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Cardiovascular and renal outcome in subjects with K/DOQI stage 1–3 chronic kidney disease: the importance of urinary albumin excretion

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Abstract

Background. The Kidney Disease Outcomes Quality Initiative guidelines aim to define chronic kidney disease (CKD) and classify its stages. Stage 3 CKD generally receives more attention than stage 1 or 2, because the more impaired glomerular filtration rate (GFR) in stage 3 suggests a higher cardiovascular and renal risk. In this study we evaluated cardiovascular and renal outcome in subjects with stage 1 and 2 CKD. For comparison, we also studied these outcomes in stage 3 CKD.

Methods. We used data of 8495 subjects of the PREVEND study, a prospective community-based cohort study, with data on urinary albumin excretion (UAE) and serum creatinine available. As measure of cardiovascular outcome, combined cardiovascular morbidity and mortality was used. As renal outcome, mean annual change of estimated GFR (eGFR) was used.

Results. 6905 subjects had no CKD; 243, 856 and 491 subjects had stage 1, 2 and 3 CKD, respectively. During a median follow-up of 7.5 years 565 cardiovascular events occurred. Incidence rates of cardiovascular events were higher ($P < 0.001$ for all groups) in subjects with stage 1–3 CKD (17.2, 22.2 and 20.9 events/1000 person-years, respectively) than in subjects without CKD (7.0 events/1000 person-years). Using subjects without CKD as reference, age- and sex-adjusted hazard ratios [HR (95% CI)] were 2.2 (1.5–3.3), 1.6 (1.3–2.0) and 1.3 (1.0–1.7), respectively. Compared to subjects without CKD but similar baseline eGFR, subjects with stage 1 or 2 CKD showed a larger decline in eGFR (-1.1 versus -1.5 and -0.2 versus -0.6 ml/min/1.73 m^2/year, respectively, both $P < 0.01$). When subjects with stage 3 CKD were stratified according to the absence or presence of a UAE >30 mg/24 h, age- and sex-adjusted HRs for CVD were 1.0 (0.7–1.4) and 1.6 (1.1–2.3) and the change in eGFR was 0.2 versus -0.3 ml/min/1.73 m^2/year, respectively.

Conclusion. Subjects with stage 1 or 2 CKD have an increased risk for adverse cardiovascular and renal outcome and should receive equal attention as subjects with stage 3 CKD. Subdividing stage 3 CKD according to the presence or absence of a UAE >30 mg/24 h improves risk stratification within this stage.

Keywords: albuminuria; cardiovascular disease; chronic kidney disease; PREVEND; renal outcome

Introduction

Chronic kidney disease (CKD) is associated with adverse outcomes, mainly being end-stage renal failure and cardiovascular disease (CVD). Both outcomes have important clinical implications and are associated with high costs. Detection and treatment of patients in an early phase of CKD may improve outcome and quality of life [1–4]. In 2002 the Kidney Disease Outcomes Quality Initiative (K/DOQI) launched a series of clinical practice guidelines on CKD. The aim of these guidelines is to define CKD and classify its stages of severity, irrespective of the underlying cause of the kidney disease, in an attempt to stratify subjects according to their risk of the development of CVD and future loss of renal function. The K/DOQI guidelines define CKD as either kidney damage (i.e. micro- or macroalbuminuria) or decreased kidney function [1,2].

Since the introduction of the K/DOQI guidelines, studies on the consequences of CKD have focused more on stage 3 and 4 CKD than on stages 1 and 2. This is likely to be due to the perception that stages 1 and 2 consist of relatively mild CKD compared to the more impaired renal function in stages 3 and 4, suggesting that stages 1 and 2 are associated with less risk for unfavourable cardiovascular and renal outcome when compared to stage 3 CKD. However, an increased urinary albumin excretion (UAE), which is an important component of stage 1 and 2 CKD, has consistently

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been found to be a powerful predictor of both the development of CVD and loss of renal function in the diabetic, hypertensive and general population [5–11]. This indicates that stage 1 and 2 CKD may deserve more attention than they currently receive. Additionally, considering the consistency of the relationship between an increased UAE and the risk of developing CVD and loss of renal function, it can be expected that UAE can also be used to improve risk stratification for these outcomes in subjects with stage 3 CKD.

In this study we therefore evaluated cardiovascular and renal outcome in subjects with stage 1–3 CKD using data from a community-based cohort study. Second, we investigated the value of measuring UAE in subjects with stage 3 CKD to improve risk stratification for the development of CVD or loss of renal function.

Subjects and methods

Study design and population

This study is part of the ongoing PREVEND Study (Prevention of Renal and Vascular End-stage Disease), a large ongoing prospective cohort study investigating the predictive value of UAE for renal and CVD progression. Details of this study have been published elsewhere [12,13]. In short, all inhabitants of the city of Groningen, the Netherlands, aged 28–75 years ($n = 85.421$) were invited to send a morning urine sample to screen for high UAE. Of these subjects 40,856 (47.8%) responded. From these 40,856 subjects the PREVEND cohort was selected with the aim to create a cohort enriched for the presence of high albuminuria. All subjects with a urinary albumin concentration >10 mg/L ($n = 7768$) were invited, of which 6000 subjects participated. Furthermore, a random sample of subjects with a urinary albumin concentration <10 mg/L ($n = 3395$) was invited, of which 2592 subjects participated. Thus in total, 8592 individuals participated in the baseline survey (1997–1998). For this study we excluded subjects with missing data on UAE or serum creatinine at baseline ($n = 86$). Furthermore, subjects with K/DOQI stage 4 ($n = 8$) or stage 5 ($n = 3$) CKD were excluded. Thus, for this study we used data of 8495 subjects. The PREVEND Study is approved by the medical ethics committee of our institution and conducted in accordance with the guidelines of the declaration of Helsinki. All participants gave written informed consent.

Measurements and definitions

For the baseline survey participants completed two visits at our outpatient unit. Before the first visit all participants completed a questionnaire on demographics, cardiovascular and renal disease history, smoking habits and use of medication for hypertension, hyperlipidaemia or diabetes. During the first visit, height and weight were measured. Before the second visit two 24-h urine samples were collected after thorough oral and written instructions on the urine collection, and at this visit a fasting blood sample was drawn. During the first and second visit blood pressure was measured, in supine position, every minute for 10 and 8 min, respectively, with an automatic device (Dinamap XL Model 9300, Johnson-Johnson Medical, Tampa, FL, USA). Furthermore, information on drug use was collected from the InterAction database of the division of pharmacoepidemiology of our institution. This database contains pharmacy-dispensing data from all community pharmacies in the city of Groningen [14] and has information on the drug use of ∼80% of the subjects in the PREVEND Study.

Urinary albumin concentration was determined by nephelometry (BN^{TM}II Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-h UAEs. Plasma creatinine, plasma cholesterol and plasma glucose were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), an automated enzymatic method. Blood pressure values are given as the mean of the last two recordings of both visits.

Hypertension was defined according to the JNC7 guidelines as a systolic blood pressure $\geq$140 mmHg, a diastolic blood pressure $\geq$90 mmHg or the use of antihypertensive medication [15]. Diabetes was defined according to the guidelines of the American Diabetes Association as a fasting plasma glucose $\geq$7.0 mmol/l, a non-fasting plasma glucose $\geq$11.1 mmol/l or the use of anti-diabetic medication [16]. Renal function was estimated with the modified Modification of Diet in Renal Disease (MDRD) formula, taking into account gender, age, race and serum creatinine concentration [17]. CKD was defined according to the K/DOQI classification [2].

Follow-up and outcomes

For cardiovascular outcome we used the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity after the baseline screening. Data on mortality were received through the municipal register. Cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by the Dutch Central Bureau of Statistics. Information on hospitalization for cardiovascular morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses. All data were coded according to the International Classification of Diseases, 9th revision, and the classification of interventions. For this study cardiovascular events were defined as the following: acute myocardial infarction (ICD-code 410), acute and subacute ischaemic heart disease (411), coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, subarachnoid haemorrhage (430), intracerebral haemorrhage (431), other intracranial haemorrhage (432), occlusion or stenosis of the precerebral (433) or cerebral arteries (434) and other vascular interventions as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels. Survival time for the participants was defined as the period from the date of urine collection of the participant to the date of first cardiovascular event or 31 December 2005, until which date information about cardiovascular morbidity and mortality was available. If a person moved to an unknown destination ($n = 396$), the date on which the person was removed from the municipal registry was used as a census date.

To study renal outcome we evaluated the mean annual change of estimated glomerular filtration rate (eGFR) during the follow-up, as calculated by change in the eGFR divided by follow-up time in years. Follow-up data on

Table 1. Baseline characteristics

	Total population ($n = 8495$)	No CKD ($n = 6905$)	Stage 1 CKD ($n = 243$)	Stage 2 CKD ($n = 856$)	Stage 3 CKD ($n = 491$)
Age (years)	49.2 (12.7)	47.4 (12.1)	48.2 (11.6)†	56.5 (11.9)*,†	63.2 (9.1)*
Age >65 year (%)	16.3	11.9	10.3†	32.0*,†	53.4*
Male (%)	50.0	48.5	66.3*,†	64.1*,†	37.9*
Caucasian (%)	95.5	95.3	92.5$^{\wedge}$	96.9	97.3
BMI (kg/m^2)	26.1 (4.2)	25.7 (4.0)	27.8 (5.9)$*$	28.0 (4.5)*	27.5 (3.9)*
Smoking (%)	37.8	38.2	49.0*,†	39.0†	25.9*
SBP (mmHg)	129 (20)	126 (18)	137 (22)*,†	143 (23)*	142 (24)*
DBP (mmHg)	74 (10)	73 (9)	78 (11)*	80 (11)*,†	78 (10)*
Use of AHT (%)	15.6	11.9	18.6*,†	28.2*,†	46.3*
Cholesterol (mmol/l)	5.6 (1.1)	5.6 (1.1)	5.6 (1.1)†	6.0 (1.2)*	6.1 (1.2)*
Use of LLD (%)	6.4	4.9	7.9$^{\#,\dagger}$	11.5*,†	18.2*
Diabetes (%)	3.8	2.4	12.8*,†	11.2*,†	5.9*
Use of GLD (%)	1.8	1.2	4.9*	5.0*	2.9*
eGFR (ml/min/1.73 m^2)	81 (14)	82.9 (12.9)	100.1 (10.1)*,†	75.4 (8.0)*,†	53.5 (5.9)*
UAE (mg/24 h)	9.4 (6.3–17.8)	8.2 (6.0–12.5)	56.0 (38.6–101.5)*,†	59.0 (39.2–107.6)*,†	13.7 (7.0–48.3)*

CKD, chronic kidney disease stage; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHT, antihypertensive treatment; LLD, lipid lowering drugs; GLD, glucose lowering drugs; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion.
Continuous data are presented as mean (standard deviation), or as median (interquartile range) in case of skewed distribution. Categorical data are presented as number (percentage).
$^{*}P < 0.001$ versus No CKD; $^{\#}P < 0.05$ versus No CKD; $^{\dagger}P < 0.001$ versus Stage 3 CKD; $^{\wedge}P < 0.05$ versus Stage 3 CKD.

renal function were collected during the second *(2001–2003*) and third *(2003–2006)* screening of the PREVEND participants [18]. The last available renal function measurement was used to calculate the mean annual change of eGFR. Of 5552 participants, renal function was measured at the third screening. Additionally, renal function data measured at the second screening were available in 1281 participants.

Statistical analyses

Analyses were performed using the statistical package SPSS 12.0 (SPSS, Chicago, IL, USA). The level of significance was determined as $P < 0.05$. Continuous data are reported as mean with standard deviation, or as median and interquartile range in case of skewed distribution. Prevalence and incidence are presented as percentages. Differences between groups were tested by Student's *t*-test or a Mann–Whitney rank test for continuous data with a normal or skewed distribution, respectively. In the case of three or more groups one-way analysis of variance or the Kruskal–Wallis test were used. Differences in prevalence or incidence were tested with a chi-square test.

Incidence rates of cardiovascular events for different outcome categories were calculated. Kaplan–Meier and log-rank test methods were used to estimate and compare survival curves. Age- and sex-adjusted survival estimates for cardiovascular outcomes were determined using Cox proportional hazards analyses. The hazard ratio (HR) and 95% confidence interval (95% CI) are given. Linear regression was used for the unadjusted and the age- and sex-adjusted comparison of annual change of renal function between groups.

Role of funding sources

The funding for this study had no role in its design, conduct and analysis nor in the decision to submit the study for publication.

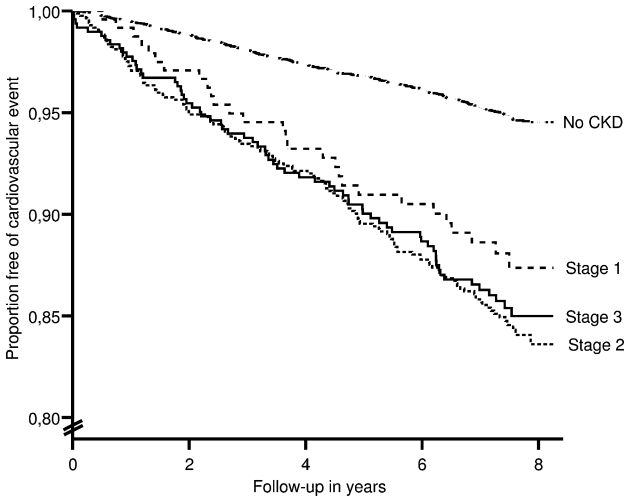

Fig. 1. Kaplan–Meier survival curves for survival of cardiovascular disease according to stages of chronic kidney disease.

Results

The baseline characteristics of the 8495 subjects are shown in Table 1. The mean eGFR in our study population was 80.9 ml/min/1.73 m^2. Of the 6905 subjects without CKD 26.4% had an eGFR >90 ml/min/1.73 m^2 and 73.6% had an eGFR between 60 and 90 ml/min/1.73 m^2. In total 18.7% of our population ($n = 1590$) was defined as having CKD, with the majority of subjects having stage 1 or 2 CKD (69%) and the remaining (31%) having stage 3 CKD. Of the 491 subjects with stage 3 CKD, 164 (33%) had a UAE >30 mg/24 h.

Cardiovascular outcome

We observed 59,508 person-years for cardiovascular events during a median follow-up of 7.5 years (interquartile range 6.9–7.8). In total 565 cardiovascular events occurred, giving a cumulative incidence of 6.7%. Figure 1 shows the

Kaplan–Meier survival curves by CKD stage. Subjects without CKD had the highest event-free survival rate. The incidence rate of cardiovascular events in this group was 7.0 events/1000 person-years. The event-free survival rates of subjects with stage 1, 2 or 3 CKD were significantly lower (all $P < 0.001$ versus no CKD). The incidence rates of cardiovascular events in these subjects were 17.2, 22.2 and 20.9 events/1000 person-years, respectively. The differences in cardiovascular event-rate between the different stages of CKD were not significant (P-values for difference >0.2).

There were substantial differences in age and sex distribution between the groups defined by the K/DOQI classification (Table 1). Therefore, analyses were repeated for cardiovascular outcome while correcting for these demographic differences. Figure 2A shows the age- and sex-adjusted survival curves for the different stages of CKD based on a Cox-regression model using the development of cardiovascular morbidity and mortality as outcome. Using no CKD as a reference group the HRs in this model were 2.2 [(95% CI) 1.5–3.3, $P < 0.001$], 1.6 (1.3–2.0, $P < 0.001$) and 1.3 (1.0–1.7, $P = 0.105$) for stage 1, 2 and 3 CKD, respectively. The differences between age- and sex-adjusted survival curves for stage 1–3 CKD did not reach statistical significance (P-values >0.09).

We further explored the relation between UAE, eGFR and cardiovascular (CV) risk in Figure 3. In the left panel (A) it can be seen that in the whole range of eGFR in our study an increase in UAE was associated with an increase in CV risk. This relationship remained after adjusting for age and sex (right panel). On the other hand, while there was an inverse association between eGFR and CV risk (left panel), this association disappeared after adjusting for age and sex. Accordingly, when subjects with stage 3 CKD were stratified according to the absence or presence of a UAE >30 mg/24 h, the crude incidence rate of cardiovascular events was significantly higher for subjects with stage 3 CKD and a UAE >30 mg/24 h (36.3 events/1000

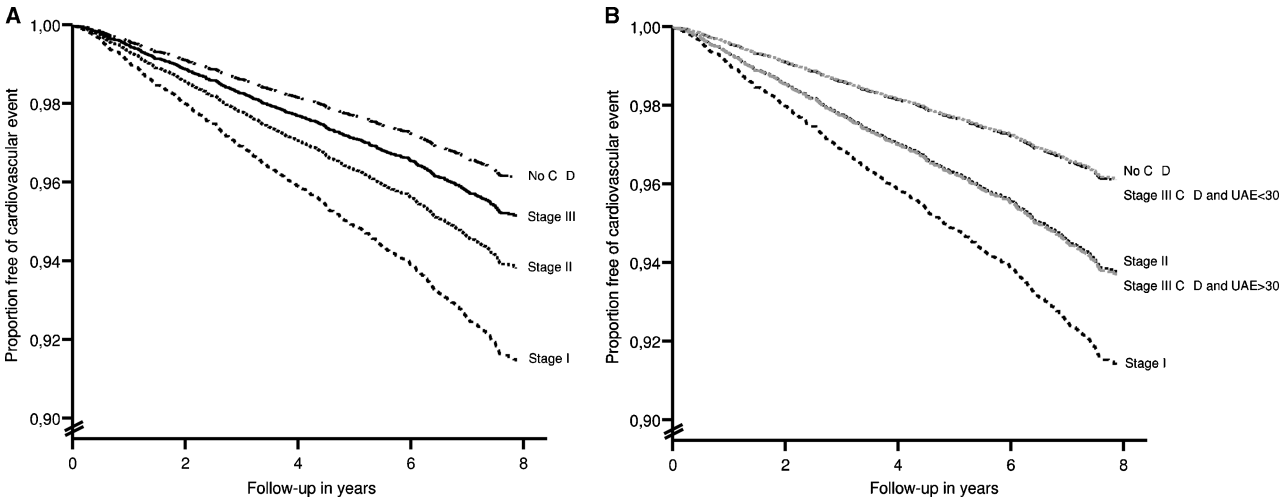

Fig. 2. Age- and sex-adjusted survival of cardiovascular disease. Left panel (**A**) shows cardiovascular survival according to the stages of chronic kidney disease. In the right panel (**B**) age- and sex-adjusted survival of cardiovascular disease is shown with subjects with stage 3 chronic kidney disease subdivided according to the presence or absence of urinary albumin excretion >30 mg/24 h. Graphs are based on cox proportional hazard analyses.

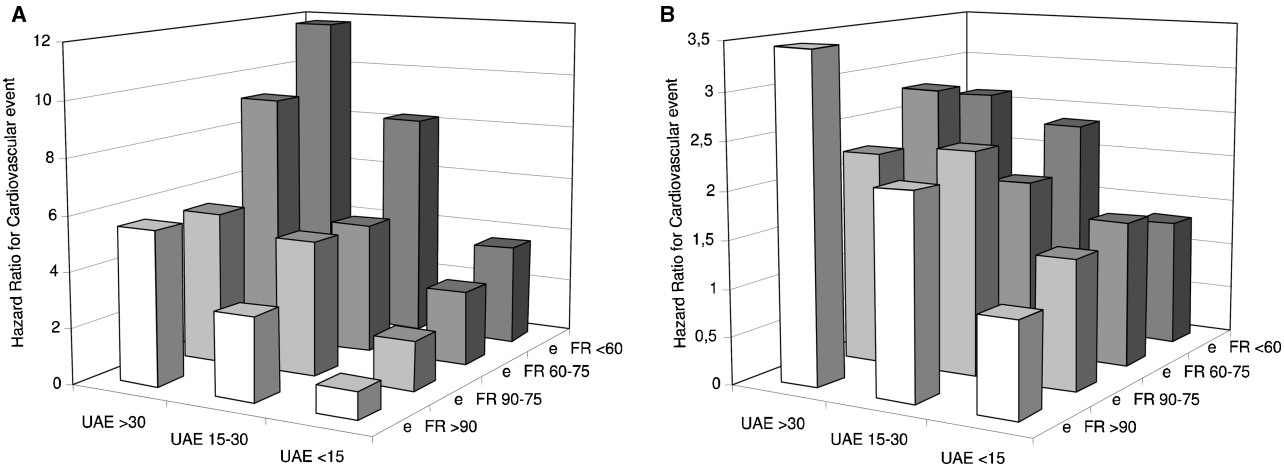

Fig. 3. Relation between urinary albumin excretion, glomerular filtration rate and risk of cardiovascular disease. Left panel (**A**) shows unadjusted results. Right panel (**B**) shows age- and sex-adjusted results.

Table 2. Annual change in eGFR according to the presence or absence of a UAE >30 mg/24 h and different levels of renal function

	Panel A		
	eGFR > 90 ml/min/1.73 m^2		
	UAE <30 mg/24 h (*no CKD*)	UAE >30 mg/24 h (stage 1 CKD)	*P*-value
Crude	−1.1 (−1.2 to −1.0)	−1.5 (−1.8 to −1.3)	0.005
Age and sex adjusted	−1.2 (−1.4 to −1.0)	−1.6 (−1.8 to −1.3)	0.019
	Panel B		
	eGFR 60–90		
	UAE <30 mg/24 h (*no CKD*)	UAE >30 mg/24 h (stage 2 CKD)	*P*-value
Crude	−0.2 (−0.3 to −0.1)	−0.6 (−0.7 to −0.4)	<0.001
Age and sex adjusted	−0.2 (−0.3 to −0.1)	−0.5 (−0.7 to −0.4)	<0.001
	Panel C		
	eGFR 30–60 (stage 3 CKD)		
	UAE <30 mg/24 h	UAE >30 mg/24 h	*P*-value
Crude	0.1 (−0.1 to 0.3)	−0.5 (−0.8 to −0.2)	<0.001
Age and sex adjusted	0.2 (0.0 to 0.5)	−0.3 (−0.7 to 0.0)	0.038

UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.
Unadjusted as well as age- and sex-adjusted data are given (mean with 95% confidence interval). Unit of annual change in eGFR is ml/min/1.73 m^2. Age- and sex-adjusted data represent mean annual change in eGFR for a male of 49.2 years (population mean). Due to the regression-to-the-mean principle annual changes in eGFR are compared only in groups with comparable renal function at baseline; panel A shows data for subjects with baseline eGFR >90 ml/min/1.73 m^2; panel B shows data for subjects with baseline eGFR of 60–90 ml/min/1.73 m^2; panel C shows data for subjects with the baseline eGFR of 30–60 ml/min/1.73 m^2.

person-years), than for subjects with stage 3 CKD and a UAE <30 mg/24 h (14.0 events/1000 person-years) ($P < 0.001$). Figure 2B shows the age- and sex-adjusted survival curves for stage 3 CKD with and without a UAE >30 mg/24 h. Adjusted for differences in age and sex the CV risk of subjects with stage 3 CKD with a UAE <30 mg/24 h was comparable to that of subjects without CKD [HR 1.0 (0.7–1.4), $P = 1.0$], whereas the risk for subjects with stage 3 CKD and a UAE >30 mg/24 h was significantly elevated [HR 1.6 (1.1–2.3), $P = 0.007$] and comparable with the CV risk of subjects with stage 1 or 2 CKD (*P*-values for difference >0.4).

It is possible that in some participants the results of the tests performed during screening may have led to institution of antihypertensive, lipid-lowering or anti-diabetic medication by their general practitioner, who was informed of our findings during screening. This screening-related start of medication may have influenced progression of cardiovascular and renal disease in the different groups of our cohort differently. As screening-related start of medication is most likely to occur in subjects with an unfavourable CV risk pattern, e.g. subjects with diabetes and stage 3 CKD, screening-related start of medication may lead to underestimation of the cardiovascular and renal disease progression in such subjects. We therefore repeated our analyses after adjustment for new use of antihypertensive, lipid-lowering or anti-diabetic medication started within 180 days after visiting our outpatient unit. This adjustment did not essentially change our results.

Renal outcome

We assessed the annual change in renal function during a median follow-up of 6.3 years (interquartile range 5.7–6.6). The mean annual change in eGFR for the total population was −0.5 ml/min/1.73 m^2 (SD 1.7). Table 2, panels A and B, show the annual change of eGFR in subjects with stage 1 or 2 CKD compared to subjects without CKD, but similar eGFR (>90 and 60–90 ml/min/1.73 m^2, respectively). Both subjects with stage 1 or 2 CKD showed a significantly larger annual decline in eGFR than subjects without CKD but comparable renal function. Adjusting for age and sex did not essentially change this finding. As can be seen in Table 2, panel C, subjects with stage 3 CKD and a UAE >30 mg/24 h showed an unfavourable change in renal function, compared to subjects with stage 3 CKD and a UAE <30 mg/24 h. This difference also remained significant after adjusting for age and sex. After adjusting for a possible screening related start of antihypertensive, lipid-lowering or anti-diabetic medication, subjects with a UAE >30 mg/24 h still showed a larger annual decline in eGFR than subjects with comparable eGFR, although in subjects with an eGFR >90 ml/min/1.73 m^2 this difference was no longer statistically significant ($P = 0.2$).

Discussion

This study shows that subjects with stage 1 or 2 CKD have a substantially increased risk for the development of

CVD and accelerated renal function loss when compared to subjects without CKD as defined according to the K/DOQI guidelines [1,2]. Furthermore, our findings show that using the additional criterion of the presence or absence of a UAE >30 mg/24 h it is possible to stratify subjects with stage 3 CKD in groups with respectively a high or low risk for the development of CVD and accelerated loss of renal function.

In our cohort there were large differences in age and sex distribution between the different stages of CKD. These differences are most likely due to loss of GFR with increasing age and the fact that women, compared to men, tend to have a relatively low GFR and less UAE [2,19–21]. Both age and sex are important potential confounders when studying risk factors for CVD. When we adjusted for these demographic differences the association between stage 3 CKD and the risk of developing a cardiovascular event was strongly attenuated. Furthermore, the survival curves after adjustment for age and sex (Figure 2A) suggest that subjects with stage 1 CKD have a higher CV risk than subjects with stage 3 CKD with similar age and sex, although this difference did not reach statistical significance. Thus, contrary to the goals of the K/DOQI guidelines, in our study population the present definition of stages of CKD did not stratify subjects with stage 1–3 CKD successfully for the risk of CVD.

Although it can be seen in Table 1 that besides demographic differences there were also other differences in baseline characteristics between CKD stages, e.g. prevalence of diabetes, it is important to realize that the aim of the K/DOQI guidelines is specifically to define CKD and classify its stages irrespective of the underlying cause [2]. We therefore chose not to report results adjusted for the other variables shown in the baseline table as these variables are strongly associated with causes of kidney disease, such as diabetic nephropathy and arteriosclerosis.

This failure to stratify successfully for CV risk may be due to the use of eGFR as the most important parameter for stratification of subjects with CKD. Whereas the presence of a UAE >30 mg/24 h is required only to define stage 1 and 2 CKD, specific eGFR values are required for the classification of all stages of CKD and are the only criterion used to define stage 3–5 CKD. Although kidney function, as indicated by the eGFR, is a marker of CV risk in high-risk populations or in subjects with a severely impaired GFR [3], the relation between kidney function and risk of CVD in low-risk populations seems modest, with most studies showing no or only a weak relation [3,22–25]. Also in our low-risk population the CV risk associated with eGFR is weak, as illustrated by the age- and sex-adjusted graph in Figure 3. In contrast, UAE has consistently been found to be a strong and independent predictor of the development of CVD, including in low-risk or community-based populations [9,11,26]. Thus, at least in the general low-risk population, the additional criterion used to define stage 1 and 2 CKD, being a UAE >30 mg/24 h, is stronger associated with CV risk than the single renal function parameter used to define stage 3 CKD. In line with these observations we found that subjects with stage 3 CKD and a UAE <30 mg/24 h did not have an increased risk of CVD after adjustment for age and sex, whereas subjects with stage 3 and a UAE >30 mg/24 h did have an increased risk of CVD comparable to the CV risk seen in subjects with stage 1 or 2 CKD.

Although, as mentioned above, in community-based populations UAE is a much stronger predictor of CV risk compared to renal function, the observations in Figure 2A and B may still be surprising at first sight. In this figure it appears (although the difference was not statistically significant) that subjects with high UAE but the best renal function (CKD stage 1) are at a higher risk of CVD than subjects with high UAE and lower renal function (CKD stages 2 and 3). It is possible that this observation is due to the biphasic pattern in renal function that is associated with the development of high UAE [12,27]. Albuminuria is associated with both glomerular hyperfiltration and impaired filtration [12,27]. The phase of hyperfiltration in fact is the first abnormality indicating progressive renal and vascular damage. In fact, it is also clear from Table 1 that in this stage 1 CKD some CV risk factors are more prominent than in the stage 3 CKD, such as male sex, smoking and diabetes. This over-representation of CV risk factors in stage 1 may also explain why CV event rates are (insignificantly) higher in stage 1 than stage 3.

Whether the K/DOQI classification of CKD successfully stratifies subjects with stage 1–CKD for risk of renal function loss cannot be answered with our data, as the renal function decline in different stages of CKD cannot be compared due to regression-to-the-mean principle [28]. This is the principle that with repeated measurements, when subjects are selected at the first measurement for having a high value for eGFR, these subjects tend to have at a repeated measurement a lower value that lies closer to the population mean than their measured value at the first measurement and vice versa. Indeed due to this principle subjects initially selected for a high eGFR (>90 ml/min/1.73 m^2) showed the largest decrease in eGFR during the follow-up, whereas subjects selected for a low eGFR (30–60 ml/min/1.73 m^2) showed only a small decrease or even an increase in eGFR (Table 2). We therefore only compared the annual change in renal function of subjects with stage 1 or 2 CKD with subjects without CKD, but comparable renal function. Our findings suggest that subjects with stage 1 or 2 CKD are at increased risk of accelerated renal function loss compared to subjects with comparable eGFR but with a UAE <30 mg/24 h.

Some limitations of our study need to be mentioned. First, the K/DOQI guidelines on CKD require increased UAE or decreased eGFR to be present for >3 months [1,2]. However, a repeated measurement of UAE or eGFR is not available in the PREVEND Study and therefore some subjects may have been falsely classified as having CKD. It cannot be excluded that this misclassification has led to an underestimation of the risk for the development of CVD and renal function loss in subjects with CKD. Second, there are data suggesting that risk of adverse events increases when eGFR drops below 45 ml/min/173 m^2 [19,24]. In our study there were not enough subjects with an eGFR <45 ml/min/173 m^2 ($n = 52$) to investigate this. Thus, we cannot exclude that our study underestimated the cardiovascular and renal risk in this subgroup. Third, due to mortality or decline of participation, we do not have data available on change in renal function in 1662 subjects.

Compared to subjects with similar CKD stage but follow-up data available, these subjects were more frequently male, older and had higher UAE at baseline, although the differences were small. As these parameters are associated with worse renal outcome, it seems likely that loss to follow-up may have led to underestimation of renal function loss in the different stages of CKD [7,29]. Fourth, the MDRD equation to estimate GFR has been derived from subjects with at least moderately impaired renal function. Studies have shown that in subjects without renal disease this equation may underestimate true renal function [30,31]. Therefore it is possible that in the current study we underestimated renal function in subjects with an eGFR >60 ml/min/1.73 m^2. However, such bias would not affect our finding that stage 1 and 2 CKD are associated with increased CV risk, especially as this risk was mainly dependent on the presence of high UAE. Finally, we did not calibrate our method for measuring serum creatinine to an international standard. Failure to calibrate may influence the estimated prevalence of the different stages of CKD [1]. However, such a calibration will not influence the association between eGFR and risk of development of CVD or loss of renal function. Furthermore, as the risk entailed by a UAE >30 mg/24 h is comparable over the whole range of eGFR (Figure 3 and Table 2) it is unlikely that calibration of our assay for measuring serum creatinine would change the essence of our findings.

Strengths of this study are the use of a large community-based cohort, the use of two 24-h urine samples to estimate UAE and the availability of longitudinal data on eGFR. Furthermore, the availability of pharmacy-dispensing data allowed us to adjust for possible screening-related start of medication, improving the generalizibility of our findings to subjects outside the setting of a prospective cohort-study. Finally, as the first study to investigate the longitudinal cardiovascular and renal outcomes in stage 1–3 CKD using a community-based cohort this study is in our opinion an important contribution to our knowledge on the use of the K/DOQI classification of CKD in practice.

In summary, our data show subjects with stage 1 or 2 CKD to be at increased risk for CVD and accelerated renal function loss. With the aim of early detection and treatment of CKD in mind we hope that this finding will increase the interest for screening for stage 1 and 2 CKD. Furthermore, subjects with stage 3 CKD but a UAE <30 mg/24 h were found not to be at increased CV risk, whereas subjects with stage 3 CKD and a UAE >30 mg/24 h had a CV risk comparable to stage 1 and 2 CKD and had more renal function loss compared to subjects with stage 3 CKD but a UAE <30 mg/24 h. These findings suggest that with the goal of risk stratification in mind, an evaluation of the current K/DOQI classification of CKD may be mandatory. This evaluation should consider to split stage 3 CKD into two groups according to the presence or absence of a UAE >30 mg/24 h.

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Conflict of interest statement. None declared.

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