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# RELIABILITY OF GFR ESTIMATED BY CREATININE-BASED FORMULAS IN MODERATE-TO-SEVERE PROTEINURIA

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**Key Points**

- GFR estimations are biased in patients with frank nephrotic syndrome, but the problem is uncharacterized in patients with non-nephrotic proteinuria.
- We investigated the bias and accuracy of eGFR formulas in patients with mild-to-moderate proteinuria participating in the ramipril in nondiabetic renal failure 1 and 2 trials.
- The CKD Epidemiology Collaboration 2009 and 2021 and European Kidney Function Consortium equations show no significant bias and sufficient accuracy in moderate-to-severe proteinuria.

**Abstract**

Background Creatinine-based GFR formulas introduce a substantial bias in GFR estimations in patients with frank nephrotic syndrome. The bias and accuracy of creatinine-based GFR estimates (eGFR) in patients with non-nephrotic proteinuria need better characterization.

Methods We used data from the Ramipril in Nondiabetic Renal Failure (ramipril in nondiabetic renal failure [REIN] 1) and REIN 2 trials involving nondiabetic CKD patients with proteinuria to compare eGFRs derived from the CKD Epidemiology Collaboration formulas (with and without race) and the European Kidney Function Consortium equations with iohexol clearance (a gold-standard GFR measure, measured GFR [mGFR]). Bias was defined as the median difference between eGFR and mGFR while accuracy was assessed using P30 and P15 metrics, which represent the percentage of eGFR values within 630% and 615% of mGFR, respectively.

Results The median bias of the three formulas being compared did not differ, being minimal and in a strict range (0.04– 0.05 ml/ml per min per 1.73 $m^2$) in the REIN 1 trial and (20.04 to 0.03 ml/min per 1.73 $m^2$) in the

REIN 2 trial. These findings were confirmed in analyses stratified by age and mGFR. The global accuracy of the three formulas regarding P30 % showed sufficient accuracy (P30 .75%) in the REIN 1 trial and all strata in the REIN 2 trial, but the mGFR stratum was ,15 ml/min per 1.73 $m^2$.
Conclusions The CKD Epidemiology Collaboration (with and without race) and European Kidney Function Consortium equations show no significant bias and sufficient accuracy in patients with proteinuria. These formulas can be safely applied to nondiabetic CKD patients with moderate-to-severe proteinuria.
Clinical Trial registry name and registration number: This is a post hoc analysis of two trials, REIN 1 and 2, published about 20 years ago.

## Introduction

The creatinine-based GFR equations are founding elements for the staging of CKD, and the 2021 CKD Epidemiology Collaboration (CKD-EPI) equation, without race, is one of the two formulas recommended in the current 2024 Kidney Disease Improving Global Outcomes guidelines.[1] Race is considered a social rather than a biological construct. For this reason, creatinine and cystatin-based eGFR formulas omitting race have been recently produced, and these formulas are more accurate and minimize differences between Black and non-Black individuals than new equations without race with either creatinine or cystatin C alone.[2] However, when applied in a predominantly White northern European population, the CKD-EPI equation omitting race overestimates eGFR, particularly at an older age and in men, and shifts a major proportion of patients with CKD to a higher eGFR category.[3] For this reason, the 2009 CKD-EPI formula with race is still predominantly applied in European countries. In 2021, Pottel et al. developed the European Kidney Function Consortium (EKFC) formula, a creatinine-based equation (EKFC eGFRcr), to estimate the GFR with a rescaled serum creatinine level, that is, creatinine level divided by the median creatinine level in healthy individuals to control for variation related to differences in age, sex, or race.[4] This equation has useful properties and performs better in estimating GFR than the current Kidney Disease Improving Global Outcomes–recommended equations, and it is increasingly applied in Europe.

It is well known that the endogenous creatinine clearance overestimates the GFR because of the renal tubular secretion of creatinine. Tubular handling of creatinine is typically altered in patients with nephrotic syndrome, and the creatinine clearance in these patients substantially exceeds the eGFR as measured by inulin clearance.[5–7] Discrepancies between eGFR using the Modification of Diet in Renal Disease (MDRD) and CKD-EPI formulas have been noted in patients with glomerular diseases and hypoalbuminemia.[8] The bias and accuracy of eGFR in patients with less severe proteinuria are still poorly characterized.

In this study, we have investigated the effect of proteinuria on the bias and accuracy of estimates of the eGFR using the 2009 CKD-EPI equation,[9] the 2021 equation without race,[2] and the EKFC consortium equation[4] in the database of the ramipril in nondiabetic renal failure (REIN) 1[9,10] and REIN 2[11] trials, two trials in CKD patients with proteinuria where iohexol clearance, a gold-standard GFR metric, was used, and the abovementioned serum creatinine-based measures of the GFR.

## Methods

The REIN 1 trial was a randomized, placebo-controlled, multicenter clinical trial including 352 patients with chronic, nondiabetic proteinuric nephropathies. The primary objective was to assess the effect of treatment with ramipril on the rate of decline in GFR and to measure the extent to which this effect depended on the drug's antiproteinuric effect. This study assessed the effect of ramipril on the evolution of the GFR over time,

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proteinuria, time to doubling of serum creatinine, and progression to kidney failure in patients with moderate-to-severe proteinuria (from .1 to .3 g/24 hour). A detailed description of the study protocol and the main results of this trial are reported elsewhere.[10,11] REIN 2 was a trial in 339 CKD patients with moderate-to-severe nondiabetic proteinuria (defined as above) receiving background treatment with the ACE inhibitor ramipril that was randomly assigned as either conventional (diastolic ,90 mm Hg; n5169) or intensified (systolic/diastolic ,130/80 mm Hg; n5169) blood pressure control.[12] This trial was designed to establish whether further BP lowering could benefit CKD on top of ACE inhibition.

In this post hoc analysis, we investigated in the two trials the relationship between the gold-standard measurement of the GFR, plasma iohexol clearance (measured GFR [mGFR]), and the GFR as estimated (eGFR) by the 2009 (with race) and 2024 (without race) CKD-EPI formula and EKFC consortium equation.

Bias is a critical measure in evaluating the performance of eGFR formulas because it indicates the systematic deviation of the eGFR from the mGFR. A median bias close to zero suggests that the eGFR formula does not systematically overestimate or underestimate the true GFR. Bias was defined as the median difference between eGFR and mGFR, with 95% confidence intervals (CIs) calculated using the binomial method, which makes no specific assumptions about the underlying distribution of the variable. Accuracy metrics, such as P30 and P15, are widely used in nephrology to assess the clinical utility of eGFR formulas. P30 represents the percentage of eGFR values that fall within 630% of the mGFR, whereas P15 represents the percentage within 615%. These metrics provide a clear indication of how often the eGFR values are close to the true GFR, which is essential for making reliable clinical decisions. The Kidney Disease Outcomes Quality Initiative considers a P30 .75% as sufficient for good clinical decision making, making these metrics highly relevant for evaluating the performance of eGFR formulas. The 95% CIs for P30 and P15 were calculated by binomial exact calculation. Another measurement of the variation in the differences between eGFR and mGFR is the root mean square error, that is, the square root of the average squared differences between eGFR and mGFR. The root mean square error is expressed in ml per minute per 1.73 $m^2$ of body surface area, and a smaller value reflects better accuracy of eGFR.[13]

Simultaneous measurements of iohexol plasma clearance and the various eGFR metrics were available in 269 patients in the REIN 1 trial and 201 patients in the REIN 2 trial. Eighty-three patients in the REIN 1 trial and 138 in the REIN 2 trial could not be included in this analysis because of missing plasma iohexol clearance or creatinine measurements.

Creatinine was measured using multichannel automatic instruments using the Jaffé method in reference laboratories of the units participating in the trial. IDMS calibration was performed according to instructions by the manufacturers of the kits used in the same laboratories.

In both trials, the iohexol plasma clearance measured the gold-standard GFR. In brief, after injection of 5 ml of iohexol (Ominipaque 300, Nycomed, Milan, Italy), blood samples were obtained at 120, 180, 240, 300, 450, and 600 minutes for patients with expected GFR ,40 ml/min per 1.73 $m^2$ and at 120, 180, and 240 minutes for patients with expected GFR .40 ml/min per 1.73 m,[213] and samples were analyzed by high-performance liquid chromatography. The plasma profiles were analyzed by an one compartment open model system,[13] and the calculated clearance of iohexol was corrected by the Brochner– Mortensen formula.[14]

## Statistical Analyses

All analyses and calculations were performed using STATA statistical package (version 16.1 for Windows, TX) and SPSS (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, New York: IBM Corp).

The performance of GFR equations was compared with standard metrics: median bias (i.e., eGFR2mGFR) with 95% CI and P30 and P15 accuracy (percentage of eGFR values within 630% or 615% of mGFR, with 95% CI). As for the median bias, the 95% CIs were calculated using a binomial method, which makes no specific assumptions about the underlying distribution of the variable. The 95% CIs for P30 and P15 were calculated by binomial exact calculation.

From a clinical perspective, the goal for P30 was 100%, yet the Kidney Disease Outcomes Quality Initiative has considered P30 .75% "sufficient for good clinical decision making."[15,16]

The effect modification analysis of serum albumin and proteinuria on the association between the three GFR estimates and the mGFR was tested using the standard approach to this analysis.[17] Significance is considered to be at the 5% significance level. The effect of serum albumin and proteinuria on the GFR estimates investigated in this study was tested by standard effect modification analysis.[18] Data analysis was performed using SPSS version 28 (IBM SPSS Statistics for Windows Armonk, New York: IBM Corp. and STATA 16 StataCorp, Lakeway Drive, College Station, Texas).

**Table 1. Demographic and clinical characteristics of REIN 1 and 2 trials**

| Characteristic | REIN 1 | REIN 2 |
|---|---|---|
| Patients, no. | 269 | 201 |
| Age, yr | 49 (±13) | 53 (±16) |
| Sex (M/F), no. (%) | 204 (76)/65 (24) | 146 (73)/55 (27) |
| Body mass index, kg/m$^2$ | 25 (±4) | 26 (±4) |
| **Kidney disease, no. (%)** | | |
| Glomerular | 138 (51.3) | 107 (53.2) |
| Interstitial | 12 (4.5) | 5 (2.5) |
| Polycystic | 3 (1.1) | 2 (1.0) |
| Other | 71 (26.4) | 32 (15.9) |
| Unknown | 45 (16.7) | 55 (27.4) |
| **Iohexol GFR, ml/min per 1·73 m$^2$** | 44 (±18) | 33 (±14) |
| Iohexol GFR >60 ml/min per 1·73 m$^2$, *N* (%) | 54 (20.1) | 10 (5.0) |
| *Serum creatinine, mg/dl* | 1.3 (±0.2) | 1.5 (±0.4) |
| *Creatinine clearance, ml/min* | 71.4 (±16.0) | 64.7 (±12.8) |
| *Urine protein excretion, g/d* | 2.1 (1.3–3.1) | 2.5 (1.6–2.9) |
| Iohexol GFR 45–60 ml/min per 1·73 m$^2$, *N* (%) | 64 (23.8) | 19 (9.5) |
| *Serum creatinine, mg/dl* | 1.7 (±0.4) | 1.7 (±0.4) |
| *Creatinine clearance, ml/min* | 58.5 (±12.7) | 56.6 (±11.4) |
| *Urine protein excretion, g/d* | 2.5 (1.5–4.1) | 2.7 (1.3–4.6) |
| Iohexol GFR 30–45 ml/min per 1·73 m$^2$, *N* (%) | 80 (29.7) | 79 (39.3) |
| *Serum creatinine, mg/dl* | 2.2 (±0.5) | 2.3 (±0.6) |
| *Creatinine clearance, ml/min* | 45.2 (±12.5) | 40.4 (±10.8) |
| *Urine protein excretion, g/d* | 3.1 (1.5–5.1) | 2.2 (1.5–3.4) |
| Iohexol GFR 15–30 ml/min per 1·73 m$^2$, *N* (%) | 67 (24.9) | 77 (38.3) |
| *Serum creatinine, mg/dl* | 3.1 (±0.6) | 2.3 (±0.6) |
| *Creatinine clearance, ml/min* | 29.7 (±7.8) | 40.4 (±10.8) |
| *Urine protein excretion, g/d* | 3.4 (1.9–4.2) | 2.2 (1.5–3.4) |
| Serum creatinine, mg/dl | 2.1 (±0.9) | 2.8 (±1.0) |
| Creatinine clearance, ml/min per 1·73 m$^2$ | 50 (±20) | 36 (±15) |
| CKD-EPI 2009, ml/min per 1·73 m$^2$ | 46 (±21) | 32 (±17) |
| CKD-EPI 2021, ml/min per 1·73 m$^2$ | 46 (±21) | 33 (±16) |
| EKFC, ml/min per 1·73 m$^2$ | 46 (±20) | 32 (±17) |
| **Urinary protein excretion, g/d, *N* (%)** | 2.7 (1.5–4.2) | 2.4 (1.5–3.6) |
| >3 | 124 (46.1) | 73 (36.3) |
| 1.5–3 | 74 (27.5) | 76 (37.8) |
| 1.0–1.5 | 56 (20.8) | 30 (14.9) |
| Systolic BP, mm Hg | 145 (±17) | 136 (±16) |
| Diastolic BP, mm Hg | 90 (±11) | 84 (±9) |
| Serum albumin g/dl | 3.8 (±0.5) | 3.7 (±0.5) |
| Hypoalbuminemia (<3.0 g/dl), *n* (%) | 16 (5.9) | 16 (8.0) |
| Serum cholesterol, mg/dl | 242 (±63) | 217 (±42) |
| Serum triglycerides, mg/dl | 156 (111–216) | 142 (±110–203) |

CKD-EPI, CKD Epidemiology Collaboration; EKFC, European Kidney Function Consortium; REIN, ramipril in nondiabetic renal failure.

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## Results

The demographic and clinical characteristics of patients in the REIN 1 and REIN 2 trials are reported in Table 1. The mGFR was, on average, approximately 11 ml/min per 1.73 $m^2$ lower in patients in the REIN 2 trial than in those in the REIN 1 trial (P 5 0.02) as it was proteinuria (median: 2.4 g/24 hours, interquartile range, 1.5–3.6 versus 2.7 g/24 hours versus 2.7 g/24 hours [1.5–4.2] interquartile range, 1.5–4.1, versus P 5 0.05) and BP (136616/8469 mm Hg versus 145617/90611 mm Hg, P , 0.001 for both pressures). Serum albumin was slightly lower in the REIN 2 trial, whereas total cholesterol and triglycerides were more deranged (P , 0.001) in the REIN 1 trial than in the REIN 2 trial. The proportion of patients with nephrotic-range albuminemia (,3 g/dl) was small and similar in the two studies (6% in the REIN 1 trial and 8% in the REIN 2 trial) (Table 1).
The relationship between iohexol GFR and the eGFR by CKD-EPI 2009 and 2021 and EKFC consortium equation in the two trials are shown in Figure 1. The regression coefficients of these relationships did not differ in the REIN 1 trial. Likewise, the same coefficient did not differ in the REIN 2 trial but was coherently lower than in the REIN 1 trial. In effect modification analyses, neither serum albumin nor proteinuria modified the association between mGFR and the three estimates of the GFR in the REIN 1 trial (P ranging from 0.12 to 0.82) and in the REIN 2 trial (P ranging from 0.10 to 0.48).
As shown in the whole population of the REIN 1 (Table 2) and REIN 2 (Table 3) trials, the median bias of the three formulas being compared did not differ, being in a strict range (0.04–0.05 ml/ml per min per 1.73 $m^2$) in the REIN 1 trial and in the REIN 2 trial (20.04 to 0.03 ml/min per 1.73 $m^2$). Similarly, analyses of the bias stratified by age and mGFR categories substantially confirmed the aggregate analysis in both studies (Tables 2 and 3).
In the REIN 1 (Table 2) and REIN 2 (Table 3) trials, the global accuracy of the three formulas in terms of P30% was superior to that registered in the European cohorts and showed sufficient accuracy (P30 .75%) in the whole population of the two studies. In the REIN 1 trial, in analyses stratified by age, all formulas but the CKD-EPI in the 18–40year stratum showed an accuracy .75%, which was also true across all mGFR categories (Table 2). In the REIN 2 trial, in the whole population, the accuracy was also satisfactory (.75%) because it coherently was in all analyses stratified by age or mGFR but in patients with an mGFR ,15 ml/min per 1.73 $m^2$ where all formulas had a 68.8% accuracy (Table 3). Both in REIN 1 and 2 trials (Tables 2 and 3), the squared root standard error was pretty good, of the same order as that registered in other studies, such as the study by Pottel et al,[19] and similar across eGFR formulas. Both in REIN 1 and REIN 2 trials, the severity of proteinuria did not affect the bias and accuracy of the GFR estimates analyzed in this study.

## Discussion

In patients with proteinuric nondiabetic CKD who took part in the REIN 1 and 2 trials, estimates of the GFR by the CKD-EPI with and without race and EKFC formulas showed a median bias similar or inferior to that in studies that established the CKD-EPI 2009[9] and 2021 (without race)[2] and EKFC[4] formulas. Accuracy for GFR estimation in the REIN 1 and 2 trials was generally satisfactory (P30 84% and 86%, respectively) and similar to that observed in the reference studies quoted above. These findings in two cohorts with moderate-to-severe proteinuria coherently indicate that moderate-to-severe proteinuria does not bias or alter the accuracy of creatinine-based estimates of the GFR.

Tubular handling of creatinine is disturbed in nephrotic syndrome. In a study by Carrie et al.,[5] the creatinine clearance in these patients substantially exceeded the GFR as measured by inulin clearance. However, this seminal study was based on 38 patients with overt nephrotic syndrome, and ten of 17 in the control group had heart failure, which is per se a condition that biases the creatinine-based estimate of the GFR.[20] A subsequent survey by Branten et al., in 42 patients with nephrotic syndrome, showed that the endogenous creatinine clearance and the MDRD-eGFR overestimate the GFR measured by inulin clearance compared with a group of 45 healthy participants.[7] Hofstra et al. registered discrepancies between eGFR using the six-variable MDRD formula and abbreviated MDRD formula compared with the CKD-EPI formula and cystatin C and b 2-microglobulin assumed as gold-standard GFR measurements in a series of one hundred forty-two patients with glomerular diseases.[8] Whether less severe or non-nephrotic proteinuria can bias eGFR estimates and affect the accuracy of these estimates is still scarcely characterized.

In this study, we systematically investigated the effect of proteinuria on the bias and accuracy of estimates of the GFR by the CKD-EPI equation with and without race and EKFC equation in the database of the REIN 1 and REIN 2 trials, two trials in nondiabetic CKD patients with moderate-to-severe proteinuria and a minimal prevalence of nephrotic hypoalbuminemia (just the 6% and 8% in the REIN 1 and 2 trials, respectively) that adopted plasma iohexol clearance as the golden standard. Of note, in all age-stratified analyses in the REIN 1 and 2 trials, median bias (0.04 and 20.03 ml/min per 1.73 $m^2$, respectively) was similar to or less than that registered in the studies that established the CKD-EPI 2009 (,60 ml/min per 1.73 $m^2$ stratum: 2.1 ml/min per 1.73 $m^2$)[9] and CKDEPI 2021 (non-Black participants: 20.5 ml/min per 1.73 $m^2$).[2] Furthermore, median bias in the REIN trials was less than that in the European Kidney Consortium cohorts,[4] where it ranged from 1.8 ml/min per 1.73 $m^2$ (40 to #65-year stratum) to 5.3 ml/min per 1.73 $m^2$ ($65-year stratum). Overall, the global accuracy (P30) in the REIN trials (REIN 1: 84%, REIN 2: 86%) was in the same order observed in the abovementioned studies. In this study, the severity of proteinuria did not affect the bias or accuracy of eGFR. This finding does not contrast with observations by Branten et al.[7] and Hofstra et al.[8] because these studies focused on patients with frank nephrotic syndrome, whereas in the REIN 1 and 2 trials, only 6% and 8% of patients, respectively, had nephrotic-range albuminemia (,3 g/L).

The similar or inferior bias in the REIN 1 and 2 trials as compared with the studies by Levey et al.,[9] Inker et al.,[2] and Pottel et al.[4] is likely attributable to plasma iohexol clearance being coherently adopted as a gold-standard measurement in the REIN trials. By contrast, various methods were used in the abovementioned studies. Significant differences exist among these gold-standard GFR methods,[21] and uniformly adopting a single technique is the best solution to maximize accuracy. The iohexol metric of the GFR adopted in the REIN trials was highly standardized, precise, and accurate.[22]

In contrast to previous pathophysiology studies in patients with overt nephrotic syndrome, proteinuria did not introduce any bias in eGFR estimates and analyses stratified by age and GFR categories substantially confirmed the aggregate analysis in both studies. In the study by Hofstra et al.,[8] bias was generally limited to patients with severe hypoalbuminemia (,2.5 g/L),[8] suggesting that in nonnephrotic patients, the tubular burden of proteinuria does not disturb the renal handling of creatinine. We provide robust evidence that moderate-to-severe proteinuria does not alter creatine-based GFR estimates' reliability.

This study has limitations that should be acknowledged. First, although findings in the REIN 1 trial were externally replicated in the REIN 2 trial, these trials were performed in Italian nephrology centers 20 years ago that did not include non-White patients. Therefore, findings in this study remain to be confirmed in cohorts including other races and ethnicities. Second, the study populations in the REIN 1 and REIN 2 trials were specific to chronic, nondiabetic proteinuric nephropathies. This specificity may limit the generalizability of the findings to other types of kidney diseases or diabetic populations. Another limitation is that we do not have a proper control group without proteinuria. However, the fact that bias and accuracy in REIN trials were similar to those in the reference cohorts in the studies that established the CKD-EPI 2009 and 2021 and EKFC formulas is sufficient evidence supporting the validity of the estimates of GFR by

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creatinine in the CKD population with moderate-to-severe proteinuria. The standardization of GFR measurement with plasma iohexol clearance as a gold standard and the accuracy of data collection in the setting of two clinical trials are two important strengths of this study.

Notwithstanding the bias of eGFR estimates by serum creatinine in this study was minimal, in line with other studies, including the seminal studies by Levey et al.,[9] Inker et al.,[2] and Pottel et al.,[4] the P30, even if nominally tolerable, was relatively high pointing to the need of measuring the GFR by gold-standard methods whenever needed for clinical and research reasons.[23] This is true for confirmation of the diagnosis of CKD in cases where there is a discrepancy between GFR estimated from serum creatinine or cystatin C and the patient's clinical status for the evaluation of kidney function in potential living kidney donors to ensure adequate renal reserve after donation, in situations where body composition is significantly altered (e.g., extreme obesity, muscle wasting), for the assessment of kidney function in patients with rapidly changing renal function and in research studies where precise GFR values are critical for the analysis.[23] Cystatin C measurements were unavailable 20 years ago so that this study could not evaluate this metric.

In conclusion, the GFR estimates by the CKD-EPI formulas with and without race and EKFC equations have minimal bias and sufficient accuracy in patients with proteinuria. These findings support the application of the same formulas in patients with non-nephrotic proteinuria.

***Figure 1.*** *Correlations among mGFR (plasma iohexol clearance) and creatinine-based GFR estimates (CKD-EPI 2021 without race, CKDEPI 2009 with race, and EKFC equation). CKD-EPI, CKD Epidemiology Collaboration; EKFC, European Kidney Function Consortium; mGFR, measured GFR; REIN, ramipril in nondiabetic renal failure.*

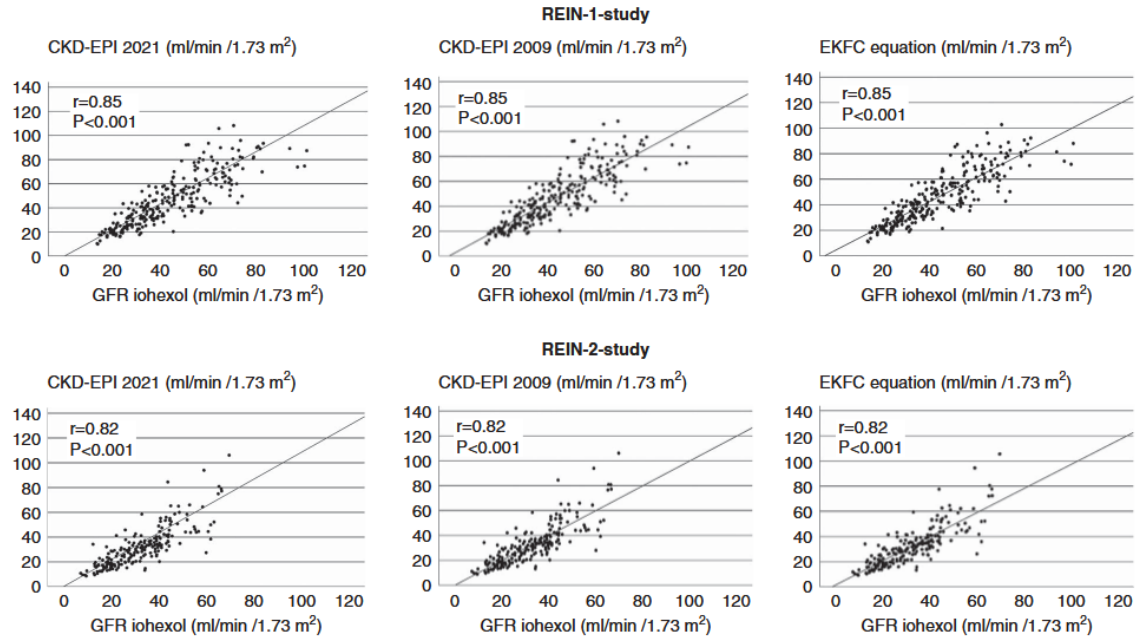

**Table 2. Bias and accuracy of creatinine-based GFR estimates in the REIN 1 trial**

| REIN 1 | CKD-EPI 2009 | CKD-EPI 2021 (without Race) | EKFC Formula |
|---|---|---|---|
| Median bias in the whole study population ($n$=269) | 0.05 | 0.04 | 0.04 |
| 95% CI | 0.01 to 0.08 | 0.003 to 0.08 | 0.01 to 0.08 |
| IQR | −0.12 to 0.22 | −0.11 to 0.21 | −0.09 to 0.2 |
| Root mean square difference | 11 (4–19) | 11 (4–19) | 11 (4–17) |
| P15 (95% CI) | 67 (61 to 72) | 68 (62 to 74) | 66.(60 to 72) |
| P30 (95% CI) | 84 (79 to 88) | 84 (79 to 88) | 84 (79 to 88) |
| Median bias by age (yr), 18–40 yr ($n$=73) | 0.19 | 0.18 | 0.17 |
| 95% CI | 0.11 to 0.22 | 0.11 to 0.22 | 0.11 to 0.2 |
| IQR | 0.02–0.33 | 0.02–0.31 | 0.03–0.3 |
| Root mean square difference (95% CI) | 14 (2 to 26) | 14 (2 to 25) | 12 (2 to 22) |
| P15 (95% CI) | 46 (34 to 58) | 47 (35 to 59) | 46 (34 to 58) |
| P30 (95% CI) | 71 (59 to 81) | 71 (59 to 81) | 76 (65 to 86) |
| Median bias by age (yr), 40–65 yr ($n$=162) | −0.02 | −0.02 | 0.0 |
| 95% CI | −0.06 to 0.03 | −0.06 to 0.03 | −0.04 to 0.04 |
| IQR | −0.16 to 0.16 | −0.16 to 0.15 | −0.13 to 0.15 |
| Root mean square difference (95% CI) | 11 (2 to 19) | 11 (2 to 19) | 10 (2 to 18) |
| P15 (95% CI) | 75 (67 to 81) | 76 (69 to 83) | 73 (66 to 80) |
| P30 (95% CI) | 89 (84 to 94) | 89 (84 to 94) | 86 (80 to 91) |
| Median bias by age (yr), ≥65 yr ($n$=34) | 0.02 | 0.02 | −0.01 |
| 95% CI | −0.04 to 0.11 | −0.04 to 0.11 | −0.08 to 0.08 |
| IQR | −0.1 to 0.22 | −0.11 to 0.22 | −0.14 to 0.17 |
| Root mean square difference (95% CI) | 10 (−2 to 23) | 10 (−2 to 22) | 9 (−1 to 19) |
| P15 (95% CI) | 73 (56 to 87) | 73 (56 to 87) | 73 (56 to 87) |
| P30 (95% CI) | 88.(72 to 97) | 88.(72 to 97) | 88.(72 to 97) |
| Median bias by mGFR >60 ml/min per 1.73 $m^2$ ($n$=54) | 0.05 | 0.04 | 0.02 |
| 95% CI | −0.01 to 0.1 | −0.01 to 0.1 | −0.03 to 0.07 |
| IQR | −0.01 to 0.15 | −0.01 to 0.14 | −0.11 to 0.12 |
| Root mean square difference (95% CI) | 15 (2 to 29) | 15 (1 to 29) | 14 (2 to 25) |
| P15 (95% CI) | 78 (64 to 88) | 82 (69 to 91) | 82 (69 to 91) |
| P30 (95% CI) | 89 (77 to 96) | 89 (77 to 96) | 93 (82 to 98) |
| Median bias by mGFR 45–60 ml/min per 1.73 $m^2$ ($n$=64) | 0.06 | 0.06 | 0.06 |
| 95% CI | −0.01 to 0.14 | −0.01 to 0.13 | −0.01 to 0.14 |
| IQR | −0.11 to 0.3 | −0.12 to 0.3 | −0.12 to 0.22 |
| Root mean square difference (95% CI) | 15 (2 to 28) | 15 (2 to 28) | 14 (3 to 25) |
| P15 (95% CI) | 66 (53 to 77) | 66 (53 to 77) | 66 (53 to 77) |
| P30 (95% CI) | 77 (64 to 86) | 77 (64 to 86) | 80 (68 to 89) |
| Median bias by mGFR 30–45 ml/min per 1.73 $m^2$ ($n$=80) | 0.02 | 0.02 | 0.02 |
| 95% CI | −0.03 to 0.13 | −0.04 to 0.13 | −0.04 to 0.12 |
| IQR | −0.2 to 0.3 | −0.2 to 0.24 | −0.13 to 0.22 |
| Root mean square difference (95% CI) | 9 (2 to 16) | 9 (2 to 16) | 9 (2 to 15) |
| P15 (95% CI) | 63 (51 to 73) | 64 (52 to 74) | 63 (51 to 73) |
| P30 (95% CI) | 83 (72 to 90) | 83 (72 to 90) | 84 (74 to 91) |
| Median bias by mGFR 15–30 ml/min per 1.73 $m^2$ ($n$=67) | 0.03 | 0.02 | 0.07 |
| 95% CI | −0.04 to 0.13 | −0.04 to 0.11 | 0.02 to 0.16 |
| IQR | −0.1 to 0.21 | −0.1 to 0.21 | −0.05 to 0.23 |
| Root mean square difference (95% CI) | 6 (0 to 11) | 6 (0 to 11) | 6 (0 to 11) |
| P15 (95% CI) | 64 (52 to 76) | 66 (53 to 77) | 58 (46 to 70) |
| P30 (95% CI) | 90 (80 to 96) | 90 (80 to 96) | 81 (69 to 89) |
| Median bias by mGFR <15 ml/min per 1.73 $m^2$ ($n$=4) | −0.19 | −0.19 | −0.12 |
| 95% CI | −0.28 to 0.22 | −0.28 to 0.22 | −0.21 to 0.25 |
| IQR | −0.27 to 0.13 | −0.27 to 0.13 | −0.2 to 0.17 |
| Root mean square difference (95% CI) | 3 (0 to 6) | 3 (0 to 6) | 3 (−1 to 6) |
| P15 (95% CI) | 75 (19 to 99) | 75 (19 to 99) | 75 (19 to 99) |
| P30 (95% CI) | 100 (40 to 100) | 100 (40 to 100) | 100 (40 to 100) |
| Median bias by urinary protein >3 g/d ($n$=124) | 0.01 | 0.01 | 0.03 |
| 95% CI | −0.04 to 0.07 | −0.04 to 0.06 | −0.02 to 0.08 |
| IQR | −0.13 to 0.21 | −0.14 to 0.2 | −0.1 to 0.2 |
| Root mean square difference (95% CI) | 10 (2 to 19) | 10 (2 to 18) | 10 (2 to 18) |
| P15 (95% CI) | 69 (60 to 77) | 70 (61 to 78) | 67 (58 to 75) |
| P30 (95% CI) | 86 (78 to 91) | 86 (78 to 91) | 85 (77 to 91) |
| Median bias by urinary protein 1.5–3 g/d ($n$=74) | 0.13 | 0.12 | 0.12 |
| 95% CI | 0.06 to 0.17 | 0.06 to 0.17 | 0.07 to 0.15 |
| IQR | 0.0 to 0.26 | −0.02 to 0.26 | 0.01 to 0.23 |
| Root mean square difference (95% CI) | 13 (1 to 25) | 13 (1 to 25) | 12 (1 to 22) |
| P15 (95% CI) | 57 (45 to 68) | 60 (47 to 71) | 60 (47 to 71) |
| P30 (95% CI) | 82 (72 to 90) | 82 (72 to 90) | 80 (69 to 88) |
| Median bias by urinary protein 1.0–1.5 g/d ($n$=56) | 0.01 | 0.01 | 0.0 |
| 95% CI | −0.14 to 0.1 | −0.14 to 0.1 | −0.11 to 0.03 |
| IQR | −0.17 to 0.15 | −0.17 to 0.15 | −0.15 to 0.17 |
| Root mean square difference (95% CI) | 12 (0 to 23) | 12 (0 to 23) | 11 (1 to 20) |
| P15 (95% CI) | 77 (64 to 87) | 77 (64 to 87) | 73 (60 to 84) |
| P30 (95% CI) | 86 (74 to 94) | 86 (74 to 94) | 91 (80 to 97) |

CI, confidence interval; CKD-EPI, CKD Epidemiology Collaboration; EKFC, European Kidney Function Consortium; IQR, interquartile range; mGFR, measured GFR; P15, accuracy within 15%; P30, accuracy within 30%; Pct, percentile; REIN, ramipril in nondiabetic renal failure.

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**Table 3. Bias and accuracy of creatinine-based GFR estimates in the REIN 2 trial**

| REIN 2 | CKD-EPI 2009 | CKD-EPI 2021 (without Race) | EKFC Formula |
|---|---|---|---|
| Median bias in the whole population ($n$=201) | −0.04 | −0.04 | −0.03 |
| 95% CI | −0.09 to 0.0 | −0.09 to 0.0 | −0.08 to 0.01 |
| IQR | −0.18 to 0.18 | −0.19 to 0.16 | −0.16 to 0.16 |
| Root mean square difference (95% CI) | 10 (2 to 17) | 10 (2 to 17) | 9 (2 to 16) |
| P15 (95% CI) | 74 (67 to 80) | 74 (68 to 80) | 74 (67 to 80) |
| P30 (95% CI) | 87 (81 to 91) | 89 (83 to 93) | 86 (81 to 91) |
| Median bias by age (yr), 18–40 yr ($n$=49) | 0.01 | 0.01 | 0.05 |
| 95% CI | −0.06 to 0.12 | −0.06 to 0.11 | −0.05 to 0.11 |
| IQR | −0.13 to 0.22 | −0.13 to 0.21 | −0.1 to 0.19 |
| Root mean square difference (95% CI) | 8 (1 to 16) | 8 (1 to 16) | 8 (0 to 16) |
| P15 (95% CI) | 69 (55 to 82) | 69 (54 to 82) | 71 (57 to 83) |
| P30 (95% CI) | 82 (68 to 91) | 88 (75 to 95) | 84 (70 to 93) |
| Median bias by age (yr), 40–65 yr ($n$=106) | −0.04 | −0.04 | −0.02 |
| 95% CI | −0.12 to 0.0 | −0.12 to 0.0 | −0.08 to 0.05 |
| IQR | −0.2 to 0.18 | −0.21 to 0.16 | −0.18 to 0.17 |
| Root mean square difference (95% CI) | 9 (1 to 18) | 9 (1 to 18) | 9 (1 to 18) |
| P15 (95% CI) | 75 (65 to 82) | 75 (65 to 82) | 73 (63 to 81) |
| P30 (95% CI) | 88 (80 to 93) | 88 (80 to 93) | 85 (77 to 91) |
| Median bias by age (yr), ≥65 yr ($n$=45) | −0.11 | −0.13 | −0.12 |
| 95% CI | −0.17 to −0.01 | −0.17 to −0.01 | −0.17 to −0.05 |
| IQR | −0.21 to 0.12 | −0.21 to 0.11 | −0.22 to 0.12 |
| Root mean square difference (95% CI) | 11 (−2 to 24) | 11 (−2 to 24) | 11 (−1 to 22) |
| P15 (95% CI) | 76 (60 to 87) | 78 (63 to 89) | 78 (63 to 89) |
| P30 (95% CI) | 89 (76 to 96) | 91 (79 to 98) | 91 (79 to 98) |
| Median bias by mGFR >60 ml/min per 1.73 $m^2$ ($n$=10) | −0.01 | −0.01 | −0.04 |
| 95% CI | −0.33 to 0.23 | −0.34 to 0.22 | −0.39 to 0.21 |
| IQR | −0.3 to 0.22 | −0.3 to 0.2 | −0.34 to 0.19 |
| Root mean square difference (95% CI) | 20 (−3 to 43) | 20 (−3 to 43) | 20 (−3 to 44) |
| P15 (95% CI) | 50 (19 to 81) | 50 (19 to 81) | 70 (35 to 93) |
| P30 (95% CI) | 90 (56 to 100) | 90 (56 to 100) | 90 (56 to 100) |
| Median bias by mGFR 45–60 ml/min per 1.73 $m^2$ ($n$=19) | 0.06 | 0.06 | 0.06 |
| 95% CI | −0.15 to 0.23 | −0.15 to 0.23 | −0.16 to 0.19 |
| IQR | −0.16 to 0.24 | −0.16 to 0.24 | −0.16 to 0.2 |
| Root mean square difference (95% CI) | 13 (−2 to 29) | 13 (−2 to 29) | 13 (−3 to 28) |
| P15 (95% CI) | 63 (38 to 84) | 63 (38 to 84) | 63 (38 to 84) |
| P30 (95% CI) | 84 (60 to 97) | 84 (60 to 97) | 84 (60 to 97) |
| Median bias by mGFR 30–45 ml/min per 1.73 $m^2$ ($n$=79) | −0.05 | −0.05 | −0.06 |
| 95% CI | −0.11 to −0.01 | −0.12 to −0.02 | −0.09 to −0.01 |
| IQR | −0.19 to 0.04 | −0.19 to 0.04 | −0.19 to 0.09 |
| Root mean square difference (95% CI) | 10 (0 to 19) | 10 (0 to 19) | 9 (1 to 17) |
| P15 (95% CI) | 85 (75 to 92) | 85 (75 to 92) | 85 (75 to 92) |
| P30 (95% CI) | 94 (86 to 98) | 95 (88 to 99) | 92 (84 to 97) |
| Median bias by mGFR 15–30 ml/min per 1.73 $m^2$ ($n$=77) | −0.07 | −0.07 | −0.02 |
| 95% CI | −0.14 to 0.01 | −0.14 to 0.01 | −0.1 to 0.07 |
| IQR | −0.19 to 0.17 | −0.19 to 0.16 | −0.16 to 0.18 |
| Root mean square difference (95% CI) | 6 (1 to 12) | 6 (1 to 12) | 6 (1 to 12) |
| P15 (95% CI) | 75 (64 to 84) | 75 (64 to 84) | 71 (60 to 81) |
| P30 (95% CI) | 83 (73 to 91) | 86 (76 to 93) | 83 (73 to 91) |
| Median bias by mGFR <15 ml/min per 1.73 $m^2$ ($n$=16) | 0.21 | 0.19 | 0.23 |
| 95% CI | −0.1 to 0.36 | −0.12 to 0.35 | −0.07 to 0.43 |
| IQR | −0.11 to 0.38 | −0.13 to 0.38 | −0.09 to 0.46 |
| Root mean square difference (95% CI) | 6 (−4 to 17) | 6 (−4 to 17) | 7 (−4 to 17) |
| P15 (95% CI) | 38 (15 to 65) | 44 (20 to 70) | 44 (20 to 70) |
| P30 (95% CI) | 69 (41 to 89) | 75 (48 to 93) | 69 (41 to 89) |
| Median bias by urinary protein >3 g/d ($n$=73) | 0.02 | 0.02 | 0.05 |
| 95% CI | −0.11 to 0.1 | −0.11 to 0.1 | −0.08 to 0.12 |
| IQR | −0.17 to 0.2 | −0.18 to 0.19 | −0.16 to 0.17 |
| Root mean square difference (95% CI) | 10 (0 to 20) | 10 (−0 to 20) | 9 (1 to 18) |
| P15 (95% CI) | 73 (61 to 82) | 73 (61 to 82) | 73 (61 to 82) |
| P30 (95% CI) | 88 (78 to 94) | 89 (80 to 95) | 88 (78 to 94) |
| Median bias by urinary protein 1.5–3.0 g/d ($n$=76) | −0.05 | −0.05 | −0.04 |
| 95% CI | −0.13 to 0.0 | −0.13 to 0.0 | −0.11 to 0.0 |
| IQR | −0.19 to 0.16 | −0.2 to 0.14 | −0.16 to 0.14 |
| Root mean square difference (95% CI) | 10 (0 to 19) | 10 (0 to 19) | 10 (0 to 19) |
| P15 (95% CI) | 75 (64 to 84) | 76 (65 to 85) | 76 (65 to 85) |
| P30 (95% CI) | 87 (77 to 94) | 88 (79 to 94) | 87 (77 to 94) |
| Median bias by urinary protein 1.0–1.5 g/d ($n$=30) | −0.11 | −0.12 | −0.08 |
| 95% CI | −0.2 to −0.03 | −0.2 to −0.03 | −0.18 to 0.02 |
| IQR | −0.22 to 0.1 | −0.24 to 0.1 | −0.19 to 0.11 |
| Root mean square difference (95% CI) | 10 (−3 to 22) | 10 (−3 to 22) | 10 (−3 to 23) |
| P15 (95% CI) | 80 (61 to 92) | 80 (61 to 92) | 77 (58 to 90) |
| P30 (95% CI) | 90 (74 to 98) | 90 (74 to 98) | 90 (74 to 98) |

CI, confidence interval; CKD-EPI, CKD Epidemiology Collaboration; EKFC, European Kidney Function Consortium; IQR, interquartile range; mGFR, measured GFR; P15, accuracy within 15%; P30, accuracy within 30%; Pct, percentile.

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**Data Sharing Statement**
Upon request to the leading investigator of REIN studies, G. Remuzzi, 6 months after the publication of the study, the study data will be made available for the following 6 months.

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