ORIGINAL ARTICLE

Is there a relationship between slow coronary flow and normal to mildly impaired renal function?

Yavaş koroner akımla normal-hafif bozulmuş böbrek fonksiyonları arasında bir ilişki var mı?

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ABSTRACT

Objective: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is more effective at estimating glomerular filtration rate (GFR) than the Modification of Diet in Renal Disease (MDRD) equation, particularly in patients with mildly impaired renal function. Recent studies have demonstrated, using the Cockroft-Gault and MDRD formulas, a significant correlation between slow coronary flow (SCF) and normal to mildly impaired renal function. However, these studies had some limitations. The aim of the present study was to investigate the relationship between SCF and normal to mildly impaired renal function using the CKD-EPI equation.

Methods: A total of 370 patients were included, 172 with normal coronary flow (NCF) and 198 with SCF. All participants had normal to mildly impaired renal function. Both the CKD-EPI and MDRD formulas were used to calculated estimated glomerular filtration rate (eGFR), which was compared between groups.

Results: No significant difference in mean values of eGFR was found between the NCF and SCF groups (CKD-EPI: 92.9±14.7 vs 92.7±14.2, p=0.72; MDRD: 89.5±19.5 vs 88.2±17.0, p=0.70, respectively). Among patients with eGFR(MDRD) ≥90 mL/min/1.73 m^2, mean eGFR levels were lower among patients with SCF (107.0±12.7 vs 102.7±10.0, p=0.02).

Conclusion: No correlation was found between SCF and normal to mildly impaired renal function.

ÖZET

Amaç: Hafif bozulmuş böbrek fonksiyonları olan hastalarda glomerül filtrasyon hızını (GFR) tahmin etmede CKD-EPI (The Chronic Kidney Disease Epidemiology Collaboration) formülü MDRD (Modification of Diet in Renal Disease) formülünden daha etkindir. Yeni yayınlar, MDRD ve Cockroft-Gault formüllerini kullanarak yavaş koroner akımla (YKA) normal-hafif bozulmuş böbrek fonksiyonları arasında ilişki olduğunu göstermiştir; ancak bu çalışmaların bazı kısıtlılıkları mevcuttur. Biz, CKD-EPI denklemini kullanarak, YKA ile normal-hafif bozulmuş böbrek fonksiyonları arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışmaya 370 hasta alındı (172 hasta normal koroner akım [NKA], 198 hasta YKA). Böbrek fonksiyonları normal-hafif bozulmuş hastalar seçildi. İki gruptaki tüm hastaların tahmini glomerül filtrasyon hızı (eGFR) CKD-EPI ve MDRD formülleri ile hesaplandı ve sonuçları karşılaştırıldı.

Bulgular: Ortalama değerler bazında NKA ve YKA arasında eGFR açısından yapılan ölçümlerde anlamlı bir fark yoktu (sırasıyla, CKD-EPI: 92.9±14.7 ve 92.7±14.2, p=0.72; MDRD: 89.5±19.5 ve 88.2±17.0, p=0.70). Ölçülen eGFR(MDRD) ≥90 mL/dk/1.73 m^2 alt grup hastalarda ortalama eGFR değerleri açısından YKA olan hastalarda daha az bulundu (107.0±12.7 ve 102.7±10.0, p=0.02).

Sonuç: Yavaş koroner akımla normal-hafif bozulmuş böbrek fonksiyonları arasında bir ilişki bulunmadı.

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Slow coronary flow (SCF) is an angiographic finding characterized by delayed progression of contrast medium through the coronary arteries.[1] While a complete understanding of the pathophysiology and clinical implications of SCF has not been attained, several potential mechanisms have been described. Microvascular disorder due to endothelial dysfunction[2,3] and histopathological abnormalities of coronary microcirculation[4,5] have been identified as underlying mechanisms. The roles of inflammation[6,7] and subclinical atherosclerosis[8,9] have also been described. It has been well established that chronic kidney disease increases risk of cardiovascular disorders. Also well established have been significant correlations between mildly impaired renal function and coronary heart disease prognosis,[10] severity of coronary lesions,[11] and reduced coronary flow reserve in patients who have undergone coronary artery bypass grafting surgery.[12]

Several equations employing creatinine levels have been used to estimate glomerular filtration rate (GFR). The Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) equations have been widely used for this purpose. The Cockroft-Gault equation seems to have been discarded, however, as neither ethnicity nor body surface area is taken into account. The MDRD equation, in which the estimate is adjusted according to body surface area, was developed in 1999. A version revised to include standardized creatinine measurement was published in 2006, gaining worldwide acceptance.

A small number of studies have demonstrated an association between SCF and normal to mildly impaired renal function using the Cockroft-Gault formula and MDRD equation.[13–15] However, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is preferred when reporting estimated glomerular filtration rate (eGFR), particularly in patients with mildly decreased GFR.[16]

The CKD-EPI equation was developed in 2009, in an effort to address underestimation in patients with eGFR ≥60 ml/min/1.73 m^2 using the MDRD equation. According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline, the CKD-EPI equation provides less bias than the MDRD equation, as well as improved risk stratification,[16] and recent studies have confirmed these findings.[17–20]

In the present study, eGFR values in patients with normal coronary flow (NCF) and SCF, who had near-normal or mildly impaired renal function were compared using the CKD-EPI and MDRD equations. The present study was the first to evaluate this relationship with the CKD-EPI equation.

Abbreviations:

CKD-EPI	*Chronic Kidney Disease Epidemiology Collaboration*
CX	*Circumflex artery*
eGFR	*Estimated glomerular filtration rate*
GFR	*Glomerular filtration rate*
KDIGO	*Kidney Disease: Improving Global Outcomes*
LAD	*Left anterior descending artery*
MDRD	*Modification of Diet in Renal Disease*
NCF	*Normal coronary flow*
RCA	*Right coronary artery*
SCF	*Slow coronary flow*

METHODS

Study population

Analyzed in the present study were 7458 digitally recorded angiograms performed between January 2008 and December 2013. A total of 370 patients, 198 with SCF and 172 with NCF, were included. Clinical characteristics and laboratory results were obtained from detailed medical records. eGFR values were measured, and patients who had near-normal or mildly impaired renal function were selected. Values of both groups were between 60 and 120 ml/min/1.73 m^2 using the CKD-EPI equation. Coronary angiographies indicated stable angina pectoris with positive noninvasive test results (high-risk criteria with exercise electrocardiography and ischemia detected in nuclear cardiac imaging) or resistance to optimal medical therapy. Patients with unstable angina (n=18), non-ST elevation myocardial infarction (n=8), severe valvular stenosis or insufficiency (n=14), atrial fibrillation (n=22), uncontrolled hypertension (n=4), systolic or diastolic heart failure (n=26), unsteady states of serum creatinine (acute renal failure, n=2), hepatic dysfunction (n=2), acute or chronic inflammatory disorder (n=6), neuromuscular disorder (n=1), neoplastic disease (n=3), or conditions that affect creatinine levels including paraplegia, amputation, use of creatine supplements, unusual dietary intake such as excess protein or vegetarianism, and use of medications such as aminoglycoside, trimethoprim, or cephalosporin (n=4) were excluded. Patients for whom this information could not be determined were also excluded. The study was approved by the institutional ethics committee. Because angiograms and

data were analyzed retrospectively, informed consent was not obtained.

Coronary angiography

All coronary angiographies were performed using the standard Judkins technique. Diagnosis of SCF was based on angiographically documented TIMI-2 flow, without obstructive coronary artery disease. Iopromide (Ultravist 370 mg I/mL; Schering AG, Berlin, Germany) was used as contrast agent in all angiographic procedures. Coronary flow was quantified objectively using TIMI frame count by 2 expert cardiologists blinded to clinical details of patients. Cineangiography frames were recorded at 30 frames/second. The first frame was defined as the frame in which contrast filled at least 75% of the proximal coronary artery lumen with forward motion. The final frame was defined as the frame in which contrast initially arrived at the distal landmark of the vessel. Distal landmarks were identified using the following criteria. For the left anterior descending artery (LAD), the distal landmark was the point with the most distal branching, called ''pitchfork'' or ''whale's tail.'' TIMI frame count of LAD was divided by 1.7 (the correction factor), as described by Gibson et al.[21] For the circumflex artery (CX), the distal landmark was the most distal branch of the last visible obtuse marginal artery. For the right coronary artery (RCA), it was the first branch of the posterolateral artery. Greater than or equal to 36.2±2.6, 20.4±3, and 22.2±4.1 frames were accepted as slow flow for the LAD, RCA, and left CX, respectively.[21]

Creatinine measurement

Blood samples were collected following an 8-hour fast, in the morning before the angiography (routine protocol). Serum creatinine levels were tested using Roche/Hitachi Modular P800 system (Roche Diagnostics GmbH, Mannheim, Germany), with Isotope Dilution Mass Spectrometry traceable assay, by compensated Jaffe's method, as recommended by the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[16]

GFR estimation

The following CKD-EPI study equation (eGFRCKD-EPI), initially described by Levey AS et al.[22] in 2009, was used:

eGFRCKD-EPI: 141 x min (Scr/k or 1) a x max (Scr/k or 1)-1.209 x 0.993 age x 1.018 (if female) x 1.159 (if black)

Where Scr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.

eGFR was also calculated using the following MDRD study equation (eGFRMDRD), initially described by Levey AS et al.[23] in 1999:

eGFRMDRD: 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if black)

This 4-variable form of the equation was re-expressed in 2006 for use with isotope dilution-mass spectrometry traceable measurement of creatinine.[24]

Patients were categorized as G1: normal or high (GFR ≥90 mL/min/1.73 m^2), G2: mildly decreased (GFR: 60–89 mL/min/1.73 m^2), and G3a: mild to moderately decreased (GFR <60 mL/min/1.73 m^2) according to GFR, as described by the KDIGO guideline in 2012.[16]

Statistical analysis

All statistical analyses were performed with SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±SD, while categorical variables were presented as numbers and percentages. Parametric data (confirmed with Kolmogorov-Smirnov test) were compared with Student's t-test, categorical data with chi-square test. While investigating associations between variables, correlation coefficients and their significance were calculated using Pearson correlation analysis due to their linear relationship. Inter-rater agreement between the 2 cardiologists determining TFC was assessed using kappa statistics, and perfect agreement was achieved (κ=0.843). All p values were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

Mean ages were 53±8 vs 52±9 years, and 42.7% vs 57.3% were male in the NCF and SCF groups, respectively (Table 1). With the exception of smoking, coronary artery disease risk factors were similar between the groups (Table 1). Among laboratory findings, red cell distribution width, mean platelet volume, sedimentation rate, and high-sensitivity C-reactive protein

Table 1. Baseline clinical and laboratory results

Variables	Normal coronary flow (n=172)			Slow coronary flow (n=198)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (yr)			53±8			52±9	0.77
Male	90	52.3		121	61.1		0.09
Hypertension	79	45.9		106	53.5		0.20
Hyperlipidemia	36	20.9		52	26.2		0.27
Diabetes mellitus	38	22		49	24.7		0.62
Smoking	85	49.4		124	62.6		0.01
Hemoglobin (g/dL)			14.0±1.4			13.9±1.7	0.56
Hematocrit (%)			41.9±4.8			41.9±5.4	0.72
Platelet (x10^3/uL)			256.5±17.4			252.7±13.3	0.59
Red cell distribution width			13.1±1.2			14.1±1.2	<0.001
Mean platelet volume (fL)			8.0±1.1			8.3±1.0	0.009
White blood cell (x10^3/uL)			7.5±1.9			7.5±2.1	0.71
Total cholesterol (mg/dL)			185.7±12.9			180.0±11.2	0.30
LDL cholesterol (mg/dL)			110.4±13.4			107.7±13.7	0.47
HDL cholesterol (mg/dL)			44.3±11.2			37.1±11.4	<0.001
Trigliseride (mg/dL)			150.5±16.3			152.3±13.7	0.39
Creatinine (mg/dL)			0.82±0.18			0.85±0.18	0.14
Blood urea nitrogen (mg/dL)			28.4±7.7			28.0±6.4	0.73
Fasting glucose (mg/dL)			108.4±12.1			107.2±12.4	0.45
Systolic blood pressure (mmHg)			126.5±19.6			123.5±19.5	0.15
Diastolic blood pressure (mmHg)			79.2±12.3			78.2±12.2	0.60
Sedimentation rate (mm/h)			8.7±7.5			17.9±11.2	<0.001
hsCRP (mg/L)			1.68±0.38			4.74±1.62	<0.001
Body mass index (kg/m^2)			27.5±3.2			27.4±4.0	0.36
TIMI frame count (LAD)			22.4±5.0			45.1±11.5	<0.001
TIMI frame count (CX)			19.6±4.9			34.7±8.1	<0.001
TIMI frame count (RCA)			13.2±4.0			27.6±7.0	<0.001
Medications							
ACEI	25	14		32	16		0.77
ARB	21	12		27	13		0.75
Diuretic	9	0.5		13	0.6		0.66
CCB	12	0.6		16	0.8		0.84
Beta blocker	12	0.6		18	0.9		0.57
Statin	21	12		30	14		0.37

SD: Standard deviation; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; hsCRP: High-sensitivity C-reactive protein; TIMI: Thrombolysis in myocardial infarction; LAD: Left anterior descending artery; CX: Circumflex artery; RCA: Right coronary artery; ACE-I: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor blocker; CCB: Calcium-channel blocker.

levels were higher, and high-density lipoprotein was lower in the SCF group (Table 1). No significant difference in levels of eGFR(CKD-EPI) (92.9±14.7 vs 92.7±14.2, p=0.72) and eGFR(MDRD) (89.5±19.5 vs

Table 2. eGFR with CKD-EPI and MDRD of patients with normal or slow coronary flow

eGFR	Normal coronary flow (n=172)	Slow coronary flow (n=198)	*p*
	Mean±SD	Mean±SD	
$eGFR_{(CKD-EPI)}$ ≥60 mL/min/1.73 m^2	92.9±14.7	92.7±14.2	0.72
$eGFR_{(MDRD)}$ ≥60 mL/min/1.73 m^2	89.5±19.5	88.2±17.0	0.70

eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; SD: Standard deviation.

Table 3. eGFR subgroups with CKD-EPI and MDRD of patients with normal or slow coronary flow

eGFR	Normal coronary flow (n=172)	Slow coronary flow (n=198)	*p*
	Mean±SD	Mean±SD	
$eGFR_{(CKD-EPI)}$ 60–89 mL/min/1.73 m^2	76.0±8.3 (63)	77.6±8.8 (77)	0.18
$eGFR_{(CKD-EPI)}$ ≥90 mL/min/1.73 m^2	102.6±6.4 (109)	102.3±6.6 (121)	0.53
$eGFR_{(MDRD)}$ 60–89 mL/min/1.73 m^2	75.0±9.9 (94)	74.3±8.7 (101)	0.55
$eGFR_{(MDRD)}$ ≥90 mL/min/1.73 m^2	107.0±12.7 (78)	102.7±10.0 (97)	0.02

eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; SD: Standard deviation.

88.2±17.0, p=0.70) was found between the NCF and SCF groups, respectively (Table 2, Figure 1). Patients were categorized according to GFR values as either 60–89 or ≥90 mL/min/1.73 m^2. Fifteen of 140 patients (10.7%) were reclassified from G2 to G3a, and 56 of 230 patients (24.3%) were reclassified from G1 to G2 when eGFR was calculated using the MDRD equation. Measurements of 60–89 and 90–120 intervals using CKD-EPI corresponded to 51–83 and 81–140 intervals using MDRD, respectively. eGFR values of

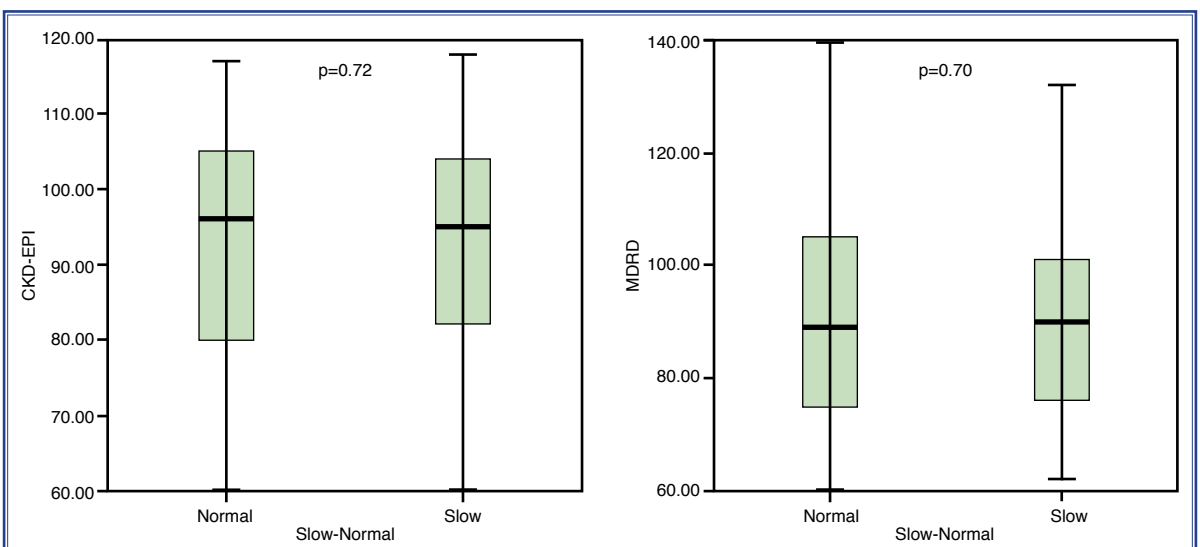

Figure 1. Estimated glomerular filtration rate of patients with normal and slow coronary flow, obtained using CKD-EPI and MDRD.

patients with eGFR (CKD-EPI): 60–89 mL/min/1.73 m^2, eGFR (CKD-EPI) ≥90 mL/min/1.73 m^2, and eGFR (MDRD): 60–89 mL/min/1.73 m^2 were not significantly different between the groups. Two reclassified eGFR ranges using MDRD were also analyzed: 51–83 and 81–140 showed no difference between the 2 groups (data not shown). Values of eGFR (MDRD) ≥90 mL/min/1.73 m^2 (eGFR [MDRD ≥90]) were found to be lower in the SCF group (Table 3). Finally, Pearson correlation analysis was used to determine possible correlations between all eGRF categories calculated by CKD-EPI or MDRD equations and TFC of the LAD, CX, and RCA individually. Significant but weak negative correlations were found between eGFR (MDRD ≥90) and TFC of CX (correlation coefficient: -0.212, p=0.005) and the RCA (correlation coefficient: -0.224, p=0.003), even after adjusting independent predictors of SCF, diabetes, and systolic and diastolic blood pressure. No correlation with TFC of the LAD (correlation coefficient: -0.084, p=0.27) was found.

DISCUSSION

Despite growing evidence of the association between impaired renal function and coronary heart disease, data has been limited regarding possible interactions of normal to mildly impaired renal function, particularly in patients with SCF. The relationship between SCF and renal dysfunction has been investigated in few clinical trials. Koc et al.[15] calculated GFR using the Cockroft-Gault formula and also a corrected GFR by adjusting for body surface area, determining a significant association between SCF and decreased GFR. However, this formula is being abandoned in clinical practice. Akin et al.[14] investigated this association in patients with normal and mildly decreased renal function using the MDRD equation and determined a significant relationship. However, the assay used for creatinine measurement was not described, and the exclusion criteria did not include certain conditions that effect serum creatinine level such as acute renal failure, neuromuscular and neoplastic diseases, and dietary habits including vegetarianism. In another study,[13] a significant negative correlation between TFC and GFR was demonstrated, though patients were not categorized according to GFR values, and eGFR levels were between 53 and 83 mL/min/1.73 m^2. It was asserted in these trials that endothelial dysfunction and inflammation were associated with worsened renal function (Table 4). However, Arı et al.[25] demonstrated that endothelial dysfunction, but not inflammation, was associated with SCF.

The CKD-EPI equation was confirmed to have less bias than the MDRD equation, with more precise GFR estimations, particularly above 60 mL/min/1.73m2. In addition, it was determined that this equation overcame the limitation of the MDRD equation (i.e., the underestimation of GFR at given range).[17–20] Stevens LA et al.[20] showed that bias was substantially decreased with the CKD-EPI equation, compared to measured GFR, particularly among people with eGFR greater than 60 ml/min/1.73 m^2. The study also found that bias was increased using the MDRD equation, when eGFR was greater than 90 ml/min/1.73 m^2. In another study, the reclassification of patients to a better GFR category using the CKD-EPI equation, compared with the MDRD equation, was related to reduction in all-cause mortality.[19] This type of reclassification was also observed in the present study.

In view of published data, the CKD-EPI equation was used in the present study to calculate eGFR, and

Table 4. Studies in which a relationship between slow coronary flow and mildly impaired renal function was found, and their limitations

Study	eGFR Method	Critique
Akin et al. (2014)	MDRD	Creatinine measurement method was not clear and exclusion criterias were not well defined.
Koc et al. (2011)	Cockroft-Gault	Cockroft-Gault is abandoned and has lots of limitations.
Yilmaz et al. (2009)	MDRD	Patients were not categorized according to GFR values and the distribution of them were between 53 to 83 mL/min/m^2 wihich did not meet a specific CKD stage.

eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease.

results calculated with MDRD were also included in analysis. No association between SCF and normal to mildly impaired renal function was found using the CKD-EPI equation. In the eGFR (MDRD ≥90) subgroup, eGFR values were lower in patients with SCF. This may be a type-1 error (false positive) and may be related to sample size. In addition, a negative correlation was determined between values of eGFR (MDRD ≥90) and TFC of the CX and RCA, but not with the LAD. The latter finding may be due to more similar values of TFC for the LAD in both the NCF and SCF groups at the given range. Independent predictors of SCF (smoking, high-density lipoprotein cholesterol, mean platelet volume, red cell distribution width, high-sensitivity C-reactive protein, and sedimentation rate) in the present study were compatible with the literature. These can be attributed to the role of inflammation[6,7] and subclinical atherosclerosis,[8,9] which have been described as pathophysiological mechanisms of SCF.

Ohsawa et al.[18] showed that all-cause mortality and cardiovascular morbidity rates were higher in subjects with normal eGFR (≥90 mL/min/1.73 m^2) compared to subjects with mildly decreased eGFR (60–89 mL/min/1.73 m^2). Although a linear relationship between cardiovascular events and decreased GFR is usually found, a U-shaped relationship between mortality and stage of chronic kidney disease has been demonstrated in recent reports.[26] This phenomenon may explain the lack of association between patients who had eGFR (MDRD) 60–89 mL/min/1.73 m^2 and SCF. However, further prospective studies are warranted.

The present study was affected by some limitations. Data regarding albuminuria and other markers of kidney damage were lacking. In addition, eGFR was assessed using serum creatinine. Other methods that provide more accurate estimates of measured GFR, such as serum cystatin C, were not used. Finally, due to retrospective design, a reference method could not be used to compare results in order to measure GFR (such as creatinine clearance with 99mTc-DTPA).

Conclusion

In conclusion, no relationship between SCF and normal to mildly impaired renal function was found using the CKD-EPI equation, a new and improved method of calculating eGFR in this population.

Conflict-of-interest issues regarding the authorship or article: None declared

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