A Novel Model of Cardiovascular Risk Based on Kidney Function

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Key Words

Cardiovascular events • Estimated glomerular filtration rate • Sensitivity • Specificity • Risk triage

Abstract

Background/Aims: Although creatinine-based estimated glomerular filtration rate (eGFR) is associated with cardiovascular events, threshold values for optimum discrimination are unclear. We aimed to identify serum creatinine and eGFR thresholds of maximum sensitivity and specificity (Max_{Sn+Sp}) for a composite outcome of coronary heart disease, stroke, and death. **Methods:** Classification tree methodology defined the hierarchical rank of serum creatinine, eGFR, and cardiovascular risk factors in adults aged 45–64 years (Atherosclerosis Risk in Communities Study, $n = 15,582$; follow-up, 13.1 years). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) Study, and Cockcroft-Gault corrected for body surface area (CG/BSA) eGFR equations were used. **Results:** The mean study population age was 54.2 years; 26.4% were African-American. The mean standardized creatinine level was 0.83 mg/dl. The mean $eGFR_{CKD-EPI}$, $eGFR_{MDRD}$, and $eGFR_{CG/BSA}$ values were 95.7, 98.6, and 99.7 ml/min/1.73 m², respectively. The composite outcome occurred for 22.1% of the population. For all eGFR measures, sensitivity was <0.05 and specificity >0.98 for thresholds of 60 ml/min/1.73 m². Max_{Sn+Sp} for serum creatinine occurred at 0.73 mg/dl (sensitivity 0.66/specificity 0.48); corresponding values for $eGFR_{CKD-EPI}$, $eGFR_{CG/BSA}$, and $eGFR_{MDRD}$ were 95 (0.52/0.59),

90 (0.44/0.67), and 75 (0.16/0.91) ml/min/1.73 m², respectively. Considering optimum thresholds for 10 modifiable risk factors, high-density lipoprotein cholesterol ≤ 44 mg/dl ranked first; rankings for optimum renal function thresholds varied between sixth and tenth. **Conclusions:** Optimum eGFR thresholds for community-based risk triage were substantially higher than 60 ml/min/1.73 m², which currently defines moderate abnormality. Utility of creatinine-based risk triage in older adults appears modest.

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Introduction

As chronic kidney disease is widespread, usually silent, and associated with cardiovascular disease, it appears rational to question whether screening for renal dysfunction in community-dwelling adults would be useful, mirroring efforts regarding more familiar risk factors like lipids, blood pressure, body mass index, and blood glucose [1–3]. Before advocating screening with renal function measures for cardiovascular prevention, it would be useful to examine how different threshold levels predict the occurrence of future episodes of cardiovascular disease. Considered within finite intervals of follow-up, thresholds at which ‘normal’ values are associated with low cardiovascular event rates (high specificity) and ‘abnormal’ values with high rates (high sensitivity) might be useful from a public health perspective, especially with regard to intensity of follow-up and treatment of modifiable risk factors.

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Regarding kidney function and cardiovascular events in the general population, much is unknown. For example, recognizing that gains in sensitivity are necessarily accompanied by losses in specificity, what threshold levels of serum creatinine and serum creatinine-based estimated glomerular filtration rate (eGFR) optimally separate people destined to develop cardiovascular events from those who are not? Which optimum kidney function threshold provides the greatest degree of discrimination? Are optimum threshold values the same in major demographic segments of the community? As declining kidney function tends to co-segregate with other classic cardiovascular risk factors, is it more efficient to screen for factors like lipid levels, body mass index, blood pressure, and blood glucose? In this long-term, community-based study, a receiver operating characteristic approach [4] was used to identify thresholds with maximum sensitivity and specificity values, and classification tree methodology was used to assess the performance of serum creatinine, eGFR, and classic cardiovascular risk factors as discriminators of cardiovascular events and death.

Methods

Objectives

Regarding serum creatinine levels and eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [5], Modification of Diet in Renal Disease (MDRD) Study [6], and Cockcroft-Gault corrected for body surface area (CG/BSA) [7] equations in community-dwelling adults aged 45 to 64 years, the objectives of this study were as follows:

- (1) To identify and compare threshold values of maximum combined sensitivity and specificity ($\text{Max}_{\text{Sn+Sp}}$) for predicting the composite outcome of coronary heart disease, stroke, or death;
- (2) To perform analyses similar to those described in objective 1 for each of the separate components of the composite event;
- (3) Based on $\text{Max}_{\text{Sn+Sp}}$ for the composite event, to use classification tree analysis to consider renal function thresholds in a framework that also considered classic cardiovascular risk factors, especially those recommended for screening in community-dwelling adults.

Subjects and Measurements

Detailed study information can be found at the Atherosclerosis Risk in Communities (ARIC) Study website [8]. ARIC is a prospective, longitudinal, community-based study of cardiovascular disease in four US communities [9]. Probability-based sampling methods were used in three of these communities (Forsyth County, N.C.; Washington County, Md.; Minneapolis, Minn.); in the fourth (Jackson, Miss.), driver's license and state identification card lists were used to select a representative group of African-American residents. Baseline examinations were performed between 1987 and 1989 and repeated at 3-year intervals.

The population for this study consisted of participants with measured serum creatinine levels, 15,582 of the original 15,732 participants (99.0%). Serum creatinine levels, measured with the modified kinetic Jaffe-picric acid method from frozen serum samples at the ARIC central laboratory (University of Minnesota), were corrected for interlaboratory difference by subtraction of 0.24 mg/dl and standardized to the isotope dilution-mass spectrometry-traceable Roche enzymatic method by multiplication by 0.95 [10–12]. Body surface area was calculated from the formula of du Bois and du Bois [13]. Estimated $\text{GFR}_{\text{CKD-EPI}}$ (ml/min/1.73 m²) was calculated from standardized serum creatinine (Scr, mg/dl) as follows [5]:

Women:

$\text{Scr} \leq 0.7$: $\text{GFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{age}} \times 1.15$ (if African-American)

$\text{Scr} > 0.7$: $\text{GFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{age}} \times 1.15$ (if African-American)

Men:

$\text{Scr} \leq 0.9$: $\text{GFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{age}} \times 1.16$ (if African-American)

$\text{Scr} > 0.9$: $\text{GFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{age}} \times 1.16$ (if African-American)

$\text{eGFR}_{\text{MDRD}}$ (ml/min/1.73 m²) was calculated as $175 \times (\text{Scr})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times 1.212$ (if African-American) [6]; $\text{eGFR}_{\text{CG/BSA}}$ was calculated from serum creatinine, age (years), sex, weight (kg), and body-surface area (m²) as $(1.73/\text{BSA}) \times [(140 - \text{age}) \times \text{weight}]/(72 \times \text{Scr}) \times 0.85$ (if female) [7]. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current antihypertensive medication. Diabetes was defined by self-report, medication use, fasting blood glucose ≥ 126 mg/dl, or any blood glucose level ≥ 200 mg/dl. Baseline coronary heart disease was defined as physician-diagnosed history of heart attack, prior myocardial infarction by electrocardiogram, prior cardiovascular surgery, or coronary angioplasty.

Analysis

Median follow-up was 13.1 years. Cardiovascular event ascertainment methodology and validation findings have been published previously [14]. Coronary heart disease events were defined as probable myocardial infarction, definite myocardial infarction, silent myocardial infarction discovered by electrocardiography between examinations, death from definite coronary heart disease, or coronary revascularization. Hemorrhagic or thrombotic strokes were defined as probable or definite events. For this study, the main study outcome was a composite event defined by the earliest occurrence of coronary heart disease, stroke, or death.

Regarding the clinical outcomes, to identify $\text{Max}_{\text{Sn+Sp}}$ levels for Scr and eGFR at different thresholds (X), sensitivity (creatinine $> X$, $\text{eGFR} \leq X$ among subjects with the event) and specificity (creatinine $\leq X$, $\text{eGFR} > X$ among subjects without the event) were computed separately for thresholds that varied in 0.01 mg/l increments, between 0.5 and 2.0, for serum creatinine and in 1 ml/min/1.73 m² increments, between 50 and 120, for eGFR; only $\text{Max}_{\text{Sn+Sp}}$ levels with $p < 0.05$ with logistic regression were considered valid.

Several subgroup analyses and sensitivity analyses were performed. As the discriminatory power of renal parameters might reflect associations with demographic or classic cardiovascular

Table 1. Baseline characteristics of the study population at study inception (n = 15,582)

Serum creatinine, mg/dl	0.83 ± 0.40 (0.15–16.97)
eGFR _{CKD-EPI} , ml/min/1.73 m ²	95.7 ± 15.5 (2.5–181.3)
eGFR _{MDRD} , ml/min/1.73 m ²	98.6 ± 22.7 (2.9–641.8)
eGFR _{CG/BSA} , ml/min/1.73 m ²	99.7 ± 22.9 (4.8–418.6)
Age, years	54.2 ± 5.7 (45.0–64.0)
Female sex, %	55.1
Race, %	
White	73.6
African-American	26.4
<12 years of school, %	23.8
Pack-years of smoking	16.1 ± 21.8 (0.0–242.6)
Current cigarette smoker, %	26.2
Ethanol intake, g/week	42.5 ± 96.2 (0.0–1,856.0)
Hypertension, %	34.8
Antihypertensive medication, %	30.5
Diabetes, %	11.8
Coronary heart disease, %	5.0
Body mass index	27.7 ± 5.4 (14.2–65.9)
Body surface area, m ²	1.88 ± 0.21 (1.33–2.62)
LDL cholesterol, mg/dl	137.7 ± 39.4 (0.0–504.6)
HDL cholesterol, mg/dl	51.6 ± 17.1 (9.6–163.0)
Triglycerides, mg/dl	131.9 ± 90.5 (24.0–1,928.0)
Glucose, mg/dl	109.0 ± 40.6 (35.0–628.0)
Systolic blood pressure, mm Hg	121.3 ± 18.9 (61.0–246.0)
Diastolic blood pressure, mm Hg	73.7 ± 11.3 (0.0–144.00)

Data are expressed as mean ± standard deviation (range) or column percentages.

Missing data (n): eGFR_{CG/BSA}, 13; years of school, 26; pack-years of smoking, 276; current cigarette smoking status, 15; ethanol intake, 89; hypertension, 74; antihypertensive medication use, 8; diabetes, 29; coronary heart disease, 322; body mass index, 13; body surface area, 13; LDL cholesterol, 335; HDL cholesterol, 109; triglycerides, 108; systolic blood pressure, 7; diastolic blood pressure, 7.

risk factors, we constructed a classification tree for the composite outcome based on the highest $\text{Max}_{\text{Sn+Sp}}$ value when all variables were considered simultaneously, with the additional proviso of $p < 0.05$, for association with the composite outcome, using logistic regression. Renal variables were handled as detailed in the preceding paragraph; for other continuous variables, thresholds were changed in one-unit increments in the following ranges: age, 46–63 years; pack-years of smoking, 1–60; alcohol intake, 25–250 g/week; body mass index (calculated as kg/m^2), 20–40; low-density lipoprotein (LDL) cholesterol, 70–200 mg/dl; high-density lipoprotein (HDL) cholesterol, 30–80 mg/dl; triglycerides, 50–250 mg/dl; glucose, 85–170 mg/dl; systolic blood pressure, 90–150 mm Hg; diastolic blood pressure, 60–100 mm Hg. The first two iterations of this process were used to define six subgroups based on $\text{Max}_{\text{Sn+Sp}}$ values for association with the composite outcome. In addition, subgroups were defined by sex, race, and presence of characteristics typically associated with renal dysfunction, name-

Fig. 1. Receiver-operator characteristic curves for associations between serum creatinine, eGFR, and the composite outcome. C-statistic values were 0.60 for serum creatinine, 0.57 for eGFR_{CKD-EPI}, 0.57 for eGFR_{CG/BSA}, and 0.54 for eGFR_{MDRD}.

ly diabetes, hypertension, or coronary heart disease. This study examined event occurrence at any time during the follow-up period, without considering time to event. Findings were similar when follow-up was truncated at 5 and 10 years, and are not reported here. Additionally, the classification tree approach was extended to five orders of dichotomization, generating 32 terminal subgroups. Terminal subgroups were then used to classify the entire population and both logistic regression and Cox regression were used to calculate risk ratios for the composite event; risk ratios with all strategies were very similar and only findings based on the first iteration of the classification tree and logistic regression are reported here. SAS, version 9.1 (SAS Institute Inc., Cary, N.C., USA) was used for data analysis.

Results

The mean age of the study population (ARIC, n = 15,582) was 54.2 years; 55.1% were women and 26.4% were African-American (table 1). Mean standardized creatinine value was 0.83 mg/dl. Mean eGFR values were 95.7 ml/min/1.73 m² using the CKD-EPI estimating equation (eGFR_{CKD-EPI}) [5], 98.6 ml/min/1.73 m² using the MDRD Study estimating equation (eGFR_{MDRD}) [6], and 99.7 ml/min/1.73 m² using the Cockcroft-Gault corrected for body-surface area estimating equation (eGFR_{CG/BSA}) [7].

The median follow-up was 13.1 years. During this period, 12.7% of the study population experienced a coronary heart disease event, 4.1% experienced a stroke, 13.3% died, and 22.1% experienced a composite of at least one

Fig. 2. Sensitivity and specificity values of different eGFR and serum creatinine values for association with the composite outcome.

of these events (the primary study outcome). Receiver operator characteristic curves for associations between serum creatinine, eGFR, and the composite outcome are shown in figure 1; c-statistic values were highest for serum creatinine (0.60), followed by eGFR_{CKD-EPI} (0.57), eGFR_{CG/BSA} (0.57), and eGFR_{MDRD} (0.54).

Corresponding c-statistics for the individual components of the composite outcome are shown in table 2. For coronary heart disease, values were 0.62 for serum creatinine, 0.58 for eGFR_{CKD-EPI}, 0.56 for eGFR_{CG/BSA}, and 0.56 for eGFR_{MDRD}. For cerebrovascular accident, values were 0.57 for serum creatinine, 0.55 for eGFR_{CG/BSA}, 0.54 for eGFR_{CKD-EPI}, and 0.50 for eGFR_{MDRD}. For death, values were 0.59 for eGFR_{CG/BSA}, 0.58 for serum creatinine, 0.57 for eGFR_{CKD-EPI}, and 0.53 for eGFR_{MDRD}.

Regarding associations with the composite outcome, figure 2 shows sensitivity and specificity values of different renal function thresholds for the composite outcome, and table 2 ranks Max_{S_n+S_p} values. For all eGFR measures, sensitivity was below 0.05 and specificity above 0.98 for thresholds of 60 ml/min/1.73 m². For serum creatinine, Max_{S_n+S_p} occurred at a level of 0.73 mg/dl (sen-

sitivity 0.66/specificity 0.48); corresponding values for eGFR_{CKD-EPI}, eGFR_{CG/BSA}, and eGFR_{MDRD} were 95 ml/min/1.73 m² (0.52/0.59), 90 ml/min/1.73 m² (0.44/0.67), and 75 ml/min/1.73 m² (0.16/0.91), respectively. Findings were generally comparable when the components of the composite event were considered separately, with broadly similar Max_{S_n+S_p} values for optimum serum creatinine, eGFR_{CKD-EPI}, and eGFR_{CG/BSA} thresholds, lower values for optimum eGFR_{MDRD} thresholds, and relatively higher specificity than sensitivity for eGFR_{MDRD}.

We also calculated c-statistic values for association with the composite outcome in subgroups defined by demographic characteristics, and in subgroups defined by dominant prognostic association (data not shown). Findings generally paralleled findings in the overall populations, with approximately similar performance of serum creatinine, eGFR_{CKD-EPI}, and eGFR_{CG/BSA}, and inferior performance of eGFR_{MDRD}. Regarding thresholds of Max_{S_n+S_p}, values were typically higher than 60 ml/min/1.73 m² for eGFR and below 1.0 for serum creatinine.

Table 3 shows findings from the first iteration of the classification tree analysis for the composite outcome, with threshold values ranked by Max_{S_n+S_p}. Eighteen or more pack-years of smoking was the highest ranked of 20 risk factors identified in the overall population; creatinine >0.73 mg/dl ranked tenth, eGFR_{CKD-EPI} ≤95 ml/min/1.73 m² fifteenth, eGFR_{CG/BSA} ≤90 ml/min/1.73 m² sixteenth, and eGFR_{MDRD} ≤75 ml/min/1.73 m² eighteenth. When 10 modifiable risk factors were considered, HDL cholesterol ≤44 mg/dl ranked first, creatinine >0.73 mg/dl tenth, eGFR_{CKD-EPI} ≤95 ml/min/1.73 m² sixth, eGFR_{CG/BSA} ≤90 ml/min/1.73 m² seventh, and eGFR_{MDRD} ≤75 ml/min/1.73 m² ninth.

Discussion

In this community-based study of older adults, we found that creatinine-based thresholds exhibiting maximum combined sensitivity and specificity values for predicting cardiovascular events and death rates were substantially higher than 60 ml/min/1.73 m², with the latter threshold distinguished by very low sensitivity and high specificity. In addition, we found that optimum thresholds based on serum creatinine appeared to perform similarly to eGFR thresholds. Regarding eGFR thresholds, those based on the MDRD Study formula appeared less efficient than those based on the other formulas. Finally, threshold renal function measures did not appear to be

Table 2. Renal function markers as continuous variables, ranked by c-statistic values, and threshold values of maximum combined sensitivity and specificity for composite event, coronary heart disease, cerebrovascular accident, and death, ranked by maximum combined sensitivity and specificity

Rank	Composite event ^a (3,441/15,582 events)	Coronary heart disease (1,975/15,582 events)	Cerebrovascular accident (633/15,582 events)	Death (2,077/15,582 events)
<i>Continuous variables ranked by c-statistics</i>				
1	creatinine 0.60	creatinine 0.62	creatinine 0.57	eGFR _{CG/BSA} 0.59
2	eGFR _{CKD-EPI} 0.57	eGFR _{CKD-EPI} 0.58	eGFR _{CG/BSA} 0.55	creatinine 0.58
3	eGFR _{CG/BSA} 0.57	eGFR _{CG/BSA} 0.56	eGFR _{CKD-EPI} 0.54	eGFR _{CKD-EPI} 0.57
4	eGFR _{MDRD} 0.54	eGFR _{MDRD} 0.56	eGFR _{MDRD} 0.50	eGFR _{MDRD} 0.53
<i>Threshold values ranked by Max_{S_n+S_p}</i>				
1	creatinine >0.73 (0.66/0.48)	creatinine >0.73 (0.71/0.47)	eGFR _{CG/BSA} ≤86 (0.38/0.73)	eGFR _{CG/BSA} ≤89 (0.46/0.68)
2	eGFR _{CKD-EPI} ≤95 (0.52/0.59)	eGFR _{CKD-EPI} ≤97 (0.61/0.52)	creatinine >0.82 (0.46/0.65)	eGFR _{CKD-EPI} ≤95 (0.53/0.58)
3	eGFR _{CG/BSA} ≤90 (0.44/0.67)	eGFR _{CG/BSA} ≤90 (0.43/0.66)	eGFR _{CKD-EPI} ≤92 (0.44/0.65)	creatinine >0.82 (0.45/0.66)
4	eGFR _{MDRD} ≤75 (0.16/0.91)	– ^b	eGFR _{MDRD} ≤74 (0.16/0.91)	eGFR _{MDRD} ≤75 (0.18/0.91)
Numbers in parentheses are sensitivity/specificity.				
^a Any event: coronary heart disease, cerebrovascular accident, or death.				
^b For eGFR _{MDRD} threshold with Max _{S_n+S_p} , p > 0.05 for association with coronary heart disease.				

Table 3. First iteration of classification tree analysis, composite outcome, threshold values ranked by Max_{S_n+S_p}^a

Rank	Risk factor ^b	Prevalence, % ^c	Sensitivity/ specificity	Odds ratio (95% CI) ^d	p ^d
1	>18 pack-years	35.1	0.54/0.70	1.7 (1.4–2.0)	<0.001
2	Male sex	44.9	0.62/0.60	1.5 (1.2–1.7)	<0.001
3	Age >53 years	52.3	0.69/0.53	2.2 (1.9–2.6)	<0.001
4	HDL cholesterol ≤44 mg/dl	37.6	0.53/0.67	1.4 (1.2–1.6)	<0.001
5	Treatment for hypertension	30.5	0.44/0.73	2.6 (2.2–3.1)	<0.001
6	Hypertension	34.8	0.48/0.69	3.5 (3.0–4.2)	<0.001
7	Glucose >106 mg/dl	27.8	0.40/0.76	2.1 (1.8–2.5)	<0.001
8	Triglycerides >110 mg/dl	49.6	0.62/0.54	1.5 (1.2–1.7)	<0.001
9	Diabetes	11.8	0.23/0.92	3.4 (2.9–4.1)	<0.001
10	Creatinine >0.73 mg/dl	55.1	0.66/0.48	1.5 (1.3–1.8)	<0.001
11	Current smoker	26.2	0.37/0.77	1.7 (1.4–2.0)	<0.001
12	<12 years of school	23.8	0.34/0.79	2.3 (2.0–2.7)	<0.001
13	Coronary heart disease	5.0	0.15/0.98	2.8 (2.2–3.6)	<0.001
14	LDL cholesterol >136 mg/dl	49.2	0.58/0.53	1.3 (1.1–1.5)	0.003
15	eGFR _{CKD-EPI} ≤95 ml/min/1.73 m ²	43.2	0.52/0.59	1.4 (1.2–1.6)	<0.001
16	eGFR _{CG/BSA} ≤90 ml/min/1.73 m ²	35.5	0.44/0.67	1.5 (1.3–1.8)	<0.001
17	Body mass index >27	49.1	0.55/0.53	1.7 (1.4–2.0)	<0.001
18	eGFR _{MDRD} ≤75 ml/min/1.73 m ²	10.3	0.16/0.91	1.7 (1.3–2.1)	<0.001
19	Ethanol intake >120 g/week	11.7	0.14/0.89	1.3 (1.0–1.6)	0.04
20	African-American	26.4	0.28/0.74	2.2 (1.9–2.6)	<0.001

^a Any event: coronary heart disease, cerebrovascular accident, or death.

^b For each risk factor, the reference group is participants without the condition of interest.

^c The proportion of the population or subgroup with the condition of interest.

^d From logistic regression, with the composite variable as outcome.

the dominant prognostic discriminators in the overall population or in the subgroups assessed. If confirmed, these findings suggest that creatinine-based estimates may not be very useful for prognostic triage and, by extension, that routine measurement in community-dwelling adults may not be an efficient strategy for predicting these diseases.

The analytical approach used in this study was based on an effort to identify measures and thresholds of kidney function that outperformed competing renal and non-renal candidate variables. Selection of a dominant entity was based on the mathematical construct of maximum combined sensitivity and specificity values. Hence, risk factor prevalence weighed heavily into the selection process. Because this approach is hierarchical, it allows comparisons of different threshold values of a single risk factor; in addition, it facilitates comparisons of optimum threshold values of multiple risk factors. Both these attributes might be useful for risk-based triage in public health settings. This study suggests that even valid tests of kidney function have modest sensitivity for predicting cardiovascular events and death. This is not surprising, given the complex etiologies of these conditions.

Associations between kidney function, cardiovascular disease, and death have been studied extensively. For example, a PubMed search of human studies carried out in September 2010 with the search terms mortality or survival or cardiovascular, and glomerular filtration rate or creatinine or chronic kidney disease, and community or general population yielded 2,156 citations, a value that fell to 140 with the addition of 'sensitivity and specificity' and to four with the addition of 'threshold', with none of these four articles directly relevant to the questions addressed in the current study. Hence, it appears that few studies have attempted to define threshold levels of kidney function that maximally discriminate between occurrence, or not, of major cardiovascular events over finite intervals. One exception was an examination of 50-year-old Swedish men, in which optimum creatinine clearance thresholds for myocardial infarction and cardiovascular death were 98 and 92 ml/min/1.73 m², respectively [15]. Our group recently reported mortality-kidney function profiles from US adults studied between 1988 and 1994 in the third National Health and Nutrition Examination Survey (NHANES) [16]. The optimum eGFR_{CKD-EPI} threshold for death/survival discrimination, 94 ml/min/1.73 m², was similar to the threshold seen in the current study, and the optimum urinary albumin-creatinine ratio,

9 mg/g, was substantially lower than the thresholds used to define abnormality in most classification systems. Unlike in this study, the albumin-creatinine ratio and eGFR appeared to compare favorably with other classic risk factors for risk triage. A limitation of the previous study was nonavailability of most components of major adverse cardiovascular end points, such as coronary heart disease and stroke; in addition, optimally discriminatory serum creatinine thresholds were not studied. The reasons underlying the disparity in discriminatory efficiency of renal function measures between the two studies are not clear. This being said, it is tempting to speculate that the age bands studied (all adults in NHANES, ages 45–65 years in ARIC) may be partly responsible. In this regard, it is also tempting to speculate that the nonsuperior mortality discrimination of eGFR over serum creatinine also reflects the comparatively narrow age distribution of the study population.

The limitations of the current study deserve consideration. Findings were generated from four populations in the US between 1987 and 1989 and generalizability to other populations is uncertain. Gold-standard techniques, such as inulin and radioisotope clearance, were not available for GFR measurement. Urinary protein excretion information was not available. As with virtually all studies reported to date, kidney function in this study was measured on one occasion. In clinical practice, an eGFR or serum creatinine test suggesting the presence of chronic kidney disease would require a confirmatory test, as current guidelines for case finding suggest that abnormalities should be present for at least 3 months for case definition [17]. This study was based on a single assessment of GFR. As GFR values vary substantially from one time point to another, it is conceivable that sensitivity values may be higher if a strategy of multiple GFR assessments had been used.

Despite its limitations, this study has some attractive features. The study was community based and designed to be broadly representative. Several commonly used risk triage measures, such as cholesterol, blood pressure, and body mass index were systematically collected at the same time that renal function was measured, and a single creatinine measurement technique was used. While confirmation is needed, this study suggests that optimum thresholds for risk identification are higher than the value currently used to define a moderately abnormal GFR (60 ml/min/1.73 m²). The utility of creatinine-based risk triage in older adults in community settings appears modest.

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Disclosure Statement

The authors have no conflicts of interest.

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