum creatinine.[22] Hypertension was defined as either a history of hypertension, antihypertensive drug use, a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90mmHg at baseline.[4] Primary kidney disease was classified according to the codes of the European Renal Association-European Dialysis and Transplantation Association.[23] We grouped patients into four classes of primary kidney disease: glomerulonephritis, diabetes mellitus, renal vascular disease, and other kidney diseases.

Outcomes

Our primary outcomes were start of dialysis, start of renal replacement therapy (RRT), and the combined endpoint RRT or death. Start of RRT was defined as start of dialysis

(hemodialysis or peritoneal dialysis) or receiving a kidney transplant during follow up. Secondary outcomes was the change in rate of decline in kidney function for the four ACEi-ARB categories. To calculate the kidney function decline rate, all available eGFR measurements from inclusion until two years of follow-up were used. Complete follow-up data were not used because the healthy and stable patients, who are still on pre-dialysis care after 2 years, would then provide a relatively large contribution to the overall renal function decline, possibly leading to a dilution of the estimated decline.

Statistical analysis

Baseline characteristics are presented according to the four ACEi-ARB categories: no ACEi or ARB use (non-users), only ACEi use, only ARB use, and dual ACEi and ARB use. Continuous variables are described with their mean ± standard deviation (SD), skewed variables with their median and interquartile range (IQR), and categorical variables are presented as number (proportion). First, absolute event rates of the primary outcomes were calculated for the four ACEi-ARB categories. To estimate the median follow up time, a reversed Kaplan-Meier was used. Second, we conducted Cox proportional hazards regression analysis, obtaining hazard ratios (HR) with 95% confidence intervals (95%CI) to estimate the effect of the four ACEi-ARB categories on the three primary outcomes. Analyses were adjusted for the potential confounders: age, sex, race, diabetes mellitus, primary kidney disease and current smoking. Follow-up time was defined as time between baseline visit of the patient and the start of dialysis, RRT, death, withdrawal or end of follow-up (October, 2016). The proportional hazard assumption was tested using a log minus log plot. Third, a Kaplan-Meier analysis was performed to produce a survival plot for the combined endpoint.

To estimate the change in rate of decline in renal function during two years of follow-up in each ACEi-ARB category a linear mixed model (LMM) was used. This model takes the correlation between the eGFR in each patient into account. In the LMM adjustments were made for the same confounders as in the Cox regression analyses.

Since severe hyperkalemia (potassium level ≥6.0 mmol/l) is a side effect of ACEi and ARB use we counted the occurrence at baseline and during follow up. We compared the prevalence and incidence of severe hyperkalemia among the four ACEi-ARB groups with a Chi Square test. Multiple imputation was used to impute missing potential confounders at baseline. The imputed data were predicted based on outcome, follow-up time, age, sex, race, smoking habits, presence of diabetes mellitus, primary kidney disease, ACEi and ARB usage during the study after baseline, and blood pressure at baseline. To test the robustness of our findings, multiple sensitivity analyses were performed. First, we expanded the Cox hazard models simultaneously with baseline proteinuria, eGFR, and cholesterol. The presence of (severe) proteinuria is an indication for combined ACEi and ARB therapy, and therefore a proxy of dual RAS blockade as well as a confounder. EGFR could be both a confounder as well as part of the causal pathway. Second, we stratified the Cox regression analysis for eGFR, at an eGFR level of 15 ml/min/1.73 m^2. In clinical practice a low eGFR

(below 15 ml/min/1.73 m^2) might be an indication to stop ACEi and/or ARB use. Third, we restricted our analysis to patients who were persistent users or non-users of ACEi and/or ARB during the entire study period, since changes in therapy during the follow up period might dilute treatment effects. Fourth, we added nephrology center into our model to remove any confounding from treatment preferences per center. Finally, we repeated all analyses without using multiple imputation for missing values. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS version 23.0 for Windows.

Results

Patient characteristics

In total, 502 incident pre-dialysis patients were included in the PREPARE-2 study. Baseline ACEi and ARB use was known in 495 patients. Of these patients, 119 (24%) were non-users of ACEi or ARB, 164 (33%) used an ACEi alone, 133 (27%) used an ARB alone and 79 (16%) patients used both an ACEi and ARB. A total of 354 (72%) patients were persistent users or non-users of ACEi and/or ARB during the entire study period. Of the ACEi only users 24 (15%) stopped using ACEi completely during follow-up, in ARB users this were 17 (13%) patients and in dual users this were 2 (3%) patients. Table 1 shows the baseline characteristics of the four ACEi-ARB categories. Dual ACEi and ARB users were younger, had more often diabetes mellitus, less often renal vascular disease and more often glomerulonephritis as primary kidney disease than the other categories. Median eGFR and proteinuria were higher in patients with dual RAS blockade. The number of patients with severe CKD at baseline (eGFR< 10ml/min/1.73m2) did not differ significantly among the four ACEi-ARB categories.

Start of dialysis, renal replacement therapy and death

Of all patients the median (IQR) follow-up time was 66 months (61 to 71). During follow up 321 (65%) patients started dialysis, 370 (75%) patients started RRT and 47 (10%) patients died. Table 2 shows the primary outcomes per ACEi-ARB category with their incidence rate per 100 person years (py). The incidence rate of the combined outcome RRT or death in the ACEi and dual user group was substantially lower compared to the non-users. Figure 1 shows the Kaplan-Meier for start of RRT or death for each ACEi-ARB category.

The proportional hazards assumption was fulfilled (plots not shown). The crude and adjusted hazard ratios (HR) for the outcomes are presented in Table 3. Compared with no RAS blockade (reference category) pre-dialysis patients who used ACEi or dual RAS blockade, had a 20-30% lower risk of start of dialysis and RRT. For the combined endpoint RRT or death we found a HR of 0.75 in ACEi users and 0.79 in dual RAS users after multivariable adjustment, corresponding to a 25% and 21% lower risk for RRT or death.

Table 1. Baseline characteristics according to ACEi or ARB drug use at baseline (n=495)

	No ACEi or ARB (n=119)	ACEi only (n=164)	ARB only (n=133)	ACEi and ARB (n=79)
Men	72 (61)	122 (74)	78 (59)	64 (81)
Age, years	72 (59-80)	67 (56-76)	68 (55-75)	63 (49-74)
Ethnicity				
Caucasian	117 (98)	155 (95)	119 (90)	66 (84)
Black	2 (2)	7 (4)	11 (8)	8 (10)
Other	0 (0)	2 (1)	1 (2)	5 (6)
Primary Kidney Disease				
Renal vascular disease	39 (33)	52 (32)	49 (37)	11 (14)
Diabetes	7 (6)	24 (15)	17 (13)	22 (28)
Glomerulonephritis	9 (8)	24 (15)	11 (8)	22 (28)
Other	64 (54)	64 (39)	56 (42)	24 (30)
Hypertension, yes[a]	96 (81)	145 (88)	121 (91)	76 (96)
Diabetes Mellitus, yes[b]	17 (14)	43 (26)	35 (26)	31 (39)
Cardio Vascular Disease, yes[c]	48 (40)	70 (43)	52 (39)	32 (41)
Current smoker, yes	30 (25)	22 (13)	28 (21)	18 (23)
Body Mass Index, kg/m^2 [e]	26 (23-29)	25 (22-30)	26 (24-30)	27 (24-30)
Systolic blood pressure, mmHg	140 (20)	140 (22)	143 (23)	149 (22)
Diastolic blood pressure, mmHg	78 (10)	77 (13)	78 (12)	79 (11)
Pulse pressure, mmHg	60 (50-71)	60 (53-72)	61 (50-80)	65 (57-80)
Serum creatinine, μmol/L	354 (282-447)	347 (256-407)	332 (270-426)	321 (270-429)
eGFR, ml/min/1.73m^2[de]	12.8 (10.1-17.3)	14.7 (11.7-19.1)	14.5 (11.1-18.0)	16.5 (11.7-19.7)
eGFR <10.0 ml/min/1.73m^2, yes	24 (20)	20 (12)	20 (15)	9 (11)
Proteinuria, g/24h[e]	1.0 (0.4-2.1)	1.0 (0.3-2.0)	0.9 (0.3-2.0)	1.7 (0.6-3.6)
Total cholesterol, mmol/L	4.3 (3.7-5.0)	4.4 (3.6-4.8)	4.7 (3.6-5.6)	3.9 (3.6-4.8)
Potassium, mmol/L[e]	4.60 (4.00-4.90)	4.90 (4.45-5.25)	4.80 (4.40-5.10)	4.70 (4.30-5.25)
Antihypertensive drug use				
Beta-blocker	57 (48)	84 (51)	77 (58)	48 (61)
Calcium antagonist	57 (48)	74 (45)	63 (47)	35 (44)
Diuretics	55 (46)	89 (54)	74 (56)	56 (71)
Other	12 (10)	13 (8)	17 (13)	17 (22)
Statin use	58 (49)	96 (59)	80 (60)	57 (72)

Values are given as number (percentage of the total), means ± SD or median (interquartile range).
[a]Defined as either a history of hypertension, antihypertensive drug use, a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg at baseline. [b]Defined as the presence of diabetes mellitus as primary kidney disease or a history of diabetes mellitus. [c]Defined as presence of coronary artery disease, a history of cardiovascular accident, peripheral vascular disease, or myocardial infarction. [d]eGFR (estimated glomerular filtration rate) is calculated with the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) formula 2009.
[e]Body mass index available for 485, eGFR for 431, proteinuria for 244, potassium for 428 patients.
ACEi; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin II Receptor Blocker

Table 2. Dialysis, RRT and combined RRT–death incidence rates (95% CIs) according to ACEi and/or ARB drug use at baseline (n=495)

	No ACEi or ARB (n=119)	ACEi only (n=164)	ARB only (n=133)	ACEi and ARB (n=79)
Person years (py)	194.6	329.2	253.0	161.1
Start dialysis, n (%)	79 (66)	97 (59)	88 (66)	57 (72)
Incidence rate /100 py (95% CI)	40.6 (29.4 to 55.6)	29.5 (20.2 to 42.8)	34.8 (24.4 to 48.7)	35.4 (24.4 to 48.7)
Start RRT, n (%)	89 (75)	116 (71)	102 (77)	63 (80)
Incidence rate/100 py (95% CI)	45.7 (33.7 to 61.4)	35.2 (24.4 to 48.7)	40.3 (28.6 to 54.5)	39.1 (27.7 to 53.3)
Combined RRT/death, n (%)	98 (82)	132 (81)	117 (88)	70 (89)
Incidence rate/100 py (95% CI)	50.4 (37.1 to 65.9)	40.1 (28.6 to 54.4)	46.2 (33.7 to 61.4)	43.5 (32.0 to 59.1)

ACEi; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin II Receptor Blocker, CI; Confidence Interval, RRT; Renal Replacement Therapy

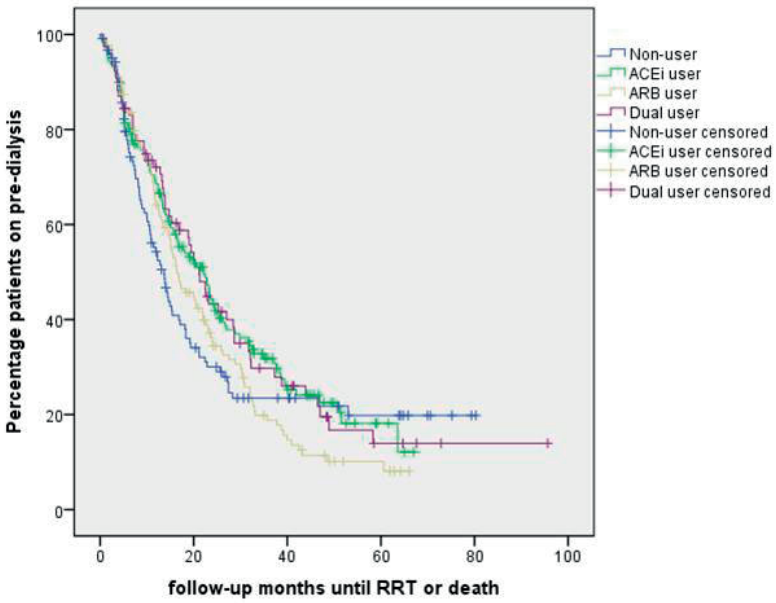

Figure 1. Kaplan Meier for the combined endpoint RRT or death for each medication category

Kidney function decline

During follow up patients had on average 2.5 (SD 1.2) measurements of serum creatinine. The mean decline in kidney function was -1.79 (95%CI -2.21 to -1.37) ml/min/1.73 m^2/year. Table 4 shows the difference in kidney function decline in the three ACEi-ARB categories compared to the non-users. After adjustment for confounding ACEi users had an extra change in kidney function of -0.16 (95% CI -1.47 to 1.16), ARB users of 0.05 (95% CI -1.26 to 1.35), and dual users of 0.63 (95% CI -0.95 to 2.20) per year. The negative number indicates

Table 3. Crude and adjusted hazard ratios (95% CI) for start of dialysis, RRT and combined RRT–death according to ACEi and/or ARB drug use at baseline (n=495)

	Start of dialysis (n=277)	RRT (n=318)	RRT or death (n=359)
No ACEi or ARB	Reference	Reference	Reference
ACEi only, crude	0.72 (0.54 to 0.98)	0.76 (0.58 to 1.00)	0.78 (0.60 to 1.02)
ACEi only, adjusted	0.69 (0.59 to 0.81)	0.70 (0.61 to 0.81)	0.75 (0.65 to 0.86)
ARB only, crude	0.85 (0.63 to 1.15)	0.86 (0.65 to 1.15)	0.90 (0.69 to 1.18)
ARB only, adjusted	0.81 (0.69 to 0.95)	0.82 (0.71 to 0.95)	0.87 (0.76 to 1.00)
ACEi and ARB, crude	0.87 (0.62 to 1.22)	0.85 (0.61 to 1.17)	0.85 (0.63 to 1.16)
ACEi and ARB, adjusted	0.81 (0.67 to 0.98)	0.78 (0.65 to 0.93)	0.79 (0.67 to 0.94)

Adjustments were made for; age, sex, ethnicity, current smoker, diabetes mellitus, and primary kidney disease. ACEi; Angiotensin Converting Enzyme Inhibitor, ARB; Angiotensin II Receptor Blocker, CI; Confidence Interval, RRT; Renal Replacement Therapy

a faster decline in ACEi users, the positive numbers a slower decline in ARB and dual users (all non-significant).

Hyperkalemia

At baseline 2 non-users (2%), 6 ACEi users (4%), 3 ARB users (3%), and 4 dual users (6%) had severe hyperkalemia (P=0.48). During follow-up 3 additional non-users (2%), 7 other ACEi users (4%), 6 other ARB users (5%), and 2 other dual users (3%) developed severe hyperkalemia (P=0.76).

Sensitivity analyses

The sensitivity analyses showed robustness of the results. Results without multiple imputation were similar for LMM and resulted in similar point estimates with wider 95%-CIs in the Cox proportional hazard analyses. Adding nephrology center as a confounder into the model did not change the results. After additional adjustment for baseline proteinuria, eGFR, and serum cholesterol into the basic model the HR (95%CI) was 1.08 (0.72 to 1.61) in ACEi users, 0.90 (95% CI 0.57 to 1.41) in ARB users, and 0.63 (95% CI 0.36 to 1.08) in dual RAS users for the combined endpoint in comparison to non-users. Stratification for baseline eGFR (<15 or ≥ 15 ml/min/1.73 m^2) revealed no differences between low and high baseline eGFR, except for the association of dual use with the combined endpoint of RRT and death. The protective effect of dual use was attenuated in patients with high baseline eGFR. Restricting the analyses to persistent users and non-users changed the adjusted HR for the combined endpoint to 0.78 (95% CI 0.67 to 0.92) in ACEi users and to 0.81 (0.66 to 0.99) in dual RAS users.

Table 4. Annual rate of decline of kidney function according to ACEi and/or ARB drug use at baseline (n=495)

Mean decline in eGFR (ml/min/1.73 m^2/y)	-1.79 (95%CI -2.21 to -1.37)	
Change in decline in eGFR ml/min/1.73m^2 per year	Crude (95%CI)	Adjusted (95%CI)
No ACEi or ARB	Reference	Reference
ACEi only	-0.23 (-1.37 to 0.91)	-0.16 (-1.47 to 1.16)
ARB only	-0.07 (-1.23 to 1.09)	0.05 (-1.26 to 1.35)
ACEi and ARB	0.19 (-1.22 to 1.59)	0.63 (-0.95 to 2.20)

Adjustments were made for; age, sex, ethnicity, current smoker, diabetes mellitus, and primary kidney disease. ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin II receptor blocker, CI; Confidence Interval

Discussion

We found in a cohort of almost 500 incident pre-dialysis patients a 20-25% lower risk of renal replacement therapy or death in patients treated with dual RAS blockade or single ACEi-users compared to non-RAS blockade-users. Dual RAS blockade medication use did not accelerate kidney function decline compared to patients with single or no RAS blockade.

There are no RCTs specifically designed among pre-dialysis patients to study the effect on renal outcome of dual RAS blockade compared to no or single use. Hsu ***et al.*** showed in a large cohort study of adults (>28,000, mean age 65y) with CKD stage 5, a 6% lower risk of dialysis or death in ACEi or ARB users compared to non RAS blockade users.[24] The only RCT in patients with advanced CKD (serum creatinine between 274 to 442 μmol/L) and proteinuria showed that starting either ACEi or ARB lowered risk of death and slowed progression of kidney function decline (doubling serum creatinine or ESRD).[25] Another study showed that treatment with ACEi or ARB in patients with CKD lowered proteinuria, an independent predictor of progression of kidney function decline.[26, 27] Taken together, these studies support continuing ACEi or ARB usage in patients with advanced kidney disease, especially if they have proteinuria.

Our study is in line with a recent meta-analysis that included nine trials on the differences between dual and single RAS inhibition in all stages of the CKD population.[15] In this meta-analysis a total of 17,750 CKD stage 2-5 patients were included, with a mean age of 65y, and a mean follow up of 3.4 years. Dual compared to single RAS inhibition resulted in a 5% lower risk for all cause death. Since only a limited number of patients included in this meta-analysis had CKD stage 4-5, the results cannot be generalized to the pre-dialysis population. Unfortunately, a sub analysis among pre-dialysis patients was not performed. Fernandez-Juarez ***et al***. showed in an RCT in 133 patients with diabetic nephropathy (mean eGFR 49 mL/min/1.73m^2) an equal risk for RRT, death or kidney function decline in dual and single RAS blockade users.[28] The ORIENT Study showed in patients with type 2 diabetes (mean age 59y, mean serum creatinine 143 μmol/L) and proteinuria that dual RAS block-

ade compared to ACEi alone was more effective with regard to reduction of proteinuria and blood pressure, but did not lower risk of ESRD or death.[29]

In the ONTARGET trial the effect of dual compared to single RAS blockade was studied in 25,620 pre-dominantly non-proteinuric individuals with preserved kidney function (mean eGFR 74 ml/min/1.73 m^2) at low risk of CKD progression (annual rate of GFR decline of <1 ml/min/1.73m^2).[7] No sub analysis in CKD stage 4-5 patients was performed. After 5 years kidney function decline in dual, single ACEi and ARB users was 6.1, 2.8 and 4.1 mL/min/1.73m^2, respectively. Start of dialysis (acute and chronic) and death were more frequent in dual RAS blockade users with an increased risk of 9%. After removal of acute hemodialysis from the renal endpoint, there was no significant difference in secondary outcome (doubling of serum creatinine or risk of chronic hemodialysis) among the three groups.[7, 16]

We found in our cohort a mean annual eGFR decline of 1.79 mL/min/1.73m^2 , which is almost similar with the finding in a study among Taiwanese patients with comparable baseline characteristics.[30] Chen ***et al.*** showed in a prospective cohort study involving >500 Taiwanese patients with CDK stage 3-5, who received a multi-disciplinary care approach (mean eGFR 33 ml/min, mean age 65 y, 77% ACEi or ARB users, 49% diabetes mellitus) a yearly kidney function decline of 1.85 ml/min/1.73m^2.[30]

We found a slightly stronger beneficial effect in single ACEi users as compared with single ARB users with regard to reducing risk of RRT or death. A larger magnitude of a beneficial effect of ACEi compared to ARB has been found in other studies.[15, 31] A possible explanation for this difference might be the different effects of ACEi and ARBs in the RAS pathway. It is possible that by blocking the angiotensin-I receptor with an ARB more alternative pathways remain open in the RAS, while with ACE inhibition both angiotensin-II and aldosterone are down regulated and less alternative pathways remain open.[12]

We found that single ACEi or ARB use did not change the annual kidney function decline compared to non-users in our cohort of pre-dialysis patients. However, the rate of kidney function decline was studied only during two years of follow-up. We assume that a longer period of follow-up would have shown a slower rate of kidney function decline in RAS-blockade users compared to non-users.

Finally, we found that additional adjustment for baseline proteinuria, eGFR, and cholesterol resulted in a smaller effect in ACEi users with wider confidence intervals, due to over-correction of factors in the causal pathway.

Main strength of this study is the specific selection of pre-dialysis patients. Pre-dialysis patients form a special group in CKD care and cannot be compared to patients in the early stages of CKD. They require special attention, often different care and are all treated according to the previously mentioned guidelines by a nephrologist.[21] Since no exclusion criteria were used for the PREPARE cohort a wide range of incident pre-dialysis patients were included, making our results generalizable to the clinical practice of pre-dialysis care. This is in contrast to RCTs with strict in- and exclusion criteria and optimized settings which

may result in lack of generalizability. Another strength is the prospective longitudinal design of the PREPARE-2 study, resulting in specific, complete information and the opportunity to track kidney function over time.

The present study also has limitations. Main limitation is the possibility of confounding by indication. The indication for prescribing dual RAS blockade is a patient's increased risk of kidney function decline based on the presence of certain risk factors.[32-34] Thus, these risk factors are associated with the probability of receiving dual RAS blockade therapy and with the probability of kidney function decline. Therefore, patients receiving dual RAS blockade have a higher probability of developing ESRD, not because of the dual RAS blockade, but because of their increased intrinsic risk.[35] Nevertheless, although patients with dual RAS blockade had more severe proteinuria compared to the non-ARB users, we found a beneficial effect on outcome. Additional correction for the known important confounders most likely limited residual confounding. Another limitation is that we included patients who were prevalent users or non-users of RAS-blockade medication. We had no information about the duration of ACEi and ARB use or a history of intolerance of RAS blockade in these patients. However, in the non-users 29 (24%) patients started an ACEi or ARB during follow-up, which may have resulted in underestimation of the beneficial effect of ACEi- or ARB use. A third limitation is that we had no information about the cause of discontinuation of RAS blockade in patients who did use ACEi and/or ARB medication at baseline but stopped using either of these drugs during follow-up. If anything, this may have resulted in an underestimation of the effect that we found. Finally, we had no information on side effects such as hospital admittance due to syncope or dizziness. The incidence of severe hyperkalemia was low and did not differ among the four ACEi-ARB groups. Unfortunately, we could not study the side effect acute kidney injury defined as a 50% reduction in kidney function within hours or days. However, in our cohort of pre-dialysis patients a reduction of 50% of kidney function would have most likely resulted in start of RRT. If anything, the risk of RRT in patients who used RAS blockade was lower compared to non-users.

In conclusion, we observed in pre-dialysis patients that compared to no RAS blockade, both dual RAS blockade as well as single ACEi-use were associated with about 20-25% lower risk of RRT or death. We did not find an accelerated kidney function decline in the single or dual RAS inhibition groups compared to non-RAS inhibition drug users. This lack of an increased RRT or mortality risk in dual RAS inhibition users suggests that there might be room for dual RAS inhibition when treating severe hypertension or proteinuria in CKD 4-5 patients.

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