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ORIGINAL ARTICLE

Accuracy and variability of equations to estimate glomerular filtration rates in renal transplant patients receiving sirolimus and/or calcineurin inhibitor immunosuppression*

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Summary

Measured glomerular filtration rates (mGFRs) were obtained by ^{99}mTc-DPTA, ^{125}I-iothalamate, iohexol, ^{51}Cr-EDTA, non-radiolabeled iothalamate, or inulin clearance from centers agreeing to perform mGFR in six completed and one ongoing Wyeth Research multicenter trials evaluating sirolimus (SRL) in regimens with or without a calcineurin inhibitor (CNI). Estimated GFRs (eGFRs) were calculated by the Cockcroft-Gault ($eGFR_{CG}$), Nankivell ($eGFR_{NK}$), and simplified Modification of Diet in Renal Disease ($eGFR_{MDRD}$) equations. Bias, precision, and accuracy for each of these equations were estimated by tertiles and by regimen. For the Rapamune Maintenance Regimen (RMR) trial, eGFR outcomes were also compared between treatments {[SRL–cyclosporine (CsA) versus SRL]} using the three eGFR formulas. In the lowest mGFR tertile (6–40 ml/min), $eGFR_{MDRD}$ gave the best accuracy with the least bias whereas $eGFR_{NK}$ and $eGFR_{CG}$ performed better in the highest mGFR tertile (58–139 ml/min). At 24 months in the RMR study, mean differences in eGFR between treatments were 13.6, 14.2, and 13.5 ml/min/1.73 m^2 for $eGFR_{CG}$, $eGFR_{NK}$, and $eGFR_{MDRD}$, respectively, favoring CsA withdrawal (*P*-values for all <0.001). The accuracy of the three eGFR equations was affected by mGFR range but not by immunosuppressive regimens utilizing SRL, SRL–CNI or CNI-based therapy.

Introduction

Serum creatinine is a simple, inexpensive, and commonly accepted measurement of renal function for a given renal transplant patient. It is not, however, an accurate indicator of true glomerular filtration rate (GFR). The limitations of serum creatinine are more apparent when renal function is compared across patient populations, which are quite heterogeneous with regards to age, gender, race, and actual GFR. Acute rejection rates have decreased over the last two decades with the introduction of new immunosuppressive drugs, and several recent articles have reported that renal function is a more important predictor of long-term graft function and survival than the occurrence of acute rejection episodes [1,2]. Consequently, renal function has become a primary efficacy outcome measurement in many, if not most, recent trials comparing immunosuppressive regimens.

Measured GFR (mGFR) techniques provide the most accurate assessment of renal function, and several methods are available (e.g. ^{99}mTc-DPTA, iohexol, ^{51}Cr-EDTA). Ideally, one of these techniques could be used to measure renal function during the conduct of a study in renal transplantation. However, they are costly, more invasive, often inconvenient, and typically labor-intensive. The utility of mGFR is further complicated by variable adoption across investigational centers so that it is often impractical in a multicenter trial to standardize mGFR to a single methodology. Many centers are reluctant to routinely measure GFR because it extends patient visits, and there are often scheduling issues with the laboratory performing the test. However, the biggest drawback to using mGFR as a primary endpoint in transplantation studies is the risk of missing data, because of patient refusal or scheduling problems. This is unacceptable for a primary endpoint as it needs to be analyzed on an intent-to-treat basis, which requires complete data for all patients.

In an effort to collect complete data, while at the same time, obtain a better assessment of GFR, numerous equations have been proposed to estimate GFR (eGFR) based on serum creatinine, age, and gender along with other demographic and laboratory parameters. Although not specifically developed for renal transplantation, the formula proposed by Cockroft and Gault has been the most widely used since it was published three decades ago [3]. Recognizing that renal transplant patients generally have a clinical profile that differs from the general population, including those with impaired renal function, Nankivell and coworkers developed and tested equations specifically in kidney transplant recipients [4]. More recently, Levey and colleagues from the Modification of Diet in Renal Disease (MDRD) study have proposed additional equations for predicting GFR [5,6], which are also of interest for estimating GFR in renal transplantation.

Clinical development of the mTOR inhibitor, sirolimus (SRL), began in the early 1990s, paralleling the growing interest in renal function as an important endpoint in renal and other solid organ transplantation. Most of the studies undertaken by the sponsor, Wyeth Research, included mGFR in centers agreeing to perform these measurements. None of the trials, however, produced sufficient mGFR data to use this parameter as a robust assessment of renal function outcome. Nonetheless, taken together, these trials gathered sufficient data to evaluate formulas for estimating GFR (eGFR) with SRL-containing regimens. The present paper assesses three of the most commonly used eGFR formulas in renal transplant patients receiving SRL, associated or not with a calcineurin inhibitor (CNI). Analyzing the performance of these eGFR equations as a function of the three immunosuppressive regimens used (CNI–SRL, SRL without a CNI, and a CNI without SRL) is useful in order to validate the differences in eGFR between these treatments that were reported during the various trials.

Methods

Measured glomerular filtration rates (mGFR) were obtained from 546 patients enrolled at centers agreeing to perform mGFRs during six completed (studies 203 [7], 207 [8], 210 [9], 212 [10], 301[11], and 310 [12]) and one ongoing (study 316 [13]) Wyeth Research multicenter, randomized trials in renal transplantation. These trials are summarized in Table 1, along with the percentage of patients from each trial that were included in the analyses. For each patient, the first mGFR value available >75 days after randomization was used. mGFR methodology was according to local practice; methodologies (percentage of values in the analysis) included ^{99}mTc-DPTA (32.6%), iohexol (22.7%), ^{51}Cr-EDTA (20.5%), nonradiolabeled isothalamate (12.1%), ^{125}I-iothalamate (10.1%), and inulin clearance (2.0%). Patients were excluded from the analysis if they did not have an mGFR determination >75 days after randomization.

Estimated GFRs (eGFRs) were calculated by the Cockcroft-Gault ($eGFR_{CG}$) [3], Nankivell ($eGFR_{NK}$) [4]

Table 1. Summary of Wyeth Research renal transplant studies used for this analysis and percentage of the 546 patients included this meta-analysis.

Study No.	Reference	Design summary (all patients received steroids)	Patients (%)
203	[7]	CsA versus full- and reduced-dose CsA–SRL combinations	16.5
207	[8]	SRL–AZA versus CsA–AZA *de novo*	5.9
210	[9]	SRL–MMF versus CsA–AZA *de novo*	1.5
212	[10]	SRL–CsA *de novo* with randomization at month 2 to SRL–CsA or SRL with CsA withdrawal	21.3
301	[11]	CsA–AZA versus CsA–SRL 2 mg or CsA–SRL 5 mg	11.0
310	[12]	SRL–CsA *de novo* with randomization at month 3 to SRL–CsA or SRL with CsA withdrawal	9.5
316	[13]	Randomization 6–60 months after transplantation to CNI continuation or conversion to SRL (all patients could receive AZA or MMF)	34.4

SRL, sirolimus; AZA, azathioprine; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor – CsA or tacrolimus.

and simplified (four-variable) Modification of Diet in Renal Disease ($eGFR_{MDRD}$) equations [6]. These equations are shown in Appendix 1. The investigational sites performed all laboratory measurements. The recommendations of Bland and Altman [14] were used to compare the eGFR with the mGFR. Bias, precision, and accuracy for each of these equations were estimated by tertiles, by regimen (SRL, SRL–CNI, and CNI), by time after transplantation (≤1 year and >1 year), and by ethnic origin. For each of the eGFR equations, unadjusted and mGFR method adjusted biases were compared across tertiles, and mGFR method × tertile interactions were tested for significance.

The mean difference between eGFR and mGFR values directly estimated the global bias. The standard deviation (SD) of the mean difference is an estimation of precision; a large SD means a low precision. The percent of eGFR values falling within 30% and 50% of mGFR (e.g. 21–39 ml/min and 15–45 ml/min, respectively, if the mGFR was 30 ml/min) was used to estimate the accuracy of the estimating equations. The combined root mean square error (CRMSE) was examined, where CRMSE is the square root of the [(mean difference between estimated and measured GFR)^2 + (SD of the difference)^2]; it measures both bias and precision. The relationship between eGFR and mGFR was also assessed using weighted least squares regression. As the variance decreases with GFR values, values were weighted $1/[(eGFR + mGFR)/2]^2$.

In order to evaluate the impact of the 3 different eGFR equations on estimations of treatment differences, eGFR outcomes in all patients in study 310 were compared between groups {[SRL–cyclosporine (CsA) versus SRL]}. All values were included in the analysis, whether or not a corresponding mGFR value was available. For each eGFR method, treatment groups were compared using ANCOVA with baseline (the last value before randomization at month 3) as covariate.

Results

The demographic characteristics of the populations analyzed are summarized by immunosuppressive treatment category in Table 2. Because these patients were not randomly assigned to one of three treatment categories within a single study, some statistically significant differences exist among the groups. Donor age was significantly lower in the SRL–CNI group, and fewer recipients were of white ethnic origin; additionally, the mean time of first mGFR occurred earlier in this group. The SRL group included significantly fewer deceased donors, and the CNI group had a lower mean mGFR. These findings are attributable to protocol-related differences in study design and the geographic distribution of the centers in the various studies included in this analysis. Furthermore, there could be selection bias in patients selected for or willing to undergo mGFR.

Figure 1 illustrates the linear regression analyses of eGFR versus mGFR, and Fig. 2 provides the Bland and Altman plots of differences between methods as a function of GFR. The performance of eGFR as a function of mGFR tertiles is shown in Table 3. $eGFR_{MDRD}$ performed the best in the lowest mGFR tertile (6–40 ml/min) whereas $eGFR_{CG}$ and $eGFR_{NK}$ performed better in the highest tertile (58–139 ml/min). Performance among estimating equations was similar in the middle tertile (41–57 ml/min); however, the best results were obtained with either $eGFR_{NK}$ or $eGFR_{MDRD}$. Overall, 63.7%, 64.3%, and 72.7% of $eGFR_{CG}$, $eGFR_{NK}$, and $eGFR_{MDRD}$ values, respectively, occurred within 30% of mGFR; 81.9%, 82.4%, and 88.8% of the values, respectively, were within 50% of mGFR.

Performance as a function of immunosuppressive regimen is presented in Table 4. These data would suggest that $eGFR_{MDRD}$ was the best of the three methods for the SRL–CNI regimen and performed particularly well with a CNI-based, SRL-free regimen. However, as stated above, the performance of the three eGFR formulas varied across

Table 2. Demography of patients in the analysis by immunosuppressive treatment category.

Parameter	SRL–CNI (n = 229)	SRL (n = 204)	CNI (n = 113)
Mean recipient age, years (range)	46 (18–75)	45 (14–71)	46 (14–72)
Mean donor age,* years (range)	35 (1–71)	41 (1–78)	41 (7–77)
% Females	36	30	31
% White ethnic origin*	65	88	81
% Deceased donor*	90	82	93
% Delayed graft function	12	17	15
Mean time post-transplantation,* days (range)	222 (77–1376)	336 (79–1728)	326 (78–764)
Mean mGFR,*† ml/min/1.73 m^2 (range)	50.2 (9–127)	52.6 (8–139)	45.9 (6–105)

SRL, sirolimus; AZA, azathioprine; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor – CsA or tacrolimus.

*Fisher exact $P < 0.05$ for comparisons among treatments.

†First value >75 days postrandomization in the Wyeth Research study.

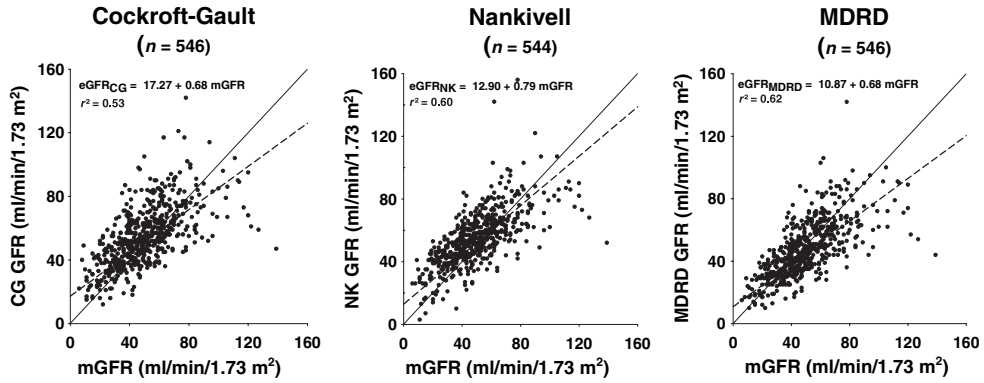

Figure 1 Linear regression plots of eGFR versus mGFR. Solid line (—), identity line; dashed line (- - -), is the weighted $[1/(CeGFR + mGFR)/2]^2$ least-squares linear regression line.

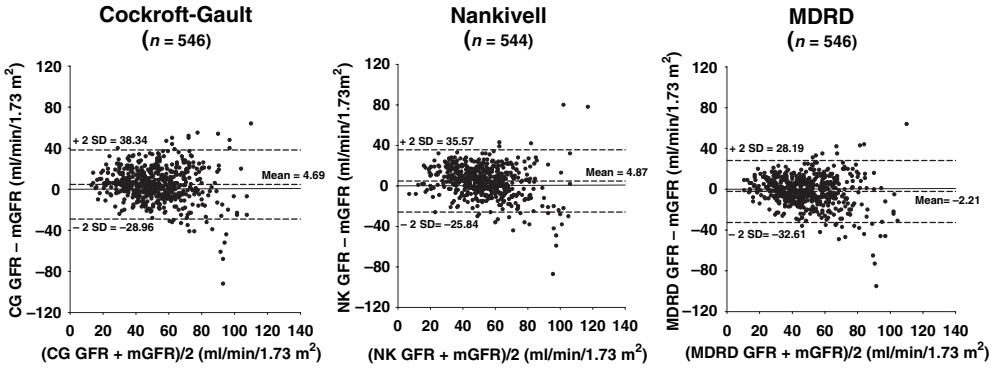

Figure 2 Bland and Altman plots of differences between eGFR and mGFR as a function of GFR (the dashed lines mark the mean ± 2 SD of the observed bias expressed in ml/min).

Table 3. Performance (expressed as ml/min/1.73 m^2) of eGFR versus mGFR as a function of mGFR tertiles.

mGFR Tertile mean (range), ml/min/1.73 m^2	eGFR	Bias	Precision	Accuracy*
1st Tertile (*n* = 176)	CG	13.0	12.1	17.8
28.9	NK	12.9	9.8	16.2
(6–40)	MDRD	4.9	9.1	10.3
2nd Tertile (*n* = 192)	CG	5.5	13.9	14.9
48.5	NK	5.9	11.5	12.9
(41–57)	MDRD	–1.2	12.1	12.2
3rd Tertile (*n* = 178)	CG	–4.4	20.0	20.5
73.1	NK	–4.1	19.3	19.7
(58–139)	MDRD	–10.4	19.5	22.1

*Combined root mean square error.

Table 4. Performance (expressed as ml/min/1.73 m^2) of eGFR versus mGFR as a function immunosuppressive treatment.

Treatment mGFR, ml/min/1.73 m^2 mean (range),	eGFR	Bias	Precision	Accuracy*
SRL–CNI (*n* = 229)	CG	4.6	17.5	18.1
50.2	NK	5.4	16.4	17.3
(9–127)	MDRD	–1.2	16.0	16.0
SRL (*n* = 204)	CG	2.9	17.7	17.9
52.6	NK	3.1	16.2	16.5
(8–139)	MDRD	–4.6	16.2	16.8
CNI (*n* = 113)	CG	8.1	15.0	17.0
45.9	NK	6.9	12.8	14.5
(6–105)	MDRD	0.1	12.4	12.4

*Combined root mean square error.

the GFR range. In the pooled data analysis, the mean mGFR was significantly lower in the CNI group. When adjusted for mGFR (Table 5), there was no difference across immunosuppressive treatments as can be seen in the treatment effect *P*-values following adjustment.

Irrespective of whether or not eGFR values were adjusted for mGFR, differences in performance were observed for all three estimating equations when the results were analyzed by ethnic origin [black (*n* = 75) versus other (*n* = 471)]. For adjusted values, the mean biases (±SEM) were 2.6 ± 1.7 vs. 5.0 ± 0.7 ml/min/1.73 m^2 (*P* = 0.185), 1.3 ± 1.5 vs. 5.4 ± 0.6 ml/min/1.73 m^2 (*P* = 0.010), and 1.4 ± 1.5 vs. −2.8 ± 0.6 ml/min/1.73 m^2 (*P* = 0.010), black versus other, for $eGFR_{CG}$, $eGFR_{NK}$,

Table 5. Bias (mean ± SEM, expressed as ml/min/1.73 m^2) by immunosuppressive treatment and according to adjustment for mGFR.

	CG		NK		MDRD	
eGFR method adjusted	No	Yes	No	Yes	No	Yes
SRL–CNI	4.6 ± 1.1	4.6 ± 1.0	5.4 ± 1.0	5.4 ± 0.9	−1.2 ± 1.0	−1.2 ± 0.9
SRL	2.9 ± 1.2	4.0 ± 1.0	3.1 ± 1.1	4.2 ± 0.9	−4.6 ± 1.1	−3.6 ± 0.9
CNI	8.1 ± 1.6	6.2 ± 1.4	6.9 ± 1.5	5.0 ± 1.2	0.1 ± 1.5	−1.7 ± 1.2
Treatment effect *P*-value	0.038	0.424	0.096	0.592	0.017	0.148

Unadjusted model: eGFR-mGFR = a + b × treatment.
Adjusted model: eGFR-mGFR = a + b × mGFR + c × treatment.

and $eGFR_{MDRD}$, respectively. Therefore, bias was less in black recipients whereas the estimates were less precise. Of note for black recipients, bias and precision were essentially the same for the $eGFR_{NK}$ and $eGFR_{MDRD}$ equations, even though $eGFR_{MDRD}$ but not $eGFR_{NK}$ contains a variable for ethnic origin. Bias and precision for the three eGFR equations were essentially the same independently of whether the mGFRs were obtained ≤1 year or >1 year after transplantation (data not shown). Furthermore, the unadjusted and mGFR method adjusted biases were relatively similar across tertiles and eGFR equations, and none of the *P*-values for the mGFR method*tertile interaction terms were significant (data not shown). This indicates that mGFR methodology did not notably affect conclusions regarding the performance of the three eGFR equations.

Data from the Rapamune Maintenance Regimen trial, study 310 [12], was used to explore the differences in eGFR outcome using the three eGFR equations. The 24-month time point was chosen for illustration purposes as there were an approximately equal number of observations available for both treatment groups (SRL–CsA, $n = 148$; SRL, $n = 141$); these data are presented in Fig. 3. The absolute values for both treatments were approximately 10 ml/min higher for both immunosuppressive regimens when either $eGFR_{CG}$ or $eGFR_{NK}$ was compared with $eGFR_{MDRD}$. On the contrary, the differences between treatments were quite similar irrespective of eGFR methodology (13.6, 14.2, and 13.5 ml/min for $eGFR_{CG}$, $eGFR_{NK}$, and $eGFR_{MDRD}$, respectively; $P < 0.001$ for all comparisons). Concordance of methods for between-treatment differences was observed over the duration of the trial for both the on-therapy and intent-to-treat analyses (data not shown).

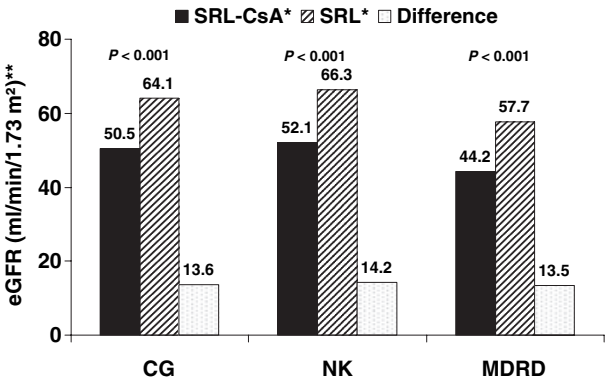

Figure 3 On therapy results from the RMR trial (Study 310) at 2 years using the three estimating equations (CG, eGFR by the method of Cockcroft-Gault; NK, eGFR by the method of Nankivell; MDRD, eGFR by the four-variable Modification of Diet in Renal Disease equation). *SRL + CsA, $n = 148$; SRL, $n = 141$. **adjusted means and adjusted mean differences, *P*-value by ANCOVA with baseline (month 3) as a covariate.

Discussion

Data for these analyses were collected over approximately 12 years, using six different mGFR methods. This notwithstanding, performance of the eGFR formulas was similar to that reported recently by others evaluating eGFR methods in renal transplant recipients. We found a mean bias of 4.7, 4.9, and −2.2 ml/min for $eGFR_{CG}$, $eGFR_{NK}$, and $eGFR_{MDRD}$, respectively. Bosma and colleagues [15] reported mean bias of 6.3, 5.8, and −3.2 ml/min for $eGFR_{CG}$, $eGFR_{NK}$, and $eGFR_{MDRD}$, respectively, compared with ^{125}I-iothalamate mGFR. Using the same mGFR methodology, Poggio *et al.* [16] found mean differences of 10.2, 8.1, and 2.6 ml/min for $eGFR_{CG}$, $eGFR_{NK}$, and $eGFR_{MDRD}$, respectively. On the contrary, neither we, nor the above referenced works, found the large bias for $eGFR_{NK}$ (36.3 ml/min) as reported by Raju *et al.* [17].

With regards to overall accuracy, measured as the percentage of eGFR values within 30% or 50% of mGFR, the performance of $eGFR_{MDRD}$ was somewhat superior to the two other eGFR equations, both in the present work and previous evaluations [15,16]. However, a clear difference in performance was observed over the range of mGFR values. $eGFR_{MDRD}$ performed the best in the lowest mGFR tertile (mean, 28.9 ml/min) whereas $eGFR_{CG}$ and $eGFR_{NK}$ performed better in the highest mGFR tertile (mean, 73.1 ml/min). Other authors have reported similar

findings, either with a tertile analysis [15], or when empirically dividing the patients into groups of mGFR <30 ml/min, 30–60 ml/min, and >60 ml/min [16].

Data collection for our meta-analysis began before two of the eGFR methods ($eGFR_{NK}$ and $eGFR_{MDRD}$) were actually published. The $eGFR_{NK}$ results have been reported in Wyeth Research trials beginning with the initial phase 3 trials, as this equation was the only one at that time having been developed specifically for renal transplant recipients. Since that time, the number of therapeutic agents and resulting combinations has multiplied, including CNI-free regimens. Consequently, there has been speculation as to whether one equation or another is more accurate for a given regimen. Using unadjusted data, there was a significant treatment effect (SRL–CNI, SRL, or CNI) on bias for both $eGFR_{CG}$ and $eGFR_{MDRD}$; the treatment effect approached significance ($P = 0.096$) for $eGFR_{NK.}$ However, in our data set, there were significant differences in mGFR among treatments ($P = 0.021$), with a lower mean value in the CNI group. If the eGFR values are adjusted for the mGFR, there are no treatment differences among the eGFR methods. As described in the previous paragraph, a treatment effect is a consequence of the observed mGFRs, not the treatment *per se*. It should be emphasized that our data derive from seven different studies, and patients were not randomly assigned to the three different treatment groups. Thus, the fact that mGFR in the CNI group was lower in our data set does not lead to the inference that mGFR is superior with SRL or SRL–CNI therapy compared with CNI alone.

Evaluations of the performance of eGFR equations often conclude that there are limitations to these formulas in accurately predicting GFR, and therefore, mGFR is to be preferred. Whereas we do not dispute this conclusion, at present, we do not feel that mGFR can be obtained consistently at all time points from every patient participating in a multicenter study so as to permit this parameter to be used as a primary endpoint in a renal transplantation trial. On the contrary, the success rate for collecting the information necessary to perform eGFR usually exceeds 95%, even over several years. Additionally, the potential number of sequential measurements is quite large and can be done at each visit during which routine laboratory tests are performed. In order to assess whether the findings would have been different according to the eGFR methodology, we retrospectively analyzed renal function outcome in one of the key SRL trials [12] using all three eGFR methods. The estimates were approximately 10 ml/min higher for both immunosuppressive regimens with either $eGFR_{CG}$ or $eGFR_{NK}$ when compared with $eGFR_{MDRD}$. However, the mean differences in change in eGFR between treatments differed by less than 5%, irrespective of eGFR methodology.

In conclusion, this pooled data analysis based on seven trials testing various SRL regimens indicated that the performance of three eGFR equations was affected principally by mGFR range. $eGFR_{MDRD}$ performed best at low levels of mGFR (<40 ml/min) whereas $eGFR_{CG}$ and $eGFR_{NK}$ performed better at mGFR values >60 ml/min. Performance of eGFR equations was not affected by the SRL regimen. When these eGFR formulas were tested as outcome measurements, between-treatment differences were very similar suggesting that all three of these equations can be used to discern treatment differences in renal function during randomized trials in kidney transplantation.

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Authorship

JB and YB performed the analyses and drafted the manuscript. BK, DH, JG and JC performed research. MP gave critical input for the analysis, and JFN performed research and gave critical input for the analyses.

References

1. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; **62**: 311.
2. Salvadori M, Rosati A, Bock A, *et al.* Estimated one-year glomerular filtration rate is the best predictor of long-term graft function following renal transplant. *Transplantation* 2006; **81**: 202.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31.
4. Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR. Predicting glomerular filtration rate after kidney transplantation. *Transplantation* 1995; **59**: 1683.
5. Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; **130**: 461.
6. Levey AS, Greene T, Kusek JW. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). *J Am Soc Nephrol* 2000; **11**: 155A.
7. Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J, for the Rapamune Study Group. Sirolimus

reduces the incidence of acute rejection episodes despite lower cyclosporine doses in caucasian recipients of mismatched primary renal allografts: a phase II trial. *Transplantation* 1999; **67**: 1526.
8. Groth CG, Backman L, Morales JM, *et al.* Sirolimus (rapamycin)-based therapy in human renal transplantation. *Transplantation* 1999; **67**: 1036.
9. Kreis H, Cisterne JM, Land W, *et al.* Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 2000; **69**: 1252.
10. Gonwa TA, Hricik DE, Brinker K, Grinyo JM, Schena FP, for the Sirolimus Renal Function Study Group. Improved renal function in sirolimus-treated real transplant patients after early cyclosporine elimination. *Transplantation* 2002; **74**: 1560.
11. Kahan BD, for The Rapamune US Study Group. Efficacy of sirolimus compared with azathioprine for the reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000; **356**: 194.
12. Johnson RWG, Kreis H, Oberbauer R, Brattstrom C, Claesson K, Eris J. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; **72**: 777.
13. Schena FP, Vitko S, Wali R, *et al.* Efficacy and safety of conversion from calcineurin inhibitor to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: 18-month results from a randomized, open-label, comparative trial (abstract). *Am J Transplant* 2006; **6**(Suppl. 2): 412.
14. Bland JM, Altman DG. Measurement agreement in method comparison studies. *Stat Methods Med Res* 1999; **8**: 135.
15. Bosma RJ, Doorenbos CRC, 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.
16. Poggio ED, Wang X, Weinstein DM, *et al.* Assessing glomerular filtration rate by estimating equations in kidney transplant recipients. *Am J Transplant* 2005; **6**: 100.
17. Raju DL, Grover VK, Shoker A. Limitations of glomerular filtration rate equations in the renal transplant patient. *Clin Transplant* 2005; **19**: 259.

Appendix

Estimated GFRs (eGFR) were calculated using the following equations, and results were then adjusted for BSA for the Cockcroft-Gault and Nankivell formulas (ml/min/1.73 m^2):

- Cockcroft-Gault ($eGFR_{CG}$):

$$eGFR_{CG} = \frac{(140 - \text{age}) \times \text{weight(kg)}}{72 \times \text{SCr(mg/dL)}} \times (0.85 \text{ for females})$$

- Nankivell ($eGFR_{NK}$):

$$eGFR_{NK} = \frac{6.7}{\text{SCr(mmol/L)}} + \frac{\text{weight(kg)}}{4} + \frac{\text{urea(mmol/L)}}{2} - \frac{100}{\text{height(m)}^2} + \begin{pmatrix} 35 & \text{for} & \text{males} \\ 25 & \text{for} & \text{females} \end{pmatrix}$$

- Four-variable MDRD ($eGFR_{MDRD}$):

$$eGFR_{MDRD} = 186 \times \text{SCr(mg/dL)}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for females}) \times (1.212 \text{ for blacks})$$

