ORIGINAL RESEARCH

Disparities in the Estimation of Glomerular Filtration Rate According to Cockcroft-Gault, Modification of Diet in Renal Disease-4, and Chronic Kidney Disease Epidemiology Collaboration Equations and Relation With Outcomes in Patients With Acute Coronary Syndrome

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***Background*—**A simple method to assess renal function is the estimated glomerular filtration rate, and it shows prognostic implications. However, it remains unknown which equation should be used in patients with acute coronary syndrome. We compared the ability and correlation of the Cockcroft-Gault, Modification of Diet in Renal Disease-4 (MDRD-4), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and their predictive performance for major adverse cardiovascular events, all-cause mortality, and major bleeding in a cohort of patients with acute coronary syndrome.

***Methods and Results*—**Multicenter prospective registry involving 1699 consecutive patients with acute coronary syndrome from 3 tertiary institutions. At entry, renal function was assessed using the Cockcroft-Gault, MDRD-4, and CKD-EPI-creatinine equations. During 12 months of follow-up, we recorded all major adverse cardiovascular events (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke), bleeding events (Bleeding Academic Research Consortium classification), and all-cause mortality. Receiver operating characteristic curve comparisons demonstrated that Cockcroft-Gault equation had higher predictive ability compared with MDRD-4 equation for major adverse cardiovascular events (0.651 versus 0.616; P=0.023), major bleeding (0.600 versus 0.551; P=0.005), and all-cause mortality (0.754 versus 0.717; P=0.033), as well as higher predictive ability compared with CKD-EPI equation for major bleeding (0.600 versus 0.564; P=0.018). Integrated discrimination improvement and net reclassification improvement analyses showed superior discrimination and reclassification of Cockcroft-Gault equation. Decision curve analyses graphically demonstrated higher net benefit and clinical usefulness of the Cockcroft-Gault equation in comparison with MDRD-4 and CKD-EPI equations.

***Conclusions*—**In patients with acute coronary syndrome, the Cockcroft-Gault equation presented superior predictive ability for major adverse cardiovascular events, major bleeding, and all-cause mortality compared with MDRD-4 equation, and superior predictive ability for major bleeding compared with CKD-EPI equation. The Cockcroft-Gault equation also showed higher net benefit and clinical usefulness. **(*J Am Heart Assoc*. 2018;7:e008725. DOI: 10.1161/JAHA.118.008725.)**

Key Words: acute coronary syndrome • glomerular filtration rate equations • hemorrhage • ischemia • renal function • risk stratification

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Clinical Perspective

What Is New?

- Renal disease is a frequent comorbidity in patients with acute coronary syndrome and is associated with worse clinical outcomes.
- This study shows that the Cockcroft-Gault equation has superior predictive ability for major adverse cardiovascular events, major bleeding, and all-cause mortality compared with Modification of Diet in Renal Disease-4 equation, and it has superior predictive ability for major bleeding compared with Chronic Kidney Disease Epidemiology Collaboration equation.
- Overall, the Cockcroft-Gault equation has higher net benefit and clinical usefulness for predicting all adverse events.

What Are the Clinical Implications?

- Renal function is commonly assessed by estimating glomerular filtration in patients with acute coronary syndrome.
- The present study has demonstrated that the Cockcroft-Gault equation can be the most appropriate equation for these patients, helping physicians to choose the best clinical management.

Renal disease, and particularly chronic kidney disease (CKD), is a frequent comorbidity in patients with acute coronary syndrome (ACS) and is associated with worse short- and long-term clinical outcomes.[1,2] For this reason, renal function should be properly assessed in all patients with ACS, to identify those with renal deterioration or at risk of deterioration and to guarantee the best management of these patients.[3]

A simple way to assess renal function is using the estimated glomerular filtration rate (eGFR) equations, such as Cockcroft-Gault, Modification of Diet in Renal Disease-4 (MDRD-4), and CKD Epidemiology Collaboration (CKD-EPI). All of these equations are widely used in everyday clinical practice, and <60 mL/min per 1.73 m^2 is considered the cutoff value for impaired renal function in all of these equations. However, the Kidney Disease Improving Global Outcomes 2012 guidelines for the evaluation and management of CKD recommend the use of CKD-EPI, because this equation seems to be more precise and to have less bias in comparison with other equations.[4]

Despite that recent evidence also suggests the use of the CKD-EPI equation[5,6]; it is still unknown which equation would be better to use in patients with ACS.

In the present study, we aimed to compare the ability and correlation of the eGFR, assessed by Cockcroft-Gault, MDRD-4, and CKD-EPI, and to evaluate the predictive performance of the 3 equations for major adverse cardiovascular events (MACEs), all-cause mortality, and major bleeding in a "real-world" cohort of patients with ACS.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because some materials are used for other unpublished projects.

Study Design and Patients

All patients discharged with definitive diagnosis of ACS in 3 tertiary hospitals were selected prospectively for this multicentric contemporary observational registry. Thus, from February 1, 2014, to December 31, 2015, we included patients fulfilling the following criteria: aged ≥18 years and confirmed ACS (ST-segment–elevation myocardial infarction [STEMI], non-STEMI [non–Q-wave myocardial infarction], or unstable angina). Only those patients who died during hospitalization or experienced an ACS during another extracardiac pathological condition (stroke, sepsis, surgery, or trauma) were excluded, without other specific exclusion criteria. More important, no patient was excluded because of his or her renal function or other comorbidity.

At baseline, clinical characteristics were recorded, and Global Registry of Acute Coronary Events and CRUSADE (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) scores were calculated. Anemia was defined as a hemoglobin level <12 g/dL in women and <13 g/dL in men.

Renal function was assessed using the Cockcroft-Gault equation, adjusted by body surface area, MDRD-4, and 2009 CKD-EPI-creatinine equations for eGFR. By either equation, renal impairment was defined as a glomerular filtration rate <60 mL/min per 1.73 m^2. Baseline creatinine was used to calculate eGFR equations. The creatinine assay was well isotope dilution mass spectrometry traceable in the 3 participating hospitals.

During 12 months of follow-up, we recorded all outcomes experienced. As primary end point, we defined MACEs (the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke), whereas bleeding events (according to the Bleeding Academic Research Consortium classification)[7] and all-cause mortality (the composite of cardiovascular death and noncardiovascular death) were secondary end points. Follow-up was performed through personal interviews in routine visits, telephone contact with patients/families, and medical records. The investigators identified, confirmed, and recorded all adverse events, as well as other clinical outcomes.

The study protocol complies with the 1964 Declaration of Helsinki and its later amendments. It was approved by the Ethics and Research Committee of the 3 hospitals and accepted by the Department for Medicinal Products for

Human Use of the Spanish Agency for Medicines and Health Products with resolution of Post-Authorization Study—Other Designs (reference JRN-NAG-2014-01). All patients provided signed informed consent to participate in the study.

An external audit of the registry data was performed by an independent Clinical Research Organization that evaluated, in all participating hospitals, proper inclusion of patients, the analyzed data, and the possible existence of patients not included during the recruitment period.

Statistical Analysis

Categorical variables were expressed as frequencies with percentage. Continuous variables were assessed by the Kolmogorov-Smirnov test and expressed as mean and SD or median and interquartile range, as appropriate.

Comparison of continuous variables was performed using the Student *t* test (Mann-Whitney *U* test if appropriate). Correlation between Cockcroft-Gault, MDRD-4, and CKD-EPI equations was tested by the Spearman's ρ.

Cox models (with hazard ratios and 2-sided 95% confidence intervals [CIs]) were used to determine the association between renal impairment and MACEs, as well as bleeding events and all-cause mortality. Survival analyses by Kaplan-Meier estimates were performed to assess differences in event-free survival distributions between subgroups of eGFR.

Receiver operating characteristic curves were applied to evaluate the predictive abilities for MACEs, major bleeding, and all-cause mortality of the Cockcroft-Gault, MDRD-4, and CKD-EPI equations. Comparisons of receiver operating characteristic curves were performed by the method of DeLong et al.[8] Discrimination and reclassification performance of the 3 equations was evaluated by calculating the integrated discrimination improvement and the net reclassification improvement, as described by Pencina et al.[9] We also estimated the clinical usefulness and the net benefit of the 3 equations using the decision curve analysis, according to the methods proposed by Vickers et al.[10,11]

$P<0.05$ was accepted as statistically significant. Statistical analyses were performed using SPSS, version 22.0 (SPSS, Inc, Chicago, IL), MedCalc, version 16.4.3 (MedCalc Software bvba, Ostend, Belgium), and STATA, version 12.0 (Stata Corp, College Station, TX) for Windows.

Results

We included 1699 patients (71.3% men) with median age of 67 (interquartile range, 56–77) years. At entry, the median eGFR by using the 3 equations was ≈81 mL/min per 1.73 m^2 and ≈25% of patients had renal impairment (eGFR <60 mL/min per 1.73 m^2) (Table 1). A comparison of the eGFR equations according to ACS severity is shown in Table 2. Other baseline clinical characteristics are summarized in Table 1, whereas distributions of patients according to eGFR

Table 1. Baseline Clinical Characteristics

Characteristics	Value (N=1699)
Demographics	
Age, median (IQR), y	67 (56–77)
Male sex, n (%)	1212 (71.3)
BMI, median (IQR), kg/m^2	27.7 (25.2–31.0)
Primary reason for hospitalization, n (%)	
STEMI	586 (33.4)
NST-ACS	1131 (66.6)
NSTEMI	742 (43.7)
Unstable angina	389 (22.9)
Comorbidities, n (%)	
Hypertension	1147 (67.5)
Diabetes mellitus type 1/2	647 (38.1)
Hyperlipemia	1016 (59.8)
Smoking history	
Smokers	627 (36.9)
History of coronary artery disease	536 (31.5)
Family history of coronary artery disease	142 (8.4)
Prior PCI or CABG	423 (25.0)
Peripheral arterial disease	151 (8.9)
History of stroke	148 (8.7)
Anemia	438 (25.8)
GRACE, median (IQR)	
GRACE in-hospital mortality	135 (108–164)
GRACE 6-mo mortality	112 (90–137)
CRUSADE, median (IQR)	28 (18–40)
Renal function	
eGFR by Cockcroft-Gault, median (IQR)	81.1 (56.2–105.8)
eGFR <60 mL/min per 1.73 m^2 by Cockcroft-Gault, n (%)	486 (28.6)
eGFR by MDRD-4, median (IQR)	80.9 (62.3–98.4)
eGFR <60 mL/min per 1.73 m^2 by MDRD-4, n (%)	380 (22.4)
eGFR by CKD-EPI, median (IQR)	80.3 (59.1–94.1)
eGFR <60 mL/min per 1.73 m^2 by CKD-EPI, n (%)	439 (25.8)

BMI indicates body mass index; CABG, coronary artery bypass grafting; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; MDRD-4, Modification of Diet in Renal Disease-4; NST-ACS, non–ST-segment–elevation acute coronary syndrome; NSTEMI, non-STEMI; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

Table 2. Comparison of the eGFR Equations According to ACS Severity

Variable	STEMI	NSTEMI	Unstable Angina	*P* Value
eGFR by Cockcroft-Gault, median (IQR)	88.6 (64.7–113.0)	75.6 (49.8–101.4)	77.2 (56.7–100.3)	<0.001
eGFR by MDRD-4, median (IQR)	86.1 (68.6–102.6)	77.6 (57.9–96.5)	79.4 (62.1–95.9)	<0.001
eGFR by CKD-EPI, median (IQR)	84.9 (67.6–98.1)	76.0 (54.5–91.9)	78.3 (58.2–90.8)	<0.001

ACS indicates acute coronary syndrome; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD-4, Modification of Diet in Renal Disease-4; NSTEMI, non-STEMI; STEMI, ST-segment–elevation myocardial infarction.

categories assessed by the 3 equations are shown in Figure 1. The median eGFR was significantly different within the 3 equations (P<0.001 for all comparisons), although a potent direct positive correlation was observed (ρ >0.8, P<0.001 within the 3 equations).

Clinical outcomes during follow-up

Of the 1699 patients included, 98.1% of them completed follow-up. During 373 (interquartile range, 365–384) days of follow-up, 173 patients (10.2%) experienced a MACE (of which 60 [3.5%] were cardiovascular deaths, 89 [5.2%] were nonfatal myocardial infarctions, and 24 [1.4%] were nonfatal ischemic strokes), 167 patients (9.8%) experienced major bleeding (Bleeding Academic Research Consortium classification, 3–5), and 105 patients (6.2%) died. Renal impairment was significantly associated with higher risk of MACEs, major bleeding, and all-cause mortality, assessed with the 3 equations. However, the Cockcroft-Gault was the equation that estimated a higher risk of MACEs, major bleeding, and all-cause mortality, with hazard ratios of 2.60 (95% CI, 1.93–3.50; P<0.001), 1.64 (95% CI, 1.20–2.24; P=0.002), and 5.74 (95% CI, 3.80–8.67; P<0.001), respectively (Table 3, Figure 2).

Prediction Performance and Clinical Usefulness

Receiver operating characteristic curves demonstrated that the 3 equations predicted MACEs, all-cause mortality, and major bleeding, as dichotomic (ie, <60 versus ≥60 mL/min per 1.73 m^2) and as categories (ie, ≥90, 60–89, 30–59, and <30 mL/min per 1.73 m^2), with C-indexes between 0.55 and 0.75 (Table 4). Comparisons of receiver operating characteristic curves did not show significantly superior predictive ability of any equation for any of the events when analyzed as dichotomic (Table 5). However, when analyzed using eGFR categories, Cockcroft-Gault equation demonstrated higher predictive ability compared with MDRD-4 for MACEs (C-index, 0.65 [95% CI, 0.63–0.67] versus 0.62 [95% CI, 0.59–0.64]; P=0.023), major bleeding (C-index, 0.60 [95% CI, 0.57–0.62] versus 0.55 [95% CI, 0.53–0.58]; P=0.005), and all-cause mortality (C-index, 0.75 [95% CI, 0.73–0.78] versus 0.72 [95% CI, 0.69–0.74]; P=0.033). For major bleeding also, a significantly higher predictive ability of Cockcroft-Gault equation compared with CKD-EPI equation was observed (C-index, 0.60 [95% CI, 0.57–0.62] versus 0.56 [95% CI, 0.54–0.59]; P=0.018) (Table 6, Figure 3). A sensitivity analysis was performed separately in patients with STEMI and

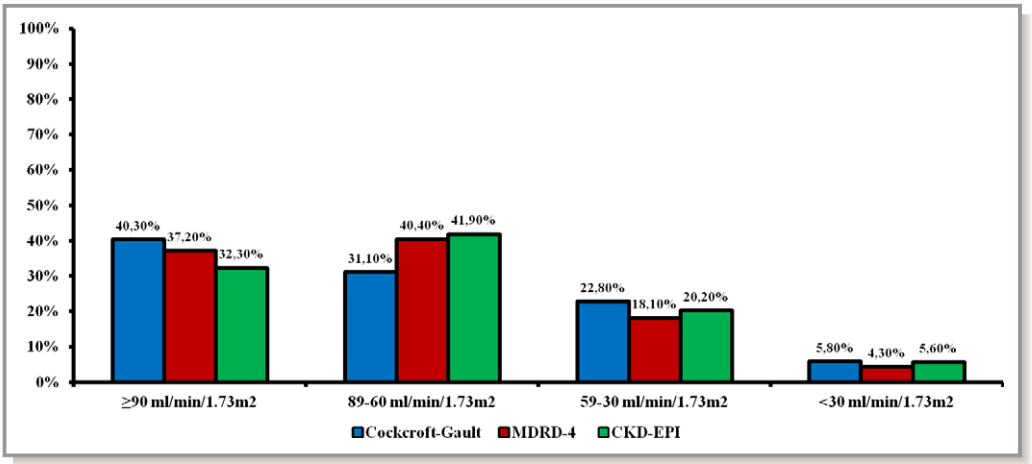

Figure 1. Distributions of patients according to the estimated glomerular filtration rate categories assessed by the Cockcroft-Gaul, Modification of Diet in Renal Disease-4 (MDRD-4), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Table 3. HRs for MACEs, Major Bleeding (BARC Classification, 3–5), and All-Cause Mortality, According to eGFR Categories Assessed by Cockcroft-Gault, MDRD-4, and CKD-EPI Equations

Variable	HR	95% CI
MACEs		
Cockcroft-Gault (eGFR <60 mL/min per 1.73 m^2)	2.60	1.93–3.50
Cockcroft-Gault (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	1.80	1.26–2.56
eGFR 59–30 mL/min per 1.73 m^2	3.13	2.11–4.6
eGFR <30 mL/min per 1.73 m^2	4.92	2.49–9.69
MDRD-4 (eGFR <60 mL/min per 1.73 m^2)	2.26	1.66–3.07
MDRD-4 (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	1.45	1.04–2.03
eGFR 59–30 mL/min per 1.73 m^2	2.44	1.58–3.75
eGFR <30 mL/min per 1.73 m^2	4.32	1.97–9.46
CKD-EPI (eGFR <60 mL/min per 1.73 m^2)	2.30	1.70–3.11
CKD-EPI (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	1.79	1.27–2.53
eGFR 59–30 mL/min per 1.73 m^2	2.73	1.79–4.17
eGFR <30 mL/min per 1.73 m^2	5.54	2.73–11.20
Major bleeding		
Cockcroft-Gault (eGFR <60 mL/min per 1.73 m^2)	1.64	1.20–2.24
Cockcroft-Gault (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	2.06	1.44–2.96
eGFR 59–30 mL/min per 1.73 m^2	2.46	1.65–3.66
eGFR <30 mL/min per 1.73 m^2	2.13	1.09–4.14
MDRD-4 (eGFR <60 mL/min per 1.73 m^2)	1.58	1.13–2.19
MDRD-4 (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	1.15	0.82–1.62
eGFR 59–30 mL/min per 1.73 m^2	1.91	1.23–2.96
eGFR <30 mL/min per 1.73 m^2	0.84	0.40–1.82
CKD-EPI (eGFR <60 mL/min per 1.73 m^2)	1.38	1.01–1.93
CKD-EPI (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	1.69	1.18–2.40
eGFR 59–30 mL/min per 1.73 m^2	2.17	1.41–3.33
eGFR <30 mL/min per 1.73 m^2	1.12	0.56–2.23
All-cause mortality		
	5.74	3.80–8.67
Cockcroft-Gault (eGFR <60 mL/min per 1.73 m^2)		
Cockcroft-Gault (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	2.64	1.68–4.16
eGFR 59–30 mL/min per 1.73 m^2	7.88	4.77–13.03
eGFR <30 mL/min per 1.73 m^2	18.02	7.40–43.89
MDRD-4 (eGFR <60 mL/min per 1.73 m^2)	4.60	3.13–6.76
MDRD-4 (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	2.44	1.59–3.75
eGFR 59–30 mL/min per 1.73 m^2	7.28	4.18–12.67
eGFR <30 mL/min per 1.73 m^2	11.37	4.09–31.58
CKD-EPI (eGFR <60 mL/min per 1.73 m^2)	4.40	2.98–6.50
CKD-EPI (eGFR categories; eGFR ≥90 mL/min per 1.73 m^2 as reference)		
eGFR 89–60 mL/min per 1.73 m^2	4.03	2.59–6.29
eGFR 59–30 mL/min per 1.73 m^2	9.89	5.73–17.06
eGFR <30 mL/min per 1.73 m^2	19.62	7.88–48.88

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular event; MDRD-4, Modification of Diet in Renal Disease-4.

non-STEMI. In patients with STEMI, there were no differences within the 3 equations. On contrary, in patients with non-STEMI, the results were similar to those of the overall population (ie, higher predictive ability of the Cockcroft-Gault equation compared with MDRD-4 equation for MACEs and all-cause mortality). However, the C-index of the Cockcroft-Gault equation was not significantly higher compared with MDRD-4 and CKD-EPI equations for major bleeding, whereas it was significantly higher compared with CKD-EPI equation for mortality (Table 6).

Integrated discrimination improvement analyses demonstrated a significant gain in sensitivity of Cockcroft-Gault equation over MDRD-4 equation for MACEs; and over CKD-EPI equation for MACEs, major bleeding, and all-cause mortality when renal impairment was analyzed as dichotomic. When we analyzed eGFR as categories, Cockcroft-Gault equation showed higher sensitivity than MDRD-4 equation for MACEs, major bleeding, and all-cause mortality, and higher sensitivity than CKD-EPI equation for major bleeding and all-cause mortality (Table 3). Net reclassification improvement did not reach significant results when the analyses were performed as dichotomic. However, when we analyzed as

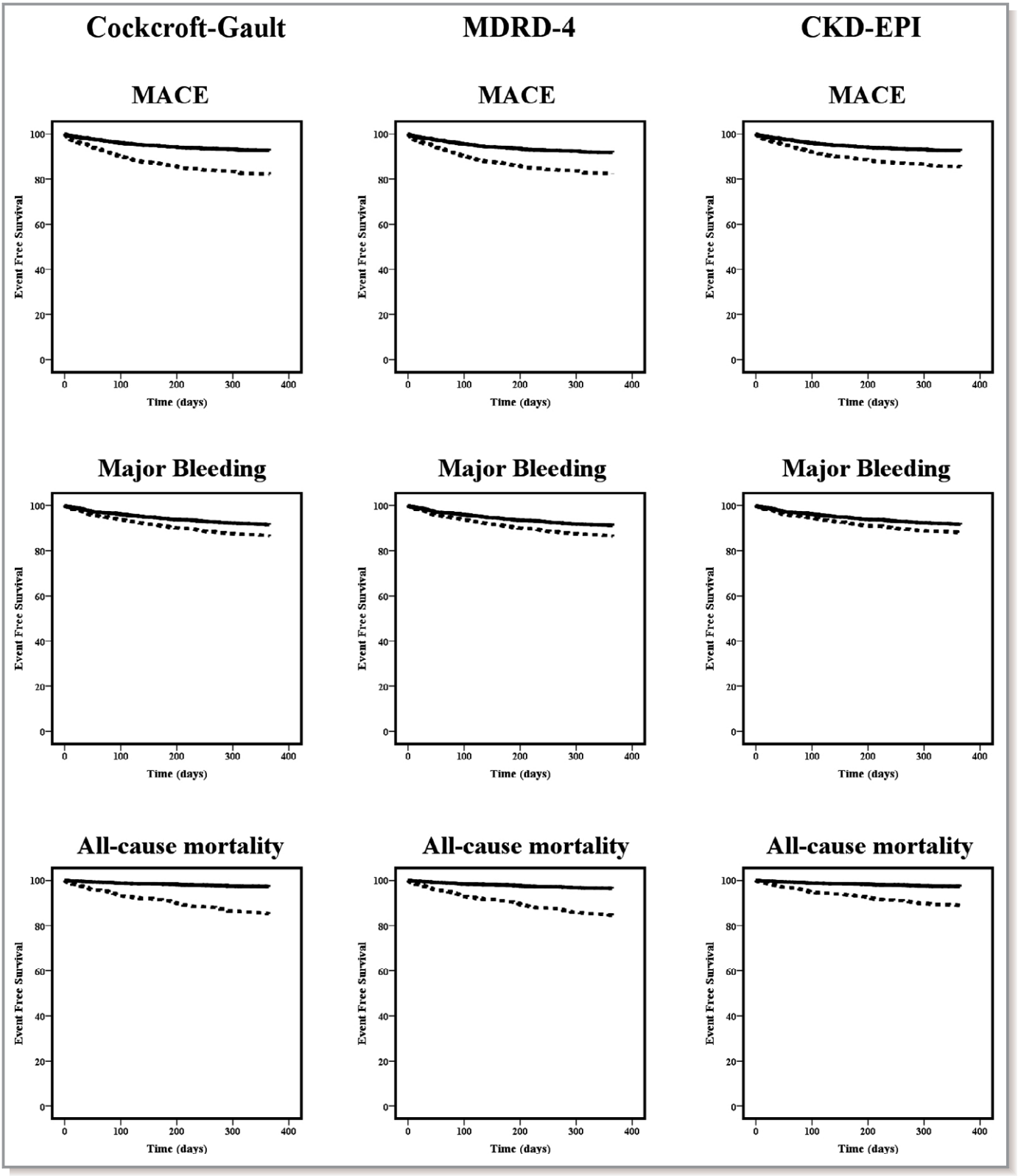

Figure 2. Event-free survival for major adverse cardiovascular events (MACEs), major bleeding (Bleeding Academic Research Consortium classification, 3–5), and all-cause mortality in patients with and without renal impairment, according to the Cockcroft-Gault, Modification of Diet in Renal Disease-4 (MDRD-4), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. Black solid line, estimated glomerular filtration rate ≥60 mL/min per 1.73 m^2; and black dashed line, estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

Table 4. C-Indexes of Cockcroft-Gault, MDRD-4, and CKD-EPI Equations for MACEs, Major Bleeding (BARC Classification, 3–5), and All-Cause Mortality

Variable	C-Index	95% CI	*P* Value
MACEs			
Cockcroft-Gault (eGFR <60 mL/min per 1.73 m^2)	0.617	0.593–0.640	<0.001
Cockcroft-Gault (eGFR categories)	0.651	0.628–0.674	<0.001
MDRD-4 (eGFR <60 mL/min per 1.73 m^2)	0.588	0.564–0.612	<0.001
MDRD-4 (eGFR categories)	0.616	0.593–0.640	<0.001
CKD-EPI (eGFR <60 mL/min per 1.73 m^2)	0.598	0.551–0.644	<0.001
CKD-EPI (eGFR categories)	0.636	0.613–0.660	<0.001
Major bleeding			
Cockcroft-Gault (eGFR <60 mL/min per 1.73 m^2)	0.557	0.533–0.581	0.004
Cockcroft-Gault (eGFR categories)	0.600	0.574–0.621	<0.001
MDRD-4 (eGFR <60 mL/min per 1.73 m^2)	0.545	0.521–0.569	0.015
MDRD-4 (eGFR categories)	0.551	0.527–0.575	0.022
CKD-EPI (eGFR <60 mL/min per 1.73 m^2)	0.536	0.512–0.560	0.057
CKD-EPI (eGFR categories)	0.564	0.540–0.588	0.002
All-cause mortality			
Cockcroft-Gault (eGFR <60 mL/min per 1.73 m^2)	0.713	0.690–0.734	<0.001
Cockcroft-Gault (eGFR categories)	0.754	0.733–0.775	<0.001
MDRD-4 (eGFR <60 mL/min per 1.73 m^2)	0.675	0.652–0.698	<0.001
MDRD-4 (eGFR categories)	0.717	0.695–0.739	<0.001
CKD-EPI (eGFR <60 mL/min per 1.73 m^2)	0.677	0.620–0.734	<0.001
CKD-EPI (eGFR categories)	0.731	0.700–0.744	<0.001

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MDRD-4, Modification of Diet in Renal Disease-4.

categories, we observed a significantly positive reclassification of Cockcroft-Gault over MDRD-4 equation for MACEs, major bleeding, and all-cause mortality, as well as significantly positive reclassification over CKD-EPI equation for major bleeding and all-cause mortality (Table 7).

Finally, we plotted decision curve analyses to investigate the clinical usefulness of each equation on the basis of a continuum of potential thresholds for adverse events (*x* axis) and the net benefit of using each equation (*y* axis) relative to assuming that no patient will have an adverse event. Thus, our decision curve analyses graphically demonstrated a *higher net benefit* and *clinical usefulness* of the Cockcroft-Gault equation in comparison with MDRD-4 and CKD-EPI equations, using eGFR as both dichotomic or categories, because the Cockcroft-Gault line (blue line) is farthest away from the slanted dashed black line (ie, assume all events) and the horizontal black line (ie, assume no event) (Figure 4).

Discussion

In this study, we demonstrated that in patients with ACS, the Cockcroft-Gault equation for the estimation of GFR is superior in predicting MACEs, major bleeding, and all-cause mortality compared with MDRD-4 and CKD-EPI equations, and is clinically more useful.

Renal function plays an important role on prognosis and management of patients with ACS. Thus, renal impairment is associated with higher risk of all-cause (and cardiovascular) mortality and with worse clinical outcomes overall.[1,2,12] For this reason, it is critical to have a standardized method to assess renal function. In this sense, the GFR is the best overall index of renal function in both health and disease.[4,13] Indeed, it has been shown that the risk of adverse events increases with decreasing categories of GFR.[14]

The 2009 CKD-EPI creatinine equation is considered as the gold standard for the eGFR by the 2012 Kidney Disease Improving Global Outcomes guidelines.[4] However, there are still controversies about which equation would be better to use in patients with ACS. For example, the rate of patients with renal impairment in this study varies from 22.4% to 41.9%, depending on the equation used.

In a study of adults without renal disease, the MDRD equation was more precise and accurate for predicting GFR compared with Cockcroft-Gault equation,[15] whereas in a study performed in the general population, the CKD-EPI equation estimated a lower prevalence of renal impairment compared with the MDRD equation.[16] This last result was confirmed in a meta-analysis comparing CKD-EPI with MDRD, in which the CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and end-stage renal disease.[17] However, Carter et al showed scarce differences between the CKD-EPI and MDRD equations, and among the elderly patients, CKD-EPI equation increased CKD prevalence.[18] Another study focusing on the effect of age, the Cockcroft-Gault equation, estimated lower eGFRs, and Cockcroft-Gault and MDRD equations predicted mortality, but not CKD-EPI.[19]

Table 5. ROC Curve Comparison for MACEs, Major Bleeding (BARC Classification, 3–5), and All-Cause Mortality Using the eGFR Dichotomic Category (ie, <60 vs ≥60 mL/min per 1.73 m^2), According to the Cockcroft-Gault, MDRD-4, and CKD-EPI Equations

Variable	C-Index	95% CI	*P* Value for C-Index Comparison		
			Cockcroft-Gault vs MDRD-4	Cockcroft-Gault vs CKD-EPI	MDRD-4 vs CKD-EPI
MACEs					
Cockcroft-Gault	0.617	0.593–0.640	0.080	0.207	0.288
MDRD-4	0.588	0.564–0.612			
CKD-EPI	0.598	0.574–0.621			
Major bleeding					
Cockcroft-Gault	0.557	0.533–0.581	0.411	0.099	0.191
MDRD-4	0.545	0.521–0.569			
CKD-EPI	0.536	0.512–0.560			
All-cause mortality					
Cockcroft-Gault	0.713	0.690–0.734	0.106	0.095	0.875
MDRD-4	0.675	0.652–0.698			
CKD-EPI	0.677	0.654–0.699			

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MDRD-4, Modification of Diet in Renal Disease-4; ROC, receiver operatingcharacteristic.

For patients with coronary artery disease, the eGFR has been demonstrated to be a predictor of adverse cardiovascular outcomes, although it is not clear which equation shows the best predictive ability. For example, in the HOMAGE (Heart Omics in Ageing) study, the body surface area–adjusted Cockcroft-Gault formula was more accurate in predicting cardiovascular mortality in patients with different degrees of cardiovascular risk, but its discriminative improvement was low compared with MDRD-4 and CKD-EPI equations, with the latter offering the best balance between renal function estimation and cardiovascular mortality prediction.[20] A study comparing Cockcroft-Gault and MDRD equations proved that MDRD was significantly more accurate in predicting the severity of coronary artery disease and 2-year cardiovascular risk in patients with myocardial infarction.[21] On contrary, in 2 studies performed in patients without STEMI, cystatin C–based CKD-EPI equations were superior to MDRD in predicting major bleeding, improving risk stratification for major bleeding and mortality, and adding complementary prognostic information to the Global Registry of Acute Coronary Events risk score.[5,6] Moreover, the CKD-EPI equation has been proposed for predicting adverse outcomes and drug-dosing recommendations after a percutaneous coronary intervention, supporting the use of this equation in patients with coronary disease.[22]

Despite this evidence, many other investigations have shown higher ability of Cockcroft-Gault equation for eGFR and for predicting adverse outcomes. Thus, in a recent report from a large registry including patients with heart failure, the Cockcroft-Gault equation predicted mortality better than the CKD-EPI and MDRD equations.[23] A previous prospective cohort study of patients with STEMI followed up during a long time also demonstrated that the Cockcroft-Gault formula was superior than MDRD and CKD-EPI equations at predicting mortality after acute myocardial infarction.[24] Similar results were found in a study including patients with ACS, in which Cockcroft-Gault equation better stratified patients according to their risk of 1-year mortality in comparison to the MDRD-4 or the CKD-EPI equations.[25] In a nationwide registry in Sweden, Cockcroft-Gault equation was better than the MDRD equation in predicting mortality after a myocardial infarction, and seems to be superior for predicting short- and long-term mortality.[26,27] In addition, a study has suggested that the Cockcroft-Gault equation may improve risk prediction of in-hospital bleeding more than the MDRD-4 or the CKD-EPI equation in patients with ACS.[28]

In the present study, the Cockcroft-Gault equation has shown superior predictive ability for adverse outcomes in comparison with MDRD-4 and the 2009 CKD-EPI-creatinine equations, therefore confirming the results of some previous studies. The Cockcroft-Gault formula includes the body weight, and in a prior study of our group, we proved the relationship between body weight and clinical outcomes.[29] This evidence could have influenced this apparent superior predictive ability of the Cockcroft-Gault equation over other equations. The clinical usefulness and net benefit of Cockcroft-Gault equation seem higher, which has important implications for everyday clinical practice.

Table 6. ROC Curve Comparison for MACEs, Major Bleeding (BARC Classification, 3–5), and All-Cause Mortality Using the eGFR Categories (≥90, 60–89, 30–59, and <30 mL/min per 1.73 m^2), According to the Cockcroft-Gault, MDRD-4, and CKD-EPI Equations

Variable	C-Index	95% CI	*P* Value for C-Index Comparison		
			Cockcroft-Gault vs MDRD-4	Cockcroft-Gault vs CKD-EPI	MDRD-4 vs CKD-EPI
MACE					
Cockcroft-Gault	0.651	0.628–0.674	0.023	0.270	0.063
MDRD-4	0.616	0.593–0.640			
CKD-EPI	0.636	0.613–0.660			
Cockcroft-Gault in STEMI	0.645	0.604–0.685	0.749	0.698	0.967
MDRD-4 in STEMI	0.655	0.614–0.694			
CKD-EPI in STEMI	0.656	0.615–0.695			
Cockcroft-Gault in NSTEMI	0.641	0.605–0.676	0.022	0.161	0.145
MDRD-4 in NSTEMI	0.593	0.557–0.629			
CKD-EPI in NSTEMI	0.615	0.579–0.651			
Major bleeding					
Cockcroft-Gault	0.600	0.574–0.621	0.005	0.018	0.245
MDRD-4	0.551	0.527–0.575			
CKD-EPI	0.564	0.540–0.588			
Cockcroft-Gault in STEMI	0.600	0.550–0.633	0.199	0.355	0.492
MDRD-4 in STEMI	0.544	0.502–0.586			
CKD-EPI in STEMI	0.560	0.518–0.602			
Cockcroft-Gault in NSTEMI	0.571	0.534–0.607	0.348	0.597	0.461
MDRD-4 in NSTEMI	0.549	0.513–0.585			
CKD-EPI in NSTEMI	0.562	0.525–0.598			
All-cause mortality					
Cockcroft-Gault	0.754	0.733–0.755	0.033	0.134	0.207
MDRD-4	0.717	0.695–0.739			
CKD-EPI	0.731	0.700–0.744			
Cockcroft-Gault in STEMI	0.764	0.726–0.798	0.610	0.593	0.992
MDRD-4 in STEMI	0.780	0.744–0.814			
CKD-EPI in STEMI	0.780	0.744–0.814			
Cockcroft-Gault in NSTEMI	0.767	0.734–0.797	0.020	0.038	0.437
MDRD-4 in NSTEMI	0.715	0.681–0.748			
CKD-EPI in NSTEMI	0.726	0.692–0.758			

BARC indicates Bleeding Academic Research Consortium; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MDRD-4, Modification of Diet in Renal Disease-4; NSTEMI, non-STEMI; ROC, receiver operating characteristic; STEMI, ST-segment–elevation myocardial infarction.

Limitations

The results of this study reflect data obtained from a multicenter registry performed in 3 tertiary hospitals. It is well known that observational registries represent better the clinical practice than clinical trials, but patients are usually heterogeneous and have different clinical characteristics, what difficult generalized conclusions about a particular therapeutic approach. On the other hand, the 3 participant hospitals had catheterization laboratory, which may be related with more invasive hospital management. By this reason, we recognize that clinical practice of the participant hospitals may not reflect the general clinical practice clinic of other hospitals.

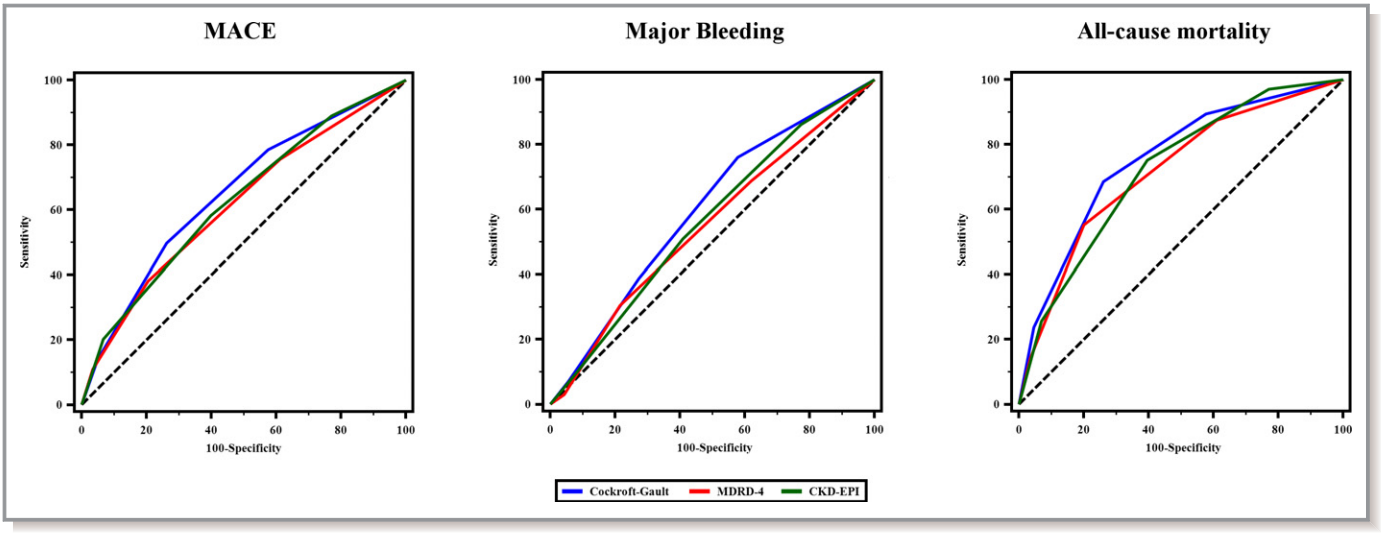

Figure 3. Receiver operating characteristic curves for major adverse cardiovascular events (MACEs), major bleeding (Bleeding Academic Research Consortium classification, 3–5), and all-cause mortality using the estimated glomerular filtration rate categories, according to the Cockcroft-Gault, Modification of Diet in Renal Disease-4 (MDRD-4), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Patient selection was based on a confirmed ACS diagnosis at discharge, and therefore, patients who died during hospitalization were not included. However, all patients with confirmed ACS diagnosis at discharge were consecutively included in the registry, avoiding possible losses.

Because this was a voluntary registry, investigators only collected data at discharge, so the patient decision did not influence the clinical management or clinical decisions taken by responsible physicians. This voluntariness of the registry guarantees a high quality of the data that have been corroborated by an external and independent audit.

We also have to acknowledge that creatinine assay variability and creatinine calibration variability between the 3 laboratories could exist. However, the eGFR was centrally calculated using the same criteria and equations, thus avoiding the bias produced by a center effect. Also, we only have data of eGFR at baseline and we must recognize that it probably changed during follow-up. Nevertheless, this study was performed to help physicians to determine which equation should be used to estimate renal impairment in patients with ACS, in a way to predict prognosis in a short/medium period.

Table 7. Discrimination and Reclassification Analyses for MACEs, Major Bleeding (BARC Classification, 3–5), and All-Cause Mortality

	MACEs				Major Bleeding				All-Cause Mortality			
Variable	IDI, %	*P* Value	NRI, %	*P* Value	IDI, %	*P* Value	NRI, %	*P* Value	IDI, %	*P* Value	NRI, %	*P* Value
eGFR dichotomic (<60 vs ≥60 mL/min per 1.73 m^2)												
Cockcroft-Gault vs MDRD-4	0.817	0.015	5.760	0.090	0.149	0.290	2.380	0.422	1.013	0.069	7.410	0.119
Cockcroft-Gault vs CKD-EPI	0.639	0.042	3.890	0.212	0.328	0.010	4.240	0.105	1.344	0.007	7.100	0.101
CKD-EPI vs MDRD-4	0.178	0.285	1.870	0.299	−0.179	0.014	−1.860	0.193	−0.332	0.147	0.300	0.877
eGFR categories (≥90, 60–89, 30–59, and <30 mL/min per 1.73 m^2)												
Cockcroft-Gault vs MDRD-4	0.952	0.001	13.300	0.008	0.641	<0.001	17.550	0.001	1.579	0.002	19.220	0.004
Cockcroft-Gault vs CKD-EPI	0.171	0.551	5.660	0.214	0.571	<0.001	13.840	0.002	1.027	0.041	12.530	0.040
CKD-EPI vs MDRD-4	0.780	<0.001	10.190	0.004	0.071	0.197	3.251	0.341	0.552	0.093	7.260	0.080

After Bonferroni correction of multiplicity, *P* value for significance is established at 0.017. BARC indicates Bleeding Academic Research Consortium; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IDI, integrated discrimination improvement; MACE, major adverse cardiovascular event; MDRD-4, Modification of Diet in Renal Disease-4; NRI, net reclassification improvement.

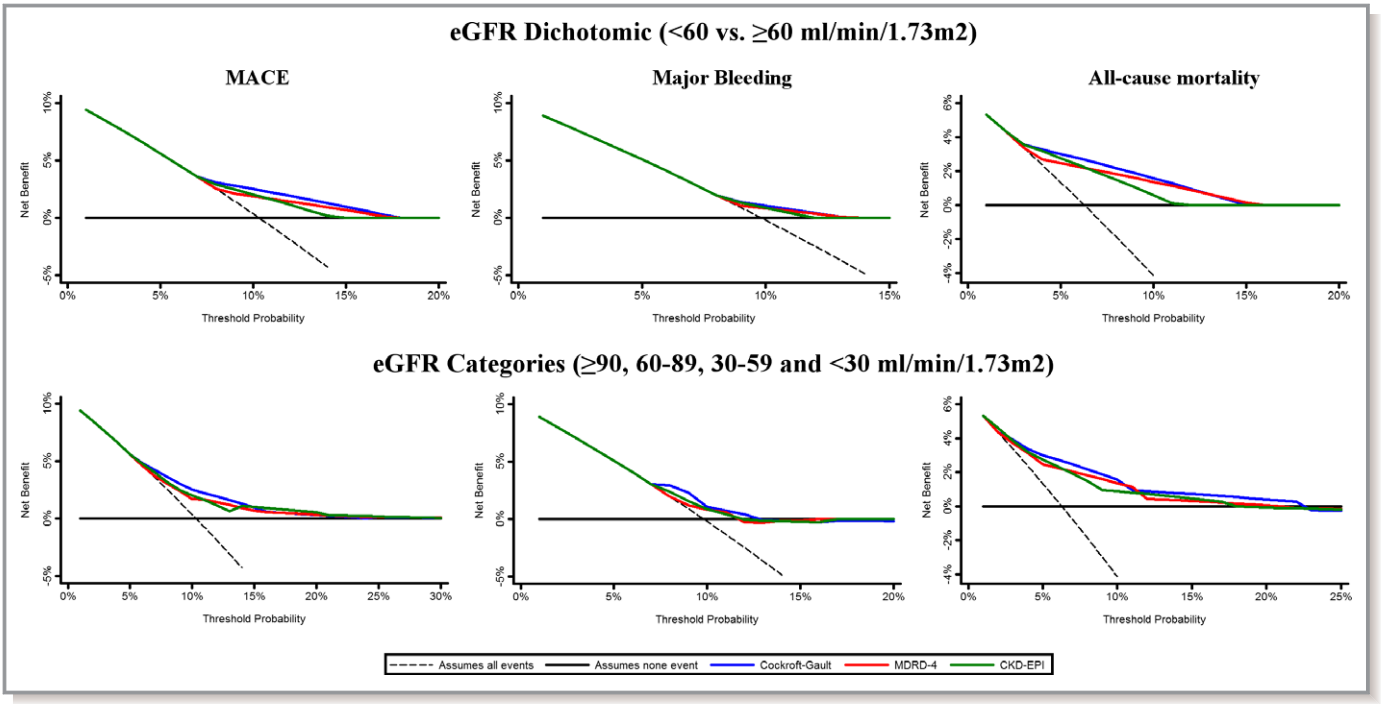

Figure 4. Decision curve analyses for major adverse cardiovascular events (MACEs), major bleeding (Bleeding Academic Research Consortium classification, 3–5), and all-cause mortality using the estimated glomerular filtration rate (eGFR) as dichotomic and as categories, according to the Cockcroft-Gault, Modification of Diet in Renal Disease-4 (MDRD-4), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Conclusions

In patients with ACS, the Cockcroft-Gault equation showed superior predictive ability for MACEs, major bleeding, and all-cause mortality compared with MDRD-4 equation, and superior predictive ability for major bleeding compared with CKD-EPI equation. The Cockcroft-Gault equation also presented higher net benefit and clinical usefulness for predicting all adverse events.

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Disclosures

None.

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