Renal Insufficiency and Mortality in Patients with Known or Suspected Coronary Artery Disease

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ABSTRACT

It remains unclear whether mild renal dysfunction is associated with adverse cardiovascular outcome. We investigated whether estimated glomerular filtration rate (eGFR) was associated with mortality and cardiac death among 6447 patients with known or suspected coronary artery disease over a mean follow-up of 7 yr. Cumulative 5- and 10-yr survival rates decreased in a graded fashion from 88% and 70%, respectively, for those with normal renal function to 43% and 33% for those with eGFR <30 ml/min. Compared with patients with normal renal function, the multivariable adjusted hazard ratios for all-cause mortality among patients with mild, moderate, and severe renal impairment were 1.33 (95% confidence interval [CI], 1.21–1.48), 1.67 (95% CI, 1.44–1.93), and 3.38 (95% CI, 2.73–4.19), respectively. Similar relationships between cardiac death and decreasing renal function were found. In conclusion, renal function is a graded and independent predictor of long-term mortality in patients with known or suspected coronary artery disease. Intense treatment and close surveillance of these patients is encouraged.

Chronic renal dysfunction has been shown to be an independent risk factor for cardiovascular mortality and morbidity in patients with coronary artery disease (CAD).[1–7] Population-based studies have shown discordant results regarding the association of mild renal dysfunction,[8–10] cardiovascular disease events, and all-cause mortality. Serum creatinine >1.5 mg/dl (133 μmol/L) was associated with a 70% increase in risk for all-cause mortality in participants who were followed for 5 yr in the Cardiovascular Health Study[11]; however, the Framingham Study did not show an association between baseline renal function and incident cardiovascular disease events.[12] Furthermore, the results of the National Health and Nutrition Examination Survey (NHANES) study did not support moderate renal insufficiency as an independent risk factor for cardiovascular disease in the general population.[13] It remains unclear whether mild renal dys-

function is related to adverse cardiovascular outcomes; therefore, the purpose of this study was to determine the association between mild renal dysfunction and mortality during long-term follow-up.

RESULTS

Mean age was 63 yr, and 26% were women (Table 1). Renal function was normal (GFR >90 ml/

Table 1. Clinical characteristics stratified by the creatinine clearance (GFR)[a]

Variable	Total (n = 6447)	GFR				P for Trend
		Normal (>90 ml/min; n = 3587; 56%)	Mild (60 to 90 ml/min; n = 1895; 29%)	Moderate (30 to 60 ml/min; n = 720; 11%)	Severe (<30 ml/min; n = 245; 4%)	
Age (mean ± SD)	61 ± 11	60 ± 18	64 ± 10	61 ± 12	58 ± 13	<0.0001
Male (%)	67	66	75	69	73	0.1
History (%)						
MI	33	35	30	22	22	<0.0001
CABG	13	17	19	13	9	<0.0001
PCI	17	18	17	11	10	0.4
heart failure	15	13	16	26	31	<0.001
angina	24	27	23	13	7	0.2
Risk factors (%)						
diabetes	15	14	15	19	23	<0.005
hypertension	45	39	55	64	72	<0.0001
dyslipidemia	36	35	37	45	44	<0.001
smoking	28	30	25	21	23	<0.0001
Cardiac medication (%)						
β blockers	42	36	46	60	63	<0.0001
nitrates	17	16	19	23	28	<0.0001
calcium antagonists	30	30	29	27	34	0.3
diuretics	11	9	15	15	11	<0.0001
ACEI	13	10	21	18	22	<0.0001
digitalis	3	3	3	4	4	0.5
Serum creatinine (μmol/L; mean ± SD)	105 ± 16	71 ± 14	101 ± 14	152 ± 30	346 ± 81	<0.0001
GFR (ml/min; mean ± SD)	89 ± 16	122 ± 21	75 ± 8	47 ± 8	15 ± 8	<0.0001

[a]CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

min) in 3587 (56%) patients, whereas 720 (11%) had moderate impairment (GFR 30 to 60 ml/min) and 245 (4%) patients had severe impairment (GFR <30 ml/min). A mild degree of renal dysfunction (GFR 60 to 90 ml/min) was present in 1895 (29%) patients. The mean follow-up time was 7 yr (range 6 mo to 12 yr). During follow-up, 37,392 patient-years were collected. Death occurred in 2007 (31%)

patients, 54% of which were cardiac. The GFR (mean ± SD 83.1 ± 16) ranged from 3.8 to 265.3 ml/min per 1.73 m^2.

After adjustment for all baseline clinical and demographic characteristics, the risk for all-cause mortality and cardiac death was significantly increased in all three groups of renal impairment compared with the group with normal renal function (Table 2). Patients with mild impaired renal

Table 2. HR for the incidence of all-cause mortality, cardiac death, and hard cardiac events (cardiac death or nonfatal MI) associated with renal function estimated by levels of the creatinine clearance (GFR).

Parameter	Events (%)	HR (95% CI)	
		Unadjusted	Adjusted[a]
All-cause mortality			
normal renal function	25	1.0	1.0
mild impaired renal function	36	1.49(1.35to1.65)	1.33(1.21to1.48)
moderate impaired renal function	45	2.07(1.80to2.37)	1.67(1.44to1.93)
severe impaired renal function	47	4.00(3.26to4.93)	3.38(2.73to4.19)
Cardiac death			
normal impaired renal function	13	1.0	1.0
mild impaired renal function	18	1.39(1.20to1.61)	1.46(1.25to1.71)
moderate impaired renal function	26	2.31(1.93to2.78)	2.31(1.90to2.81)
severe impaired renal function	40	6.28(5.00to7.89)	5.57(4.38to7.08)

[a]Adjusted for age, gender, previous MI, previous CABG, previous PCI, history of heart failure, history of typical angina, diabetes, hypertension, dyslipidemia, and current smoking.

function had 33% increased risk for mortality (hazard ratio [HR] 1.33; 95% confidence interval [CI] 1.21 to 1.48) as compared with patients with normal renal function. The risk for mortality was increased 1.5-fold with moderate renal insufficiency (HR 1.67; 95% CI 1.44 to 1.93) and threefold with severe renal impairment (HR 3.38; 95% CI 2.73 to 4.19). Although renal function is related to age, no significant interaction was found. Similar strong relations with cardiac death with decreasing renal function were found. The adjusted HR for GFR as a continuous variable for all-cause mortality or cardiac death were 0.82 (95% CI 0.80 to 0.84) and 0.85 (95% CI 0.82 to 0.88), respectively.

Age-adjusted cumulative Kaplan-Meier survival curves for all-cause mortality according to renal function were 88, 83, 68, and 43% for normal, mild, moderate, and severe, respectively, at 5 yr and 70, 58, 51, and 33%, respectively, at 10 yr ($P < 0.0001$; Figure 1). Similar relations with cardiac death with decreasing renal function were found.

DISCUSSION

The main finding of this study is that mild renal dysfunction defined as a GFR of 60 to 90 ml/min is a graded and independent predictor of long-term outcome of mortality and hard cardiac events. Mild or moderate impairment of renal function has also been shown to be associated with worse prognosis in patients with congestive heart failure,[14] those with myocardial infarction (MI),[15] and those in a normal population[16]; however, why even a mild renal dysfunction is related with worse prognosis is not known. One possibility might be that renal dysfunction may be a pathogenetic factor in causing the progression of cardiac deterioration. Furthermore, cardiac pump failure may lead to diminished renal function, and thus early renal dysfunction may be a marker of increased cardiac function; however, we still observed an independent association between renal function and all-cause mortality and cardiac death after adjusting for cardiovascular risk factors. Therefore, renal impairment itself might initiate and accelerate adverse cardiac events.

Usually, kidney disease is defined as GFR <60 ml/min per 1.73 m², a cutoff value recently proposed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Advisory Board to identify patients who have moderate renal impairment[17] and American Heart Association's Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention.[5]The results of this study show an increased risk for mortality and hard cardiac events, starting at earlier stages of renal dysfunction than commonly thought. This mildly decreased renal dysfunction, one quarter of this study, represent patients without symptoms and signs of renal dysfunction. As patients get older, mild degrees of renal insufficiency will become progressively more important because renal function declines with elderly age; therefore, early recognition of renal dysfunction may be a key target to prevent worsening renal function.

Treatment of patients with impaired renal function and CAD is problematic. Evidence of medical therapy both in trials and in clinical practice is limited and frequently sub-
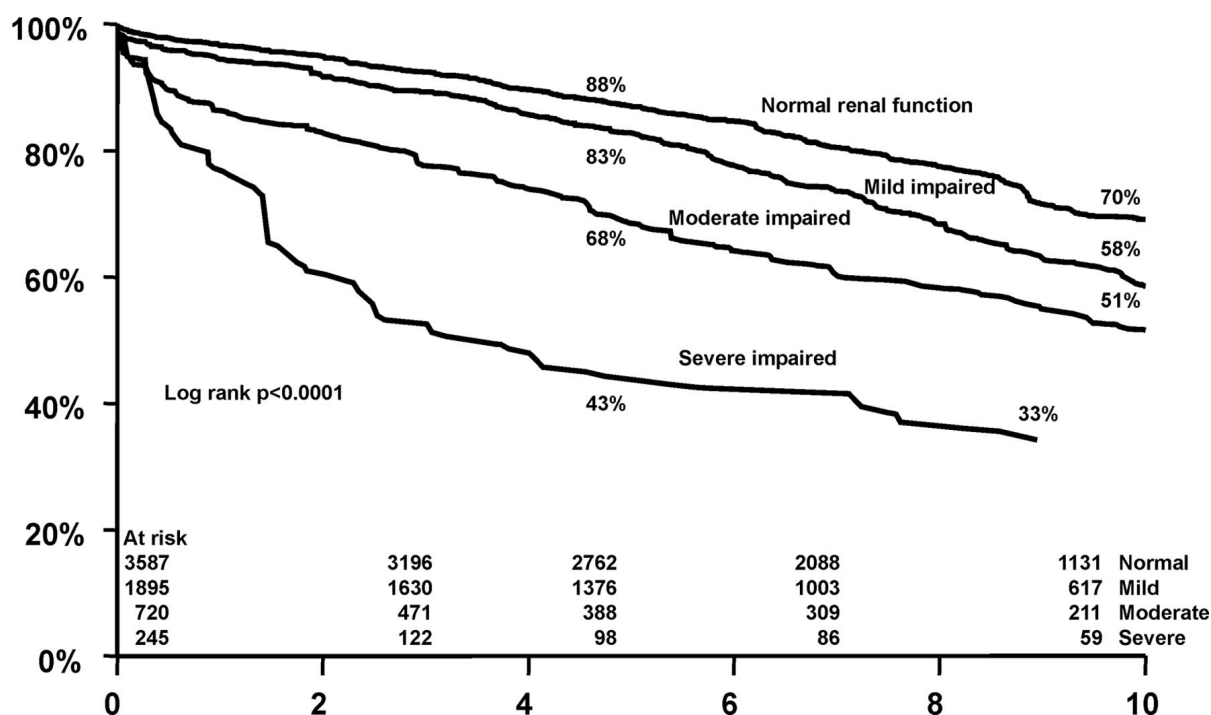

Figure 1. Age-adjusted all-cause mortality in 6447 patients with known or suspected CAD according to the GFR.

optimal. Acetylsalicylic acid (ASA)[18] and β blockers[19] were shown to reduce mortality among patients with CAD and may also reduce mortality and morbidity in asymptomatic patients who are at increased risk for CAD. Also evidence continues to accrue that angiotensin-converting enzyme inhibitors ACEI reduce vascular morbidity and mortality.[20–22] Furthermore, a systematic review demonstrated in patients who had renal insufficiency and were treated with ACEI a strong association between creatinine levels and slowing of the renal disease progression in the long term.[8] The authors concluded that ACEI therapy should be offered to all patients with left ventricular systolic dysfunction and renal insufficiency, and also the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommends use of ACEI for control of hypertension in patients with renal insufficiency.[9] The use of statins has also been shown to reduce mortality. Although there might be a slight increase of myositis, statins are generally considered safe for use in patients with renal insufficiency[9]; however, these therapies are still underused among patients with renal impairment. Although there may be exceptions, therapies that have been beneficial at normal levels of kidney function are increasingly being shown also to be beneficial at lower levels of kidney function[23]; therefore, intensive medical treatment, especially in patients with only mild renal dysfunction and without any signs of renal disease, including β blockers, ACEI, and statins, should be considered.

Although data were prospectively collected, this analysis is retrospective. Only patients for whom a single baseline creatinine value was available were included in this study, which may have introduced a selection bias in the analysis. Thus, this study cohort was per definition a preselected one, already having a higher risk for death earlier than an average population. This includes the renal reference group; therefore, all conclusions regarding the outcome of the four GFR groups must take this into account. Another limitation is the lack of data on albuminuria, which may contribute to the cardiovascular effects of renal dysfunction.[24]

This study shows that renal function is a graded and independent predictor of long-term adverse cardiac outcome. In particularly, even mild renal dysfunction is an important predictor of all-cause mortality and cardiac death. Intense treatment and close surveillance of these patients is warranted.

CONCISE METHODS

Study Design and Patient Selection
We studied a cohort of 6447 patients who had known or suspected CAD, had had baseline serum creatinine determined, and were referred to the outpatient clinics of the Erasmus University Medical Center between January 1993 and January 2005. Patients who were included in our analysis were intermediate- to high-risk patients who had atherosclerotic disease and were referred for cardiac evaluation, management of underlying risk factors, or follow-up of their known ischemic heart condition.

Patients who presented at the time of examination with a history of angina, previous MI, or myocardial revascularization (*i.e.*, previous percutaneous coronary intervention and/or coronary artery bypass graft) were considered as CAD patients. Patients with atypical chest pain, dyspnea, atypical electrocardiogram abnormalities (ST-T changes without Q-waves), or multiple risk factors for coronary disease were considered to have suspected CAD. Patients who were on hemodialysis therapy or had undergone a renal transplant were excluded. The study protocol was approved by the local medical ethics committee and was conducted in accordance with the Declaration of Helsinki.

Renal Function Assessment
Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method.[25] GFR was estimated by using the Modification of Diet in Renal Disease (MDRD) equation[26]: GFR (ml/min per 1.73 m² body surface area) = $175 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female).

Clinical Follow-up and End Points
In-hospital clinical information for patients was retrieved from an electronic database that is maintained in our hospital and by review of hospital records. Survival status was obtained from the municipal civil registries. Follow-up was performed by mailed questionnaires and telephone interviews. Patients who were lost to follow-up were considered at risk until the date of last contact, at which point they were censored. When needed, referring physicians and institutions were contacted for additional information. Events and cause of death were verified by contacting the patient's primary physician and reviewing medical records. The follow-up was complete in 98.3%. The end points considered were all-cause mortality and cardiac death. Death was considered cardiac when it was caused by acute MI, significant arrhythmias, or refractory heart failure. Sudden unexpected death occurring without another explanation was included as cardiac death.

Statistical Analyses
Continuous variables are presented as the mean ± SD or as a percentage. Patients were subsequently categorized as having normal renal function (GFR >90 ml/min), mild renal impairment (GFR 60 to 90 ml/min), moderate impairment (GFR 30 to 60 ml/min), and severe impairment (GFR <30 ml/min).[5] Tests of trend were performed using the four GFR groups as a categorical measurement. Continuous variables are presented as the mean ± SD or as a percentage. Cox proportional hazard regression analysis was used to investigate the independent effect of renal function on the outcome events. Analyses were conducted for crude values and adjusted for age; gender; previous MI; previous percutaneous coronary intervention; previous coronary artery bypass graft surgery; history of typical of angina; history of heart failure (defined according the New York Heart Association classification); diabetes (defined as the presence of a fasting blood glucose ≥126 mg/dl or

requirement for insulin or oral hypoglycemic agents); hypercholesterolemia (defined as total cholesterol of >200 mg/dl); hypertension (defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication); smoking; and the use of statins, β blockers, nitrates, calcium antagonists, ACEI, digitalis, and diuretics. The association between GFR and outcome events was also assessed with GFR as a continuous variable. To investigate the relation between GFR and age, we performed a test for interaction in the Cox regression. Using Cox regression, age-adjusted Kaplan-Meier survival curves of the four GFR groups in relation to all-cause mortality were constructed and examined using the log-rank test.

DISCLOSURES

None.

REFERENCES

1. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629–636, 2001

2. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 351: 1285–1295, 2004

3. Al Suwaidi J, Reddan DN, Williams K, Pieper KS, Harrington RA, Califf RM, Granger CB, Ohman EM, Holmes DR Jr; GUSTO-IIb, GUSTO-III, PURSUIT. Global Use of Strategies to Open Occluded Coronary Arteries. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; PARAGON-A Investigators: Platelet IIb/IIIa antagonism for the reduction of acute coronary syndrome events in a Global Organization Network: Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 106: 974–980, 2002

4. Gibson CM, Pinto DS, Murphy SA, Morrow DA, Hobbach HP, Wiviott SD, Giugliano RP, Cannon CP, Antman EM, Braunwald E, TIMI Study Group: Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol* 42: 1535–1543, 2003

5. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108: 2154–2169, 2003

6. Szczech LA, Best PJ, Crowley E, Brooks MM, Berger PB, Bittner V, Gersh BJ, Jones R, Califf RM, Ting HH, Whitlow PJ, Detre KM, Holmes D, Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation. *Circulation* 105: 2253–2258, 2002

7. Blackman DJ, Pinto R, Ross JR, Seidelin PH, Ing D, Jackevicius C, Mackie K, Chan C, Dzavik V: Impact of renal insufficiency on outcome after contemporary percutaneous coronary intervention. *Am Heart J* 151: 146–152, 2006

8. Bakris GL, Weir MR: Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? *Arch Intern Med* 160: 685–693, 2000

9. The sixth report of Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 157: 2413–2446, 1997

10. Kasiske BL: Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis* 32: S142–S156, 1998

11. Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins JA, Gardin JM: Risk actors for 5-year mortality in older adults: The Cardiovascular Health Study. *JAMA* 279: 585–592, 1998

12. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56: 2214–2219, 1999

13. Garg AX, Clark WF, Haynes RB, House AA: Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 61: 1486–1494, 2002

14. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW: The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 35: 681–689, 2000

15. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM, Valsartan in Acute Myocardial Infarction Trial Investigators: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 349: 1893–1906, 2003

16. Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC: Renal function and risk of myocardial infarction in an elderly population: The Rotterdam Study. *Arch Intern Med* 165: 2659–2665, 2005

17. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G, National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 139: 137–147, 2003

18. Collaborative overview of randomised trials of antiplatelet therapy: I—Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 308: 81–106, 1994 [published erratum appears in *BMJ* 308: 1540, 1994]

19. Jonas M, Reicher-Reiss H, Boyko V, Shotan A, Mandelzweig L, Goldbourt U, Behar S: Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease: Bezafibrate Infarction Prevention (BIP) Study Group. *Am J Cardiol* 77: 1273–1277, 1996

20. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342: 145–153, 2000

21. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001

22. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW: Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 354: 131–140, 2006

23. Coresh J, Astor B, Sarnak MJ: Evidence for increased cardiovascular disease risk in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens* 13: 73–81, 2004

24. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S, HOPE

Study Investigators: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421–426, 2001

25. Perrone RD, Madias NE, Levey AS: Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem* 38: 1933–1953, 1992

26. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology Collaboration: Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 145: 247–254, 2006