Influence of Age and Measure of eGFR on the Association between Renal Function and Cardiovascular Events

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Background and objectives: This study investigates whether the association between estimated GFR (eGFR) and cardiovascular (CV) outcome differs for different measures of eGFR and different age groups.

Design, setting, participants, & measurements: Between 1997 and 1998, 8047 participants visited our outpatient clinic for measurement of serum creatinine, serum cystatin C, urinary creatinine, and urinary albumin excretion. GFR was estimated by the Modification of Diet in Renal Disease formula, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, a cystatin C–based formula, a formula combining serum creatinine and cystatin C, and 24-hour creatinine clearance. Subjects had follow-up on CV events until 2005.

Results: During follow-up, 530 subjects had a CV event. The association between eGFR and CV events was significantly modified by age, except when GFR was estimated by 24-hour creatinine clearance. In subjects <60 years of age, all measures of eGFR were independently and significantly associated with CV events, whereas in subjects ≥60 years of age only 24-hour creatinine clearance had a weak but significant association with CV events. For all measures and all levels of eGFR, subjects with elevated levels of albuminuria were at higher risk of CV events compared with subjects with normoalbuminuria.

Conclusions: In the general population, all measures of eGFR are independently and significantly associated with CV events in individuals <60 years of age, but in subjects ≥60 years of age, only 24-hour creatinine clearance is. In general, the association between eGFR and risk of CV events is weaker in elderly subjects than in younger subjects.

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Nowadays it is often assumed that impaired renal function or chronic kidney disease (CKD) is associated with an increased risk of cardiovascular (CV) events (1,2). There seems to be a continuous and inverse relation between the level of renal function and the risk of CV disease (3,4), although some studies report that estimated GFR (eGFR) is associated with CV risk only beyond a certain threshold (2,5). Therefore, CKD patients are regarded as being high CV risk patients.

Nevertheless, some studies have shown contradictory findings that, in the general population, an eGFR as low as 30 to 59 ml/min per 1.73 m^2 (stage 3 CKD) is not associated with increased CV risk when there is no microalbuminuria or proteinuria present (5–7). This could be explained by the finding that the prognosis associated with eGFR level may vary based on presence and level of proteinuria (8). Another reason why some studies may not have found an association between eGFR and CV events could be that, in these studies, GFR was estimated by the Modification of Diet in Renal Disease (MDRD) formula. In the general population, values derived by this formula may not be reliable estimates of true GFR (9). Other GFR estimation equations based on serum creatinine

(Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) (10) or serum cystatin C (CysC) could be more accurate (11,12). A third reason for different findings with regard to the association of eGFR with CV risk may be differences in age between study populations. It has been shown by O'Hare *et al.* (13) that the association between eGFR (MDRD) and mortality differed among different age groups, with no increased risk of mortality for moderately reduced eGFR in elderly. Nevertheless, other studies did find an increased risk of mortality for eGFR <60 ml/min per 1.73 m^2 in the elderly (14).

Given these considerations, we wanted to investigate, first, whether, in the general adult population, impaired renal function is associated with increased risk of CV events independent of albuminuria level. Second, we wanted to assess the association between various measures of eGFR based on serum creatinine and/or CysC with CV events. Third, we studied whether the association between the various measures of eGFR and CV events differs for different age groups.

Materials and Methods
Study Design and Population
The Prevention of Renal and Vascular Endstage Disease (PREVEND) study is a prospective observational cohort study designed to investigate the association between urinary albumin excretion (UAE) and renal and cardiovascular outcome in the general population. In 1997 to 1998, the participants of the PREVEND cohort were selected from 40,856 inhabitants of the city of Groningen, The Netherlands. Selection was based on the albumin concentration in a spot morning urine

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sample, to obtain a cohort enriched for the presence of elevated albuminuria levels. In total, 8592 subjects joined the PREVEND study cohort who participated in the first screening round in 1997 to 1998. Details of the study protocol have been published elsewhere (15–17).

For this study, subjects who had missing values for either serum creatinine, serum CysC, urinary creatinine, or UAE were excluded (n = 545). Therefore, for all subjects in this study, all aforementioned variables are available. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

Baseline Measurements and Definitions

At baseline, PREVEND study participants had two visits to the study outpatient clinic within ~3 weeks. Participants filled out a questionnaire on demographics, CV and renal history, and known CV risk factors. Known CV disease was defined as having a history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and/or a history of a cerebrovascular accident, as indicated on the baseline questionnaire. "Known hypertension" was assigned when the subjects received medical treatment for high blood pressure (BP), whereas "known with diabetes mellitus" was assigned when the patient received treatment for diabetes mellitus according to their local pharmacy registry or as indicated by the patient on the baseline questionnaire. Active smoking was defined as current smoking or cessation of smoking less than a year before the study visit. During both study visits, BP was measured in the right arm in the supine position, 10 times at the first visit and 8 times at the second visit, with a 1-minute interval, by an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, FL). For systolic and diastolic BP, the means of the last two recordings from each of the two visits were used. Anthropometric measurements were performed. Within 1 week before the second study visit, subjects collected urine for two consecutive periods of 24 hours. The samples were allowed to be stored for a maximum of 4 days at a temperature of 4°C before turning them in. At the second study visit, fasting blood samples were taken. Concentrations of total cholesterol and glucose were measured using standard methods. Serum and urine creatinine were measured by dry chemistry (Eastman Kodak, Rochester, NY). In 2006, an isotope dilution mass spectrometry (IDMS)-traceable method was introduced in the hospital (Roche P-Modular). A conversion factor was calculated between the Eastman Kodak and Roche enzymatic measurements by measuring 200 samples on both machines and using regression analysis according to Passing and Bablock (18). This conversion factor was used to calculate IDMS-traceable eGFR values that are used in our sensitivity analysis. Urinary albumin concentration was determined in fresh urine samples by nephelometry (Dade Behring Diagnostic, Marburg, Germany), and UAE was given as the mean of the two 24-hour urinary excretions.

GFR was estimated by 24-hour creatinine clearance and four different equations—the MDRD equation, the CKD-EPI equation, an equation based on cystatin C, and an equation based on cystatin C and serum creatinine (Combi)—which are listed in Supplemental Information. Twenty-four-hour creatinine clearance was adjusted for body surface area (BSA) and calculated by the following formula: (urine creatinine [mmol/L] × 1000/serum creatinine [μmol/L]) × (24 hr volume urine [ml]/1440) × (1.73 m²/BSA). The Dubois Dubois formula was used to calculate BSA (19).

Follow-up Measurements and Definitions

During follow-up, information was obtained on CV endpoints until December 31, 2005. The CV endpoint was defined as the incidence of fatal and nonfatal CV events. Causes of death were obtained from the Dutch Central Bureau of Statistics. Hospital diagnoses were obtained from the Dutch registry of hospital discharge diagnoses (PRISMANT). The validity of this database has been shown to be good, with 84% of primary diagnoses and 87% of secondary diagnoses matching the diagnoses recorded in patients' charts (19). All data were coded according to the International Classification of Diseases (ICD), 9th revision, and the classification of interventions. For this study, CV events were defined in concordance with definitions used previously by other studies publishing on eGFR and CV events (2,20), being acute myocardial infarction (ICD 410), acute and subacute ischemic heart disease (ICD 411), subarachnoid hemorrhage (ICD 430), occlusion or stenosis of the precerebral (ICD 433) or cerebral arteries (ICD 434), coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, and other vascular interventions as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels. Survival time of a subject was defined as the time between the date of UAE measurement to the date of first CV event or December 31, 2005. People who moved to an unknown destination were lost to follow-up and censored from that time on.

Statistical Analyses

Analyses were performed using the statistical package SPSS 16.0 (SPSS, Chicago, IL) and R statistical software version 2.8.0 (21). $P \leq 0.05$ was adopted to indicate statistical significance. Normally distributed data are reported as means with SD, whereas data with skewed distribution are given as medians with interquartile range. Differences between groups were tested by t test for continuous data. Differences in prevalence or incidence were tested with a χ^2 test.

Cox proportional hazards analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (95% CI) for cardiovascular events. Complex sample analysis was used to correct for the enrichment of subjects with elevated albuminuria that was introduced by the study design.

Results

The baseline characteristics of the 8047 subjects in this analysis are shown in Table 1, showing that the various measures of eGFR differ with respect to the mean values that are obtained for the study population. eGFR by MDRD was lowest with 81 ml/min per 1.73 m², whereas the mean eGFR by CysC was highest with a mean of 101 ml/min per 1.73 m². Differences between measures of eGFR values are also shown in Figure 1. Figure 1 shows that for all measures except for measures based on serum creatinine solely, i.e., MDRD and CKD-EPI, the majority of subjects belonged to the group of eGFR >90 ml/min per 1.73 m². Furthermore, ~6 to 8% of the subjects had an eGFR <60 ml/min per 1.73 m² when estimated with the MDRD or CKD-EPI equation or 24-hour creatinine clearance. The equations including CysC estimated that only 3.8% of the subjects had a value <60 ml/min per 1.73 m².

During a mean follow-up time of 7.0 ± 1.6 years, 530 subjects had a CV event. Myocardial infarction was the most common event (n = 160, 30.2%), followed by ischemic heart disease (n = 103, 19.4%), percutaneous transluminal coronary angioplasty (n = 76, 14.3%), ischemic cerebrovascular accidents 13.5% (n = 50), and hemorrhagic cerebrovascular accidents (n = 27, 5.1%). The association between the different measures of eGFR was first analyzed continuously using linear and quadratic terms to allow for nonlinear associations. For this purpose, a quadratic term of eGFR was introduced in the linear regression models

Table 1. Baseline characteristics

	Total ($n = 8047$)
Age	49 (13)
Male, %	50
Body mass index, kg/m^2	26 (4)
BSA, m^2	1.91 (0.2)
Known hypertension, %	16
Known diabetes mellitus, %	1.8
Known cardiovascular disease, %	5.2
Smoking, %	38
Systolic BP, mmHg	129 (20)
Diastolic BP, mmHg	74 (10)
Anti-hypertensive medication, %	16
Cholesterol, mmol/L	5.6 (1.1)
Lipid-lowering medication, %	4.9
Glucose, mmol/L	4.9 (1.2)
Glucose lowering medication, %	1.8
eGFR MDRD, ml/min per 1.73 m^2	81 (15)
eGFR CKD EPI, ml/min per 1.73 m^2	84 (16)
eGFR CysC, ml/min per 1.73 m^2	101 (28)
eGFR combined, ml/min per 1.73 m^2	91 (18)
24-hour creatinine clearance, ml/min per 1.73 m^2	92 (23)
UAE, mg/24 h	9.4 (6.3 to 17.8)

Values are mean (SD) or median (interquartile range).
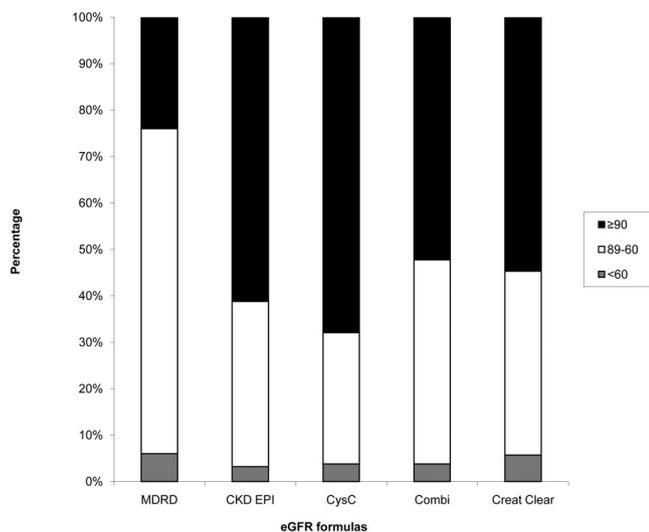

Figure 1. Distribution of eGFR classes for the five different measures of eGFR.

including age, gender, and eGFR. The quadratic term did not seem to be significant for any of the measures of eGFR.

Therefore, the association of the five different measures of eGFR with CV events was established by linear Cox regression models (Table 2). In univariate analysis, all measures of eGFR were inversely and significantly associated with CV events: the higher the eGFR, the lower the risk of CV events. After the

Table 2. Hazard ratio of eGFR for CV outcomes in continuous models

eGFR by	Model 1: Crude		Model 2: + Age + Gender		Model 3: + ln UAE		Model 4: + CV Risk Factors		Interaction Term: Age × eGFR	
	HR	CI	HR	CI	HR	CI	HR	CI	HR	P
MDRD (per 10 ml/min per 1.73 m^2)	0.76	0.71 to 0.82	0.93	0.86 to 1.01	0.96	0.88 to 1.03	0.95	0.88 to 1.02	1.01	<0.001
CKD EPI (per 10 ml/min per 1.73 m^2)	0.68	0.64 to 0.73	0.92	0.85 to 1.00	0.94	0.87 to 1.02	0.94	0.87 to 1.02	1.02	<0.001
CysC (per 10 ml/min per 1.73 m^2)	0.77	0.74 to 0.80	0.90	0.86 to 0.95	0.91	0.87 to 0.96	0.95	0.90 to 0.99	1.01	0.002
Combi (per 10 ml/min per 1.73 m^2)	0.69	0.64 to 0.73	0.87	0.82 to 0.94	0.90	0.84 to 0.96	0.93	0.86 to 0.99	1.01	<0.001
Creatinine clearance (per 10 ml/min per 1.73 m^2)	0.86	0.82 to 0.90	0.94	0.90 to 0.98	0.94	0.89 to 0.98	0.95	0.91 to 0.99	1.01	0.40

CV risk factors: body mass index, systolic BP, total cholesterol (mmol/L), fasting glucose (mmol/L), smoking status, history of CV disease.

adjustment for age and gender (model 2), the associations of all measures of eGFR with CV events become weaker (the HRs get closer to 1), but eGFR by MDRD does not reach statistical significance anymore ($P = 0.09$). After further adjustment for the level of albuminuria, eGFR by CKD-EPI is not significant anymore ($P = 0.16$). In contrast, the associations of eGFR calculated using CysC-based formulas and that of 24-hour creatinine clearance with CV events remain significant, even after further adjustment for albuminuria level (model 3) and CV risk factors (model 4). An interaction term of age with eGFR (age × eGFR) was tested for all five measures of eGFR in model 4, which included eGFR, age, gender, age × eGFR, and CV risk factors. For the association with risk of CV events, there was a significant interaction between age and eGFR for all measures of eGFR derived by equations: MDRD ($P < 0.001$), CKD EPI ($P < 0.001$), CysC ($P = 0.005$), and Combi ($P < 0.001$). In contrast, there was no interaction between age and 24-hour creatinine clearance in the association with CV risk ($P = 0.4$; Table 2). Because of the interactions with age for the measures of eGFR derived by equations, further analyses were stratified for age. Interaction terms consisting of eGFR times a dichotomous variable for age, for example <40/≥40 years, were made including age cut-points for every 5 years between 40 and 70 years. It appeared that the interaction term reached significance around 55 to 65 years of age, depending on the specific eGFR measure. Because guidelines recommend to screen subjects ≥60 years of age and this cut-off point was supported by the data, a cut-off point at 60 years was chosen (1). To support this decision, it was checked whether the dichotomous variable <60 or ≥ 60 years also showed a significant interaction with eGFR. This was true for all GFR equations, but again not for 24 h-creatinine clearance ($P = 0.96$).

The results of the continuous association between eGFR and CV events for different age groups are shown in Table 3. The interaction with age is reflected by the finding that, for all eGFRs derived by equations, there is a significant association of eGFR with risk of CV events in subjects younger than 60 years of age, even after adjustment for multiple variables (model 4), whereas there is no independent significant association in subjects 60 years of age and over. For 24-hour creatinine clearance, however, the association with the risk of CV events is present in both the younger and older population (HR = 0.93, 95% CI = 0.87 to 1.00 and HR = 0.94, 95% CI = 0.88 to 0.99, respectively, for every 10 ml/min per 1.73 m² increase in eGFR).

The differences in the association between eGFR and CV events in older and younger subjects is shown in Figure 2. In Figure 2, data are shown in clinical classes using eGFR estimated by the MDRD formula, with cut-points being comparable to the Kidney Disease Outcomes Quality Initiative classification of CKD. For the subjects younger than 60 years of age, the risk of CV events increases linearly with decreasing eGFR. In subjects older than 60 years of age, however, there is no relation with eGFR and the risk of CV events. The pattern of association for the other GFR equations are rather similar to eGFR MDRD, being that there is a significant linear association between eGFR level and risk of CV events in the younger age group but that there is no relation between eGFR and risk of CV events in the

Table 3. Adjusted hazard ratios of eGFR for CV outcomes for subjects younger and older than 60 years of age

eGFR by	Model 1: Crude		Model 2: + Gender		Model 3: + ln UAE		Model 4: + CV Risk Factors	
	HR	CI	HR	CI	HR	CI	HR	CI
Age <60 years								
MDRD (+10 ml/min per 1.73 m²)	0.76	0.67 to 0.86	0.66	0.58 to 0.75	0.68	0.60 to 0.78	0.71	0.63 to 0.81
CKD EPI (+10 ml/min per 1.73 m²)	0.70	0.62 to 0.79	0.65	0.58 to 0.73	0.67	0.60 to 0.75	0.70	0.62 to 0.79
CysC (+10 ml/min per 1.73 m²)	0.80	0.75 to 0.86	0.80	0.75 to 0.85	0.81	0.76 to 0.86	0.86	0.79 to 0.92
Combi (+10 ml/min per 1.73 m²)	0.69	0.62 to 0.76	0.66	0.60 to 0.73	0.68	0.61 to 0.75	0.74	0.66 to 0.82
Creatinine clearance (+10 ml/min per 1.73 m²)	0.86	0.78 to 0.95	0.82	0.75 to 0.91	0.80	0.73 to 0.89	0.93	0.87 to 1.00
Age ≥60 years								
MDRD (+10 ml/min per 1.73 m²)	1.08	0.98 to 1.19	1.00	0.91 to 1.11	1.03	0.93 to 1.13	1.03	0.94 to 1.14
CKD EPI (+10 ml/min per 1.73 m²)	1.03	0.93 to 1.14	0.97	0.88 to 1.08	1.03	0.93 to 1.13	1.02	0.92 to 1.13
CysC (+10 ml/min per 1.73 m²)	0.93	0.87 to 0.99	0.92	0.86 to 0.98	0.94	0.88 to 1.00	0.97	0.91 to 1.04
Combi (+10 ml/min per 1.73 m²)	0.96	0.88 to 1.05	0.92	0.85 to 1.01	0.95	0.87 to 1.04	0.99	0.90 to 1.08
Creatinine clearance (+10 ml/min per 1.73 m²)	0.92	0.85 to 0.99	0.88	0.81 to 0.95	0.88	0.82 to 0.95	0.94	0.88 to 0.99

CV risk factors: body mass index, systolic BP, total cholesterol (mmol/L), fasting glucose (mmol/L), smoking status, history of CV disease.
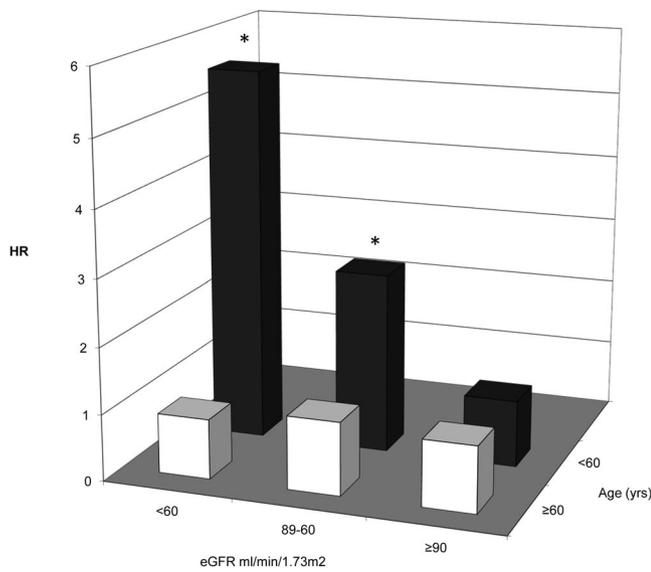
Figure 2. Hazard ratios for CV events per clinical class of eGFR by MDRD, in younger and older subjects, with reference cells being eGFR ≥90 in both age groups. Hazard ratios are adjusted for gender, UAE, total cholesterol, fasting glucose, systolic BP, smoking status, and CVD history. *P < 0.05.

older age group. Only for creatinine clearance is there a stepwise, linear association between eGFR and the risk of CV events in elderly subjects. In Table 4, the association between the clinical classes of different measures of eGFR and the risk of CV events in elderly is shown, but now also stratified by the level of albuminuria (normoalbuminuria *versus* elevated levels of albuminuria, being UAE ≥30 mg/24 h). It is shown that subjects with elevated levels of albuminuria are at increased risk of CV events compared with subjects with normoalbuminuria for any given level of eGFR and for every eGFR measure.

Two sensitivity analyses were performed. First, the former analyses were repeated after excluding subjects with diabetes mellitus. This did not change the results. Second, a correction factor was used to obtain serum creatinine values that are IDMS traceable, as explained in the Materials and Methods section. The appropriate MDRD equation was used (10), and the other eGFR equations using serum creatinine were recalculated and used for the sensitivity analysis. Again, the results did not change essentially.

Discussion

This study showed that, in the general adult population, there seems to be an association between eGFR and CV events. However, this association differs for different measures of eGFR and among different age groups. The GFR equations based solely on serum creatinine (MDRD and CKD EPI) were not independently associated with CV events, whereas other measures of eGFR (equations including CysC solely or including both CysC and serum creatinine) and 24-hour creatinine clearance were. Our findings show that age modifies the relation between eGFR and risk of CV events for all measures of eGFR based on equations but not for 24-hour creatinine clearance. In individuals younger than 60 years of age, all measures of eGFR were continuously and linearly associated with CV risk, whereas in the individuals 60 years of age or older, only 24-hour creatinine clearance had an independent, continuous association with CV risk. Of note, elderly with increased levels of UAE were at increased risk of CV events compared with subjects with normoalbuminuria, irrespective of the level of eGFR.

Guidelines recommend that "all patients with chronic kidney disease should be considered to belong to the 'highest risk' group for cardiovascular disease, irrespective of levels of traditional CVD risk factors" (1). The same guidelines define CKD by levels of eGFR calculated by the MDRD formula. Logically, it is implied that lower levels of eGFR are associated with

Table 4. Adjusted hazard ratios for CV events for clinical classes of eGFR, split for UAE < 30 mg/24 h (MA−) and UAE ≥ 30 mg/24 h (MA+)

eGFR by	eGFR ≥ 90	eGFR 89 to 60	eGFR < 60
MDRD			
MA+	2.7 (1.1 to 6.6)	1.5 (0.8 to 2.8)	2.5 (1.2 to 5.2)
MA−	1	1.4 (0.8 to 2.3)	0.8 (0.4 to 1.6)
CKD EPI			
MA+	1.3 (0.4 to 2.9)	1.4 (0.7 to 2.7)	2.1 (1.0 to 2.4)
MA−	1	1.1 (0.6 to 1.9)	0.8 (0.4 to 1.6)
CysC			
MA+	1.7 (0.9 to 3.1)	1.4 (0.9 to 2.3)	2.1 (1.0 to 4.3)
MA−	1	1.1 (0.8 to 1.5)	1.5 (0.9 to 2.4)
Combi			
MA+	1.4 (0.7 to 3.0)	1.1 (0.7 to 1.9)	1.6 (0.8 to 3.1)
MA−	1	0.8 (0.6 to 1.2)	0.8 (0.5 to 1.5)
24-hour creatinine clearance			
MA+	1.2 (0.7 to 2.3)	1.8 (1.1 to 2.9)	2.1 (1.1 to 4.0)
MA−	1	1.1 (0.8 to 2.6)	1.2 (0.8 to 2.9)

CV risk factors: body mass index, systolic blood pressure, total cholesterol (mmol/L), fasting glucose (mmol/L), smoking status, history of CV disease.

increased risk of CV events, as has also been shown by several studies (2–4,14). However, this study showed that whether a low eGFR is associated with increased risk of CV events depends on the measure of eGFR that is used and the patient's age. These findings could have important implications for CV risk assessment based on the presence of CKD, for which it would be important to identify the measure of eGFR that is the best predictor of CV events.

Nowadays, the MDRD formula is the most commonly used measure of eGFR. However, eGFR MDRD is based on serum creatinine levels, which are not an ideal way to estimate renal function because serum creatinine is not only affected by the level of GFR, but also by factors independent of GFR, especially muscle mass. Although the MDRD formula is developed to correct for differences in muscle mass by use of information on age, gender, and race, corrections are incomplete and errors in using serum creatinine as a measure of GFR remain. Furthermore, the equation may not be suitable for individuals with a true GFR >60 ml/min per 1.73 m^2 (9). Recently, the CKD EPI equation was developed, which has claimed to correlate better with true GFR, especially in the higher ranges (10). However, the findings of this study showed that CKD EPI did not perform substantially better than the MDRD in predicting CV events. In this study, eGFR equations that include CysC seem to be stronger correlated with the risk of CV events than eGFR using serum creatinine alone. However, whether equations using CysC may be more accurate predictors of true GFR is still under debate (11,12,22). We want to emphasize that better prediction of CV events by one eGFR measure does not necessarily imply that this eGFR measure is a more accurate reflection of true GFR. Studies have shown that CysC is associated with inflammatory markers (23), which are themselves associated with an increased risk of CV events (24). Therefore, the strong association between eGFR based (partly) on CysC and the risk of CV events may not reflect eGFR CysC being a more accurate measure of true eGFR, but CysC being associated with other markers associated with CV events.

Our data showed for most GFR estimates a significant interaction with age in predicting CV outcome, including eGFR CysC, which has previously been claimed to be independent of age (25). In younger subjects, all measures of eGFR are associated with the risk of CV events. In contrast, in the elderly, all measures of eGFR calculated by estimating equations are not independently associated with CV risk. These data are in line with other studies. O'Hare *et al.* (13,26) showed less association between eGFR MDRD and risk for mortality and ESRD in older age groups. Drey *et al.* (27) also showed that the age- and gender-standardized mortality ratio in subjects with increased levels of serum creatinine (≥1.7 mg/dl) decreases with increasing age. Also, Raymond *et al.* (29) have shown that with increasing age, the relative risk of mortality for decreasing eGFR becomes less strong, with (at age >75 years) stage 3a CKD (eGFR 59 to 45 ml/min per 1.73 m^2) not being associated with increased risk of mortality compared with stage 1 and 2 CKD. On the other hand, the Cardiovascular Health Study (CHS) did describe an association between eGFR and mortality in a population with only elderly subjects (14). Although this latter finding may seem conflicting with the aforementioned studies, the results in the CHS study are for a large part in line with

these studies. First, the association between eGFR and CV risk in the CHS study had a J-shaped form. The association between and eGFR of 120 and 45 ml/min per 1.73 m^2 was modest (HR = 1.0 to 1.5) and only got stronger in subjects with an eGFR <45 ml/min per 1.73 m^2. In this study, which is a sample of the general adult population, there are very few data on subjects with an eGFR <45 ml/min per 1.73 m^2. Furthermore, the CHS study showed a stronger association between CysC and mortality, comparable to our findings.

Do our data imply that, in the elderly, there is no association between renal function and CV risk? Probably not. First, as mentioned above, there seems to be an increased risk of mortality below an eGFR of 45 ml/min per 1.73 m^2. Second, in this study, 24-hour creatinine clearance, which is a more direct measure of GFR, did show an association between eGFR and CV events in the young and the elderly. Of course 24-hour urinary creatinine clearance is not the gold standard for assessing true GFR. For this purpose, one should assess an inulin or iothalamate clearance. However, for large-scale epidemiologic studies, use of these gold standard measurements is not feasible. Therefore, creatinine clearance may the best alternative to assess true GFR, especially in subjects with relatively low or high muscle mass, where serum creatinine–based GFR estimates will result in over- and underestimation, respectively, of true GFR. The findings of this study underscore the use of 24-hour creatinine clearance for the assessment of CKD. However, collecting 24-hour urine is a cumbersome procedure and prone to collection errors. Therefore, assessing 24-hour creatinine clearance is less suitable for screening purposes. A practical solution may be to screen for CKD by use of serum creatinine–based GFR estimates, and in case of low eGFR, especially in the elderly with high or low muscle mass, to confirm this finding by a 24-hour creatinine clearance.

Conclusions

In conclusion, in individuals younger than 60 years of age, all measures of eGFR are independently associated with risk of CV events, whereas in the elderly, there is only a weak association between 24-hour creatinine clearance and CV risk. In contrast, elderly patients with increased albuminuria are at increased risk of CV events. These results question eGFR <60 ml/min per 1.73 m^2 as a CV risk marker in the elderly and emphasize the importance of assessment of albuminuria for CV risk prediction.

Acknowledgments

Disclosures
None.

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