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Performance of MDRD study and CKD-EPI equations for long-term follow-up of nondiabetic patients with chronic kidney disease

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Abstract

Background. Chronic kidney disease (CKD) typically extends over decades. Longitudinal monitoring of kidney function in CKD is thus of great importance. Here, we retrospectively evaluate use of the Modification of Diet in Renal Disease (MDRD) study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations to monitor long-term course of kidney function and to identify individuals with progressive kidney function loss.

Methods. Patients were selected from our outpatient clinic for having four glomerular filtration rate measurements (mGFR, ^{125}I-iothalamate) and at least ≥ 4 years of follow-up. Renal function slopes were obtained by within-individual linear regression.

Results. Sixty-five nondiabetic CKD patients (40 male, mean baseline age 44 ± 12 years) with a median (range) of 9 (4–16) mGFR measurements and a median follow-up of 11 (4–33) years were included. Both equations significantly underestimated $mGFR_{BSA}$ at baseline and at the end of follow-up. mGFR slope was significantly underestimated by the MDRD study but not by CKD-EPI equation (slopes -1.41 ± 2.06, -1.07 ± 1.72 and -1.39 ± 1.77 mL/min/1.73m^2/year, respectively). Sensitivity and specificity to identify progressive kidney function loss ($mGFR_{BSA}$ slope > 1.5 mL/min/1.73m^2/ year, $n = 23$) were 78 and 88% for the MDRD study and 91 and 80% for CKD-EPI equation. In the subgroup of progressors, both MDRD study and CKD-EPI equation underestimated the rate of mGFR loss ($P < 0.05$)

Conclusions. Long-term course of mGFR is reasonably well estimated by CKD-EPI and slightly underestimated by MDRD study equation. Patients with progressive kidney function loss may, however, not be reliably identified, so caution is warranted when using these equations in clinical practice.

Keywords: CKD-EPI equation; glomerular filtration rate; kidney function decline; MDRD study equation; renal hemodynamics

Introduction

Reliable monitoring of kidney function over time is of major importance for the treatment and prevention of progressive kidney function loss. For simple assessment of kidney function, several creatinine-based kidney function equations have been developed. The Modification of Diet in Renal Disease (MDRD) study equation [1, 2] is most extensively used. Although this equation has proven its performance in patients with kidney impairment, performance in subjects with better kidney function [measured glomerular filtration rate (mGFR) > 60 mL/min/1.73m^2] is poor [3–10]. For this reason, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [11] recently presented a new equation. This CKD-EPI equation was empirically developed from a large cross-sectional data set in different populations, including renal patients as well as healthy subjects and specifically pursues a better performance in the higher ranges of GFR.

For the clinical applicability of these equations in the management of CKD, it is crucial that they provide a reliable estimate of the changes in kidney function over time over an extended period, as CKD typically evolves and progresses over decades. Their validation, however, mainly relies on cross-sectional data. Longitudinal performance studies are sparse so far and were mainly conducted in transplant recipients [12–17] and diabetic patients [18, 19]. In nondiabetic CKD patients, no studies are available with a follow-up beyond 4 years [20–21].

In this study, we aim to assess, first, the performance of the MDRD study and CKD-EPI equations compared to gold standard kidney function measurement in the long-term follow-up of nondiabetic CKD patients. Moreover, we studied their performance in detecting individuals with progressive kidney function loss.

Patients and methods

We retrospectively evaluated data on kidney function of renal patients of the nephrology outpatient clinic of the University Medical Center Groningen. To ensure long-term follow-up, we retrieved data from all patients enrolled in renal hemodynamic studies performed between 1972 and 1995 at our center. Of these 156 patients, 99 had follow-up of renal function at our center, of which 15 had a renal transplant at baseline and were excluded from this study. We further selected patients for having a minimum of four GFR measurements and at least 4 years of follow-up, giving 72 eligible patients. Seven patients were lost due to missing data on weight or height. Of the 65 patients enrolled in this study, 27 had essential hypertension, 17 membranous glomerulopathy, 5 focal glomerulosclerosis, 5 IgA nephropathy, 3 a single kidney after nephrectomy for reasons other than kidney donation, 2 polycystic kidney disease and 6 other diagnoses like ischemic lesions and Bartter syndrome. Patients with diabetes mellitus were excluded to preclude effects of temporary hyperfiltration on slope analysis. Follow-up was ended from the moment patients received renal replacement therapy or a kidney transplant to avoid effect on kidney function of dialysis and immunosuppressant drugs.

GFR measurement

Glomerular filtration rate (GFR) was measured by constant infusion of low-dose ^{125}I-iothalamate as described by Apperloo *et al.* [23]. Simultaneously, effective renal plasma flow is measured as the clearance of ^{131}I-hippurate. For the measurements, subjects are seated in a quiet room, in a semi-supine position. After drawing a blank blood sample, the priming solution containing 0.04 mL/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippurate/ mL saline) plus an extra 0.6 MBq of ^{125}I-iothalamate was given, followed by constant infusion at 12 mL/h. To attain stable plasma concentrations of both tracers, a 2-h stabilization period follows, after which the clearance periods start. Clearances are measured over the next 2 h and calculated as $(U \times V)/P$ and $(I \times V)/P$, respectively. $U \times V$ represents the urinary excretion of the tracer, $I \times V$ represents the infusion rate of the tracer and P represents the tracer value in plasma at the end of each clearance period. GFR is calculated from $U \times V/P$ of ^{125}I-iothalamate and corrected for voiding errors by multiplying the urinary clearance of ^{125}I-iothalamate with the ratio of the plasma and urinary clearance of ^{131}I-hippurate. The day-to-day variability for GFR is 2.5% [23]. Creatinine was determined from blood samples drawn at the start of the GFR measurement. This procedure was unaltered over the duration of the observation period.

Calculations

We used the abbreviated four-variable MDRD study equation that was reexpressed for standardized serum creatinine samples [2]. The MDRD study equation was calculated as follows

$$\text{MDRD} = 175 \times (\text{serum creatinine in mg/dl})^{-1.154}$$
$$\times (\text{age})^{-0.203} (\times 0.742 \text{ if female}).$$

CKD-EPI equation was calculated gender specific and stratified by creatinine levels. The following calculations were used [11]:

Female with serum creatinine ≤ 0.7 mg/dl :

$$\text{GFR} = 144 \times (0.993)^{\text{age}} \times (\text{serum creatinine}/0.7)^{-0.329}$$

Female with serum creatinine ≤ 0.7 mg/dl :

$$\text{GFR} = 144 \times (0.993)^{\text{age}} \times (\text{serum creatinine}/0.7)^{-1.209}$$

Male with serum creatinine ≤ 0.9 mg/dl :

$$\text{GFR} = 141 \times (0.993)^{\text{age}} \times (\text{serum creatinine}/0.9)^{-0.4111}$$

Male with serum creatinine ≤ 0.9 mg/dl :

$$\text{GFR} = 141 \times (0.993)^{\text{age}} \times (\text{serum creatinine}/0.9)^{-1.209}$$

No correction for ethnicity was applied in either the MDRD study or the CKD-EPI equations, as none of the patients were of African ethnicity. From here, these equations are referred to as estimated glomerular filtration rate (eGFR). Body surface area (BSA) was calculated according

to DuBois and DuBois [24]. mGFR was normalized by dividing the raw sample by BSA and multiplying it with 1.73, giving mGFR$_{/\text{BSA}}$. The slope of kidney function loss was calculated by within-individual linear regression.

Analysis of predictive performance

Performance of the MDRD study and CKD-EPI equations against mGFR/$_{\text{BSA}}$ was analyzed as proposed by Bostom *et al.* [25] and Stevens *et al.* [26], presenting bias, precision, and accuracy. Bias was calculated as median of the absolute difference (mGFR/$_{\text{BSA}}$ − eGFR) and of the percentage difference ((mGFR/$_{\text{BSA}}$ − eGFR)/mGFR/$_{\text{BSA}}$ × 100), giving a numeric or arithmetic value and a relative value. Precision represents the overall 'fit' of the new model against the gold standard. It is represented by the interquartile range (IQR) of (mGFR/$_{\text{BSA}}$ − eGFR). Accuracy reflects the proportion of subjects with eGFR values within ±30% of mGFR/$_{\text{BSA}}$ (P$_{30}$).

Calibration of serum creatinine samples

Serum creatinine was measured by enzymatic assay on the Roche Modular in blood samples drawn after 1 March 2006. Before this date, samples had been measured by Jaffe alkaline picrate assay on the MEGA (Merck KGaA, Darmstadt, Germany). Both methods were calibrated to the reference standard, i.e. Cleveland Clinic Laboratory measurements, as proposed by Coresh *et al.* [27]. For this purpose, a total of 516 blood samples with a broad range of creatinine were sent to the Cleveland Laboratory of which 177 were from before 1 March 2006. Samples for calibration purposes were stored at −80°C until measured on the Roche P module enzymatic assay with verified traceability to the reference standard IDMS. Calibration equations were as follows: calibrated serum creatinine = [−0.300 + 1.217 × (UMCG Jaffe creatinine values in mg/dL)] for measurements before 1 March 2006 and [0.011 + 1.087 × (UMCG Roche creatinine values in mg/dL)] for measurements after 1 March 2006. MDRD Study and CKD-EPI equations were calculated from calibrated creatinine values.

Calculation of kidney function slope and definition of progressive kidney function loss

Individual slopes of kidney function loss were calculated by within-individual linear regression. To confirm linearity of individual kidney function slopes, we collected all creatinine samples available within the study period for each patient and performed residual analysis on the individual creatinine slopes. Two patients had a nonlinear creatinine slope, though mGFR slope was confirmed to be linear. As control of the abovementioned method, kidney function loss was also estimated by means of linear mixed effect models with random coefficients and random intercepts. Since both methods provided very similar estimates of mean slopes, within-individual linear regression was used for further analysis. To evaluate the performance of the equations to detect progressive kidney function loss, we identified 'progressors', defined as patients with a rate of renal function loss of at least 2-fold higher than in the general population. In the Baltimore Longitudinal Study of Aging, the normal age-related renal function decline was −0.75 mL/min/year [28], so we classified a GFR decline >1.5 mL/min/1.73m^2/year as progressive function loss. We tested the sensitivity and specificity of both equations to identify progressors. Additionally, we studied the predictive performance of the equations in the subgroup of progressors as described above.

Statistical analysis

Analyses were performed using SPSS software version 16.0, SAS version 9.1, Stata version 10.0, Microsoft Office Excel 2003 and Graph-Pad Prism version 5 for Windows. Data are given as mean ± SD or median (IQR). Paired samples *t*-test and Wilcoxon's signed-rank test were used to analyze differences between baseline and last observation values and to analyze differences between mGFR/$_{\text{BSA}}$ and eGFR and MDRD study and CKD-EPI equations. Differences between groups were tested by independent samples *t*-test, Mann–Whitney *U*-test and Kruskal–Wallis test. Differences between accuracy were tested with chi-square test.

For baseline and last observation values of MDRD study and CKD-EPI equations, Bland–Altman analyses were performed. Determinants of bias at baseline and at the end of follow-up and bias of slope were examined by backward linear regression.

Results

Data on kidney function measurements of 65 patients (42 male) were obtained for the analyses. The median (IQR) number of GFR measurements was 9 (6–11) with a median follow-up time of 11 (7–18) years. Patient characteristics for baseline and last observation values are listed in Table 1. Age increased from 45 ± 11 to 58 ± 13 years. Kidney function declined over long-term follow-up, from 78 ± 27 to 58 ± 29 for $mGFR/_{BSA}$, from 63 ± 24 to 47 ± 23 for the MDRD study equation and from 70 ± 27 to 51 ± 25 mL/min/1.73m^2 for the CKD-EPI equation ($P < 0.01$). CKD-EPI equation provided significantly higher values than the MDRD study equation ($P < 0.01$), but both equations significantly underestimated $mGFR/_{BSA}$ at both time points ($P < 0.01$).

Table 2 compares the cross-sectional performance of the equations at baseline and at the end of follow-up. At baseline, bias of the MDRD study equation, expressed in mL/min/1.73m^2, was significantly larger than for the CKD-EPI equation ($P < 0.05$). At the end of follow-up, bias of the MDRD study equation had decreased significantly ($P < 0.05$), whereas for the CKD-EPI equation, it had remained stable. Expressed as percentage difference, bias was stable during follow-up for both equations. At both time points, CKD-EPI had higher accuracy than the MDRD study equation (all $P < 0.001$). The biases of both the MDRD study and the CKD-EPI equations were best predicted by $mGFR/_{BSA}$ (adjusted $R^2 = 0.23$ and 0.12, respectively, $P < 0.01$, for baseline bias and adjusted $R^2 = 0.47$ and 0.25, $P < 0.01$, for end of follow-up, respectively). In all analyses, age, duration of follow-up

and 24-h urinary creatinine excretion had no influence on bias (data not shown).

Slopes for change in $mGFR/_{BSA}$ and eGFR over time are shown in Table 3. $mGFR/_{BSA}$ slope and CKD-EPI equation slope were not significantly different. Both slopes were significantly steeper than the MDRD Study equation slope ($P < 0.05$). Figure 1 displays scatter plots for the regression of, respectively, the MDRD Study and CKD-EPI equation slope on $mGFR/_{BSA}$ slope. The CKD-EPI slope had a stronger relation with $mGFR/_{BSA}$ than the MDRD Study slope ($R^2 = 0.52$ and 0.45, respectively, $P < 0.01$). Figure 2 displays the performance of $eGFR/_{BSA}$ slope by Bland–Altman analysis: no systematic error was found for either of the equations.

Figure 3 displays distribution of within-subject bias between the MDRD study and CKD-EPI equation slope and mGFR slope and median $mGFR/_{BSA}$ slope values for the different categories. The majority of subjects had a bias between -1.5 and 1.5 mL/min/1.73m^2/year, 69 and 72% for MDRD study and CKD-EPI equations. Respectively, 20 and 14 % had a bias >1.5 mL/min/1.73m^2, and thus, an eGFR slope more positive than $mGFR/_{BSA}$ slope. In 11 and 14% eGFR slope bias was <-1.5 mL/min/1.73m^2. For both equations, median $mGFR/_{BSA}$ slope decreased over the groups ($P < 0.01$).

Next, we studied the performance of the equations in the detection of progressive kidney function loss. A mean loss of $mGFR/_{BSA}$ >1.5 mL/min/1.73m^2/year was present in 23/65 patients, classified as progressors. Individual values for the slopes of mGFR and eGFR are given in Figure 4 with a breakup by progressor status. Sensitivity and specificity for detection of progression were 78 and 88%, respectively, for the MDRD study and 91 and 81%, respectively, for the CKD-EPI equation. No differences in baseline patient characteristics, duration of follow-up, number of kidney function measurements, kidney function or 24-h creatinine excretion were found between patients correctly and wrongly classified as progressor (data not shown). Positive and negative predictive values for progression were 78 and 88%, respectively, for the MDRD study and 72 and 94%, respectively, for the CKD-EPI equation. In progressors, the slope of $mGFR/_{BSA}$ (-3.6 ± 1.7 mL/min/1.73m^2/year) was significantly underestimated by both equations, with values of -2.4 ± 1.8 and -2.8 ± 1.8 mL/min/1.73m^2 for the MDRD study and CKD-EPI equations, respectively ($P < 0.05$; Figure 4), whereas in the stable subjects, the slopes were similar for

Table 1. Patient characteristics at baseline and at the end of follow-up[a]

	Baseline	Last observation	P
Age (years)	45 ± 11	58 ± 13	<0.01
BMI (kg/m^2)	25.6 ± 3.7	26.4 ± 4.2	<0.01
Serum creatinine (mg/dL)	1.30 ± 0.52	1.84 ± 1.12	<0.01
$mGFR/_{BSA}$ (mL/min/1.73m^2)	78 ± 27	58 ± 29	<0.01
MDRD study equation (mL/min/1.73m^2)	63 ± 24*	47 ± 23*	<0.01
CKD-EPI (mL/min/1.73m^2)	70 ± 26*,†	51 ± 25*,†	<0.01

[a]Data are expressed as mean $\pm$ SD. *$P < 0.01$ versus mGFR; †$P < 0.01$ versus MDRD (paired samples t-test).

Table 2. Overall performance of MDRD study and CKD-EPI equations[a]

	Baseline		Last observation	
	MDRD	CKD-EPI	MDRD	CKD-EPI
Bias (mL/min/1.73m^2)	15 (7–19)	8 (1–13)†	9 (6–13)*	6 (4–9)†
Precision (mL/min/1.73m^2)	22 (0–32)	21 (−8 to 25)	16 (0–22)	16 (−3 to 19)
Bias (%)	21 (11–28)	12 (2–21)†	20 (12–23)	12 (7–19)†
Precision (%)	28 (0–35)	31 (−10 to 29)	22 (−1 to 32)	23 (−10 to 27)
P$_{30}$ (%)	66	82†	77	82†

[a]Bias values represent median [95% confidence interval (CI)], precision values IQR (95% CI). *$P < 0.05$ versus baseline value; †$P < 0.001$ compared to MDRD value.

mGFR, MDRD study and CKD-EPI equations: 0.3 ± 0.8 versus -0.4 ± 1.2 and -0.6 ± 1.2 mL/min/1.73m^2/year, respectively. Baseline level of mGFR and both equations were similar between the groups (data not shown). Performance analysis showed that bias remained stable between baseline and the end of follow-up in the nonprogressors, whereas in the progressors, bias was significantly smaller at the end of follow-up (Table 4).

Discussion

This study evaluated the MDRD Study and CKD-EPI equations for long-term follow-up of nondiabetic CKD patients. The MDRD study equation underestimated

kidney function decline, but the CKD-EPI equation more accurately quantified the mean rate of kidney function loss over time. The sensitivity and specificity of both equations to detect progressive kidney function loss were limited, and in progressors, the rate of kidney function loss is underestimated. This warrants caution in the application of the equations in the monitoring of kidney function in clinical practice.

Previous studies evaluating the performance of MDRD study equation for longitudinal follow-up focused mainly on transplant recipients. In kidney [12–15], lung [16] and liver [17] transplant recipients, the MDRD Study equation had a reasonable performance on a group level. However, it tended to underestimate the rate of kidney function loss and the number of patients developing kidney function impairment. Two studies in patients with type II diabetes mellitus showed underestimation of kidney function slope, with especially large underestimation in early stages of nephropathy (hyperfiltration and normal kidney function) [18, 19].

In our study, the CKD-EPI equation performed well in the prediction of mean mGFR, while MDRD study equation showed slight underestimation. However, the sensitivity and specificity to detect individuals with progressive kidney function loss were limited. In particular, the positive predictive values were suboptimal, and in progressors, the rate of kidney function loss was

Table 3. Slopes of mGFR and MDRD Study and CKD-EPI equations[a]

	Slopes
mGFR/$_{BSA}$	-1.5 ± 2.0
MDRD	-1.1 ± 1.7*
CKD-EPI	-1.4 ± 1.8†

[a]Slopes are expressed in mL/min/1.73m^2/year. Values represent mean $\pm$ SD. *$P < 0.05$ compared to mGFR/$_{BSA}$ slope; †$P < 0.01$ compared to MDRD slope (paired samples *t*-test).
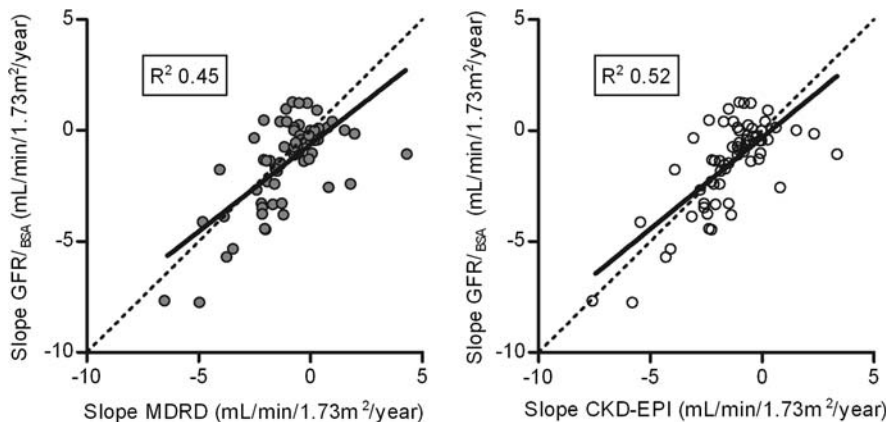
Fig. 1. Scatter plots of regression of MDRD study equation slope on mGFR/$_{BSA}$ slope (left panel) and CKD-EPI equation slope on mGFR/$_{BSA}$ slope (right panel). R^2 for MDRD study and CKD-EPI equations are 0.45 and 0.52 (both $P < 0.05$), respectively.
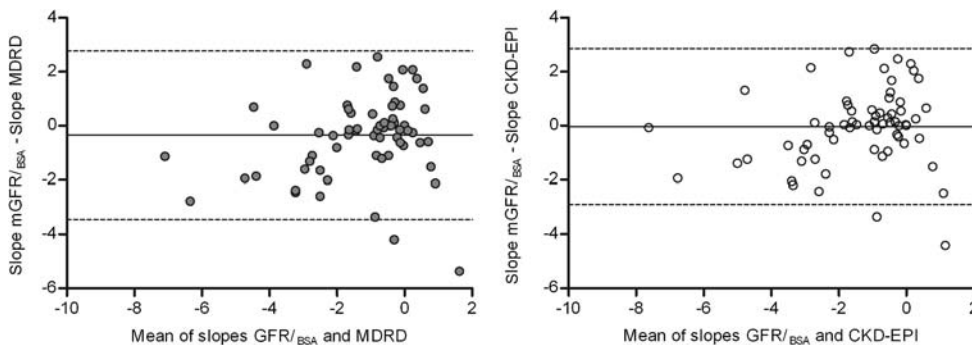
Fig. 2. Bland–Altman analysis of performance of MDRD Study equation slope against mGFR slope (left panel) and CKD-EPI equation slope against mGFR slope (right panel). Solid line represents mean bias and dotted lines represent ± 2 SD interval.

underestimated. This is consistent with previous studies [13, 16, 18, 19, 22] where the MDRD study equation underestimated kidney function loss as well and did not reliably detect progressive function loss. In the original MDRD population, Xie *et al.* [22] evaluated longitudinal performance of the MDRD study equation. In 542 patients with a follow-up of 2.6 years, the mean rate of mGFR decline, being -3.9 mL/min/1.73m^2/year, was underestimated by the MDRD Study equation by some 28%. In the African American Study of Kidney Disease and Hypertension' (AASK) population, Lewis *et al.* [21]

showed that in their 4-year study period, the AASK equation underestimated kidney function loss as well (-1.6 versus -1.9 mL/min/1.73m^2/year).

Our data demonstrate that underestimation of mGFR slope is due to the change in bias over time, with less underestimation at the end of follow-up. This is more likely due to loss of kidney function rather than time span as such since it was only found in progressors. It is well established by cross-sectional studies that underestimation of mGFR by eGFR is smaller at lower absolute levels of mGFR, as is also the case in our population. Recent studies by Lee and our own group, in predialysis patients and healthy kidney donors, respectively, showed that a within-individual decrease in mGFR is associated with a decrease in bias as well [20, 29]. Inherent to this mGFR dependency of bias, eGFR bias decreases over time in subjects with progressive kidney function loss and thus eGFR slope will be less steep compared to mGFR slope. Other kidney function-related factors, like diminished creatinine excretion and altered muscle mass over time may further influence eGFR performance.

In our population, the CKD-EPI equation performed better than MDRD study equation, both cross-sectionally and longitudinally. It was less influenced by the level of mGFR$_{BSA}$, in line with its development and validation in data sets with a broad range in mGFR and a spline for creatinine. Therefore, bias is more stable over the range of kidney function, and accordingly, the deviation of its slope from mGFR slope is stable over time as well.

What could be the implications of our findings? In clinical practice, reliable monitoring of kidney function is important to assess long-term prognosis and accordingly allocation of preventive measures and timely referral for specialist care and renal replacement therapy. The shortcomings of creatinine and the reciprocal of creatinine to this purpose are well established [30]. Our data show that eGFR has shortcomings for longitudinal monitoring as well. In particular, the distinction between stable patients and progressors, which is essential for applicability in clinical practice, is hampered by the limited sensitivity and specificity of eGFR to detect progressive renal function loss, which occurred in spite of a prolonged observation period and multiple measurements. For individual patients, positive and negative predictive values are the relevant characteristics of a diagnostic test to consider, and these are strongly affected by the a priori probability of progression in the population. Thus, whereas the positive and negative predictive values for progression were rather acceptable in our university hospital population with one-third progressors, in the general population or in
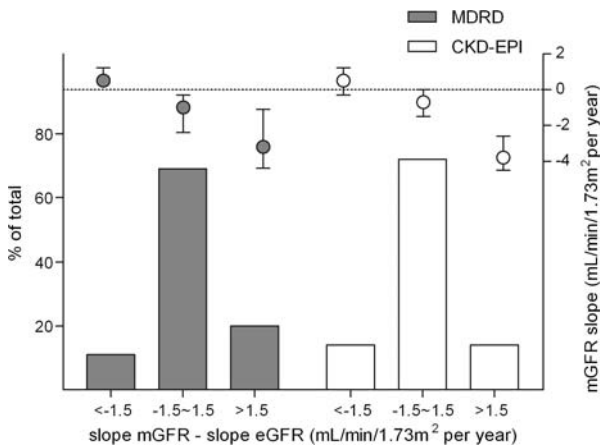
Fig. 3. Distribution of bias of slope (mGFR$_{BSA}$ slope $-$ eGFR slope) for MDRD Study (left, gray bars) and CKD-EPI equations and median mGFR$_{BSA}$ slope for the particular categories. Bars represent % of total (left y-axis) and circles and error bars represent median (IQR) value of mGFR$_{BSA}$ slope (right y-axis).
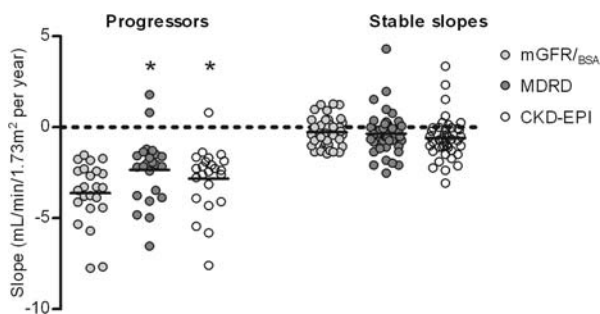
Fig. 4. Slopes of mGFR$_{BSA}$, MDRD Study and CKD-EPI equation for individual patients with progressive kidney function loss (mGFR$_{BSA}$ slope < -1.5 mL/min/1.73m^2/year, left) and stable slope (> -1.5 mL/min/1.73m^2/year, right). Error lines represent group mean value. * P < 0.05 versus mGFR$_{BSA}$ slope.

Table 4. Bias (mL/min/1.73m^2) of MDRD study and CKD-EPI equations by breakup by rate of kidney function loss[a]

Bias	Progressive slopes (n = 23)			Stable slopes (n = 42)		
	Baseline	Last observation	P	Baseline	Last observation	P
MDRD	16 (7–22)	6 (0–8)	0.002	11 (4–19)	14 (7–18)	0.788
CKD-EPI	11 (2–16)[†]	4 (−2 to 6)[†]	0.016	7 (−1 to 13)[†]	9 (4–16)[†]	0.218

[a]Values represent median (95% confidence interval). [†]P < 0.01 compared to corresponding MDRD value (Wilcoxon's signed-rank test).

general practice, identification of progressors will be blurred by the lower proportion of progressors. For instance, in a population with 10% progressors, the positive and negative predictive value for MDRD study and CKD-EPI equations would be 42 and 97% and 35 and 99%, respectively. This will result in an unwarranted number of falsely positive progressors being identified, whereas on the other hand, true progressors still escape from being detected. For a more severe definition for progression, i.e 2 mL/min/1.73m^2/year, the results were essentially similar (data not shown). This performance is the reason for concern as regards the use of eGFR for follow-up of renal function in general practice.

It should be noted that to evaluate kidney function slopes, often linearity is assumed. Although in this study all but two patients were shown to have a linear kidney function slope, this does not always apply. The two patients with the nonlinear creatinine slope were not among the missed progressors.

The use of creatinine-based parameters as an outcome parameter in clinical trials in CKD has been criticized and it has been argued that hard end point studies would be preferable [31, 32]. However, this is not feasible for intervention studies in earlier stages of CKD. Accordingly, and supported by our current data, it has been argued [14] that reference methods should be used for monitoring kidney function in clinical trials.

Our study has several limitations, the most important being the relatively small sample size, the monocentric character and the lack of standardized timing of measurements. The conclusions do not apply to patients with African ethnicity, diabetic patients and kidney transplant recipients all of whom were not included. Due to our inclusion criteria of a minimum of four mGFR measurements and 4 years of follow-up, subjects with an extreme progressive slope, reaching end stage renal disease and the need of renal replacement therapy within this time span, were excluded. All these limitations hamper generalizability. Still, these data derived from clinical practice may have better applicability than that derived from clinical trials.

In conclusion, this study shows acceptable performance of CKD-EPI equation and slight underestimation of mean function loss by the MDRD study equation in long-term follow-up of CKD patients. Individual patients with more progressive kidney function loss might, however, be missed. Thus, caution is warranted in the application of the equations in the monitoring of kidney function in individual patients.

References

1. Levey AS, Bosch JP, Lewis JB *et al*. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470
2. Levey AS, Coresh J, Greene T *et al*. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145: 247–254
3. Rule AD, Gussak HM, Pond GR *et al*. Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis* 2004; 43: 112–119
4. Rule AD, Larson TS, Bergstralh EJ *et al*. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004; 141: 929–937
5. Lin J, Knight EL, Hogan ML *et al*. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. *J Am Soc Nephrol* 2003; 14: 2573–2580
6. Mahajan S, Mukhiya GK, Singh R *et al*. Assessing glomerular filtration rate in healthy Indian adults: a comparison of various prediction equations. *J Nephrol* 2005; 18: 257–261
7. Poggio ED, Wang X, Greene T *et al*. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 2005; 16: 459–466
8. Ibrahim HN, Rogers T, Tello A *et al*. The performance of three serum creatinine-based formulas in estimating GFR in former kidney donors. *Am J Transplant* 2006; 6: 1479–1485
9. Stevens LA, Coresh J, Feldman HI *et al*. Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol* 2007; 18: 2749–2757
10. Issa N, Meyer KH, Arrigain S *et al*. Evaluation of creatinine-based estimates of glomerular filtration rate in a large cohort of living kidney donors. *Transplantation* 2008; 86: 223–230
11. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
12. Hossain MA, Zahran A, Emara M *et al*. Accuracy to estimate rates of decline in glomerular filtration rate in renal transplant patients. *Transplantation* 2007; 84: 490–497
13. Gera M, Slezak JM, Rule AD *et al*. Assessment of changes in kidney allograft function using creatinine-based estimates of glomerular filtration rate. *Am J Transplant* 2007; 7: 880–887
14. Gaspari F, Ferrari S, Stucchi N *et al*. Performance of different prediction equations for estimating renal function in kidney transplantation. *Am J Transplant* 2004; 4: 1826–1835
15. Bosma RJ, Doorenbos CR, Stegeman CA *et al*. Predictive performance of renal function equations in renal transplant recipients: an analysis of patient factors in bias. *Am J Transplant* 2005; 5: 2193–2203
16. Broekroelofs J, Stegeman CA, Navis GJ *et al*. Creatinine-based estimation of rate of long term renal function loss in lung transplant recipients. Which method is preferable? *J Heart Lung Transplant* 2000; 19: 256–262
17. Gonwa TA, Jennings L, Mai ML *et al*. Estimation of glomerular filtration rates before and after orthotopic liver transplantation: evaluation of current equations. *Liver Transpl* 2004; 10: 301–309
18. Fontsere N, Salinas I, Bonal J *et al*. Are prediction equations for glomerular filtration rate useful for the long-term monitoring of type 2 diabetic patients?. *Nephrol Dial Transplant* 2006; 21: 2152–2158
19. Rossing P, Rossing K, Gaede P *et al*. Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. *Diabetes Care* 2006; 29: 1024–1030
20. Lee D, Levin A, Roger SD *et al*. Longitudinal analysis of performance of estimated glomerular filtration rate as renal function declines in chronic kidney disease. *Nephrol Dial Transplant* 2009; 24: 109–116
21. Lewis J, Greene T, Appel L *et al*. A comparison of iothalamate-GFR and serum creatinine-based outcomes: acceleration in the rate of GFR decline in the African American Study of Kidney Disease and Hypertension. *J Am Soc Nephrol* 2004; 15: 3175–3183
22. Xie D, Joffe MM, Brunelli SM *et al*. A comparison of change in measured and estimated glomerular filtration rate in patients with nondiabetic kidney disease. *Clin J Am Soc Nephrol* 2008; 5: 1332–1338
23. Apperloo AJ, de ZD, Donker AJ *et al*. Precision of glomerular filtration rate determinations for long-term slope calculations is improved by simultaneous infusion of 125I-iothalamate and 131I-hippuran. *J Am Soc Nephrol* 1996; 7: 567–572

24. DuBois B, DuBois E. A formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine* 1916; 17: 863–871

25. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *J Am Soc Nephrol* 2002; 13: 2140–2144

26. Stevens LA, Zhang Y, Schmid CH. Evaluating the performance of equations for estimating glomerular filtration rate. *J Nephrol* 2008; 21: 797–807

27. Coresh J, Eknoyan G, Levey AS. Estimating the prevalence of low glomerular filtration rate requires attention to the creatinine assay calibration. *J Am Soc Nephrol* 2002; 13: 2811–2812

28. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; 33: 278–285

29. Tent H, Rook M, Stevens LA *et al*. Renal function equations before and after living kidney donation: a within-individual comparison of performance at different levels of renal function. *Clin J Am Soc Nephrol* 2010; 11: 1960–1968

30. Levey AS. Measurement of renal function in chronic renal disease. *Kidney Int* 1990; 38: 167–184

31. Mariat C, Alamartine E, Barthelemy JC *et al*. Assessing renal graft function in clinical trials: can tests predicting glomerular filtration rate substitute for a reference method?. *Kidney Int* 2004; 65: 289–297

32. Slagman MC, Navis G, Laverman GD. Reversible effects of diuretics added to renin-angiotensin-aldosterone system blockade: impact on interpretation of long-term kidney function outcome. *Am J Kidney Dis* 2010; 56: 601–602