The Predictive Value of Coronary Artery Calcium Scoring for Major Adverse Cardiac Events According to Renal Function (from the Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter [CONFIRM] Registry)

Ji Hyun Lee, MD[a,b,c], Asim Rizvi, MD[a,d], Bríain Ó. Hartaigh, PhD[a], Donghee Han, MD[a,c], Mahn Won Park, MD, PhD[a], Hadi Mirhedayati Roudsari, MD[a], Wijnand J. Stuijfzand, MD[a], Heidi Gransar, MSc[e], Yao Lu, MSc[f], Tracy Q. Callister, MD[g], Daniel S. Berman, MD[h], Augustin DeLago, MD[i], Martin Hadamitzky, MD[j], Joerg Hausleiter, MD[k], Mouaz H. Al-Mallah, MD[l], Matthew J. Budoff, MD[m], Philipp A. Kaufmann, MD[n], Gilbert L. Raff, MD[o], Kavitha Chinnaiyan, MD[o], Filippo Cademartiri, MD, PhD[p], Erica Maffei, MD[q], Todd C. Villines, MD[r], Yong-Jin Kim, MD[s], Jonathon Leipsic, MD[t], Gudrun Feuchtner, MD[u], Gianluca Pontone, MD, PhD[v], Daniele Andreini, MD[v], Hugo Marques, MD, PhD[w], Pedro de Araújo Gonçalves, MD, PhD[w], Ronen Rubinshtein, MD[x], Stephan Achenbach, MD[y], Leslee J. Shaw, PhD[a], Benjamin J.W. Chow, MD[z], Ricardo C. Cury, MD[aa], Jeroen J. Bax, MD, PhD[bb], Hyuk-Jae Chang, MD, PhD[c], Erica C. Jones, MD[a], Fay Y. Lin, MD[a], James K. Min, MD[a], and Jessica M. Peña, MD[a,*]

The prognostic performance of coronary artery calcium score (CACS) for predicting adverse outcomes in patients with decreased renal function remains unclear. We aimed to examine whether CACS improves risk stratification by demonstrating incremental value beyond a traditional risk score according to renal function status. 9,563 individuals without known coronary artery disease were enrolled. Estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) was ascertained using the modified Modification of Diet in Renal Disease formula, and was categorized as: ≥90, 60 to 89, and <60. CACS was categorized as 0, 1 to 100, 101 to 400, and >400. Multivariable Cox regression was used to estimate hazard ratios (HR) with 95% confidence intervals (95% CI) for major adverse cardiac events (MACE), comprising all-cause mortality, myocardial infarction, and late

[a]Dalio Institute of Cardiovascular Imaging, Department of Radiology, New York-Presbyterian Hospital and Weill Cornell Medicine, New York, New York; [b]Division of Cardiology, Department of Internal Medicine, Myongji Hospital, Hanyang University Medical Center, Goyang-si, South Korea; [c]Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [d]Department of Radiology, Mayo Clinic, Rochester, Minnesota; [e]Department of Imaging, Cedars Sinai Medical Center, Los Angeles, California; [f]Department of Healthcare Policy and Research, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, New York; [g]Tennessee Heart and Vascular Institute, Hendersonville, Tennessee; [h]Department of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, California; [i]Capitol Cardiology Associates, Albany, New York; [j]Department of Radiology and Nuclear Medicine, German Heart Center, Munich, Germany; [k]Medizinische Klinik I der Ludwig-Maximilians-Universität München, Munich, Germany; [l]Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, Texas; [m]Department of Medicine, Los Angeles Biomedical Research Institute, Torrance, California; [n]Department of Nuclear Medicine, University Hospital and University of Zurich, Zurich, Switzerland; [o]Department of Cardiology, William Beaumont Hospital, Royal Oak, Michigan; [p]Cardiovascular Imaging Center, Department of Radiology, SDN IRCCS, Naples, Italy; [q]Department of Radiology, Area Vasta 1/ASUR Marche, Urbino, Italy; [r]Department of Cardiology, Walter Reed National Military Medical Center, Bethesda, Maryland; [s]Seoul National University Hospital, Seoul, South Korea; [t]Department of Medicine and Radiology, University of British Columbia, Vancouver, British Columbia, Canada; [u]Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria; [v]Centro Cardiologico Monzino, IRCCS Milan, Milan, Italy; [w]UNICA, Unit of Cardiovascular Imaging, Hospital da Luz, Lisboa, Portugal; [x]Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [y]Department of Cardiology, Friedrich-Alexander-University Erlangen-Nuremburg, Erlangen, Germany; [z]Department of Medicine and Radiology, University of Ottawa, Ottawa, Ontario, Canada; [aa]Department of Radiology, Miami Cardiac and Vascular Institute, Miami, Florida, USA; and [bb]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands. Manuscript received October 5, 2018; revised manuscript received and accepted January 22, 2019.

The research reported in this publication was supported by the National Institutes of Health (Bethesda, Maryland) under grant number R01 HL115150. The research was also supported, in part, by a generous gift from the Dalio Institute of Cardiovascular Imaging (New York, New York) and the Michael Wolk Foundation (New York, New York). Further, this research was supported by Leading Foreign Research Institute Recruitment Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (MSIT) grant number 2012027176.

See page 1441 for disclosure information.

*Corresponding author: Tel: (646) 962-6192; fax: (646) 962-0129.

E-mail address: jmp2003@med.cornell.edu (J.M. Peña).

0002-9149/Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2019.01.055

revascularization (>90 days). Mean age was 55.8 ± 11.5 years (52.8% male). In total, 261 (2.7%) patients experienced MACE over a median follow-up of 24.5 months (interquartile range: 16.9 to 41.1). Incident MACE increased with higher CACS across each eGFR category, with the highest rate observed among patients with CACS >400 and eGFR <60 (95.1 per 1,000 person-years). A CACS >400 increased MACE risk with HR 4.46 (95% CI 1.68 to 11.85), 6.63 (95% CI 4.03 to 10.92), and 6.14 (95% CI 2.85 to 13.21) for eGFR ≥90, 60 to 89, and <60, respectively, as compared with CACS 0. Further, CACS improved discrimination and reclassification beyond Framingham 10-year risk score (FRS) (AUC: 0.70 vs 0.64; category free-NRI: 0.51, all p <0.001) for predicting MACE in patients with impaired renal function (eGFR < 90). In conclusion, CACS improved risk stratification and provided incremental value beyond FRS for predicting MACE, irrespective of eGFR status. Published by Elsevier Inc. (Am J Cardiol 2019;123:1435−1442)

In patients with chronic kidney disease (CKD), coronary artery disease (CAD) represents the leading cause of morbidity and mortality, with coronary calcification reflecting an index of atherosclerosis severity that may predict future adverse events.[1−3] The risk of all-cause and cardiovascular mortality is amplified during early stages of CKD, particularly on the background of an estimated glomerular filtration rate (eGFR) <75 ml/min/1.73 m^2.[4] Coronary artery calcium score (CACS) determined by cardiac computed tomography (CT) is an established diagnostic imaging modality for the detection of subclinical CAD.[5] Although the association between CACS and cardiovascular mortality in persons with end-stage renal disease has been evaluated, the bulk of these observations have remained somewhat equivocal.[6−9] Furthermore, studies examining whether CACS improves prediction of cardiovascular outcomes and provides further incremental value over existing clinical risk factors in those with mild-to moderately impaired renal function are limited.[10,11,22] In light of the scant evidence, further large-scale prospective studies would appear warranted for assessing the usefulness of CACS for prognostication among patients with varying stages of renal function. Using data from a large international multicenter cohort of patients with suspected CAD, we sought to determine the extent to which CACS improves prediction of major adverse cardiac events (MACE) according to baseline renal function, and whether CACS provides incremental value beyond established risk factors.

Methods

The design of the CONFIRM (COronary CT Angiography EvaluatioN for Clinical Outcomes: An InteRnational Multicenter) registry has been previously described elsewhere.[12] Briefly, the CONFIRM registry is a large, prospective, international dynamic observational study of 27,125 patients in 6 countries designed to evaluate the prognostic value of coronary CT angiography (CCTA) findings for predicting future mortality and MACE. Patients were considered eligible if they were 18 years or older, had undergone evaluation by CCTA scanner with 64-detector rows or greater, and presented with an interpretable CCTA. Patients with the following were excluded: missing information for baseline factors including age or gender (n = 106), creatinine (n = 12,131), and CACS (n = 2,386), known previous CAD at the time of CCTA, as defined by previous MI or coronary revascularization such as coronary artery bypass graft surgery and percutaneous coronary intervention (n = 821), eGFR >150 ml/min/1.73 m^2 (n = 119), missing information for MACE (n = 1,653), and early revascularization <90 days from index CCTA (n = 346). Overall, the analytic sample comprised 9,563 patients, where current analysis largely includes symptomatic individuals. Each of the study centers' institutional review boards approved the study protocol, and all participants provided written informed consent.

All patients were assessed at the time of CCTA examination. Baseline demographics and traditional cardiovascular risk factors including age, gender, hypertension, diabetes, dyslipidemia, and current smoking status were collected for all patients. Subsequently, we calculated Framingham 10-year coronary heart disease risk scores (FRS).[13]

Standardized serum creatinine was utilized to evaluate renal function and eGFR was calculated for each patient using the Levey Modification of Diet in Renal Disease (MDRD) formula: eGFR = 175 × serum creatinine − 1.154 × age − 0.203 [× 0.742, if female].[14] The eGFR was expressed as ml/min/1.73 m^2. For the purpose of this study, all enrolled patients were stratified into 3 categories according to renal function status: normal (eGFR ≥ 90 ml/min/1.73 m^2), mildly decreased (eGFR 60 to 89 ml/min/1.73 m^2), and moderate-to-severely decreased (eGFR < 60 ml/min/1.73 m^2) on the basis of the Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guidelines for the Evaluation and Management of CKD.[15] In addition, we defined eGFR <60 ml/min/1.73 m^2 as the presence of CKD.[15]

All testing, data acquisition and image postprocessing, and data interpretation for CCTA and CACS in CONFIRM were performed according to the Society of Cardiovascular Computed Tomography guidelines.[16] Multidetector row CT scanners consisting of 64 rows or greater acquired CACS as well as CCTA. Strategies for radiation dose reduction, which included prospective electrocardiographic (ECG)-gated axial acquisition or ECG-gated tube-current modulation and tube voltage reduction, were employed. CACS was calculated in accordance with the methods described previously by Agatston et al.[17] CACS was then categorized into 4 groups as: 0 (very low), 1 to 100 (mild), 101 to 400 (moderate), and >400 (severe), respectively.

The primary study end point was a composite of MACE, which included all-cause mortality (ACM), nonfatal myocardial infarction (MI), unstable angina, and late target vessel revascularization (>90 days). Specific causes of death were not recorded in the CONFIRM registry. Follow-up

procedures were approved by all study centers' institutional review boards. Trained personnel from each site adjudicated ACM by direct interview with physicians and/or witnesses, by review of hospital records, or by querying national medical databases. Other nonfatal events such as MI as defined by the Universal Definition of MI,[18] unstable angina, and late target revascularization were collected via a combination of direct questioning of patients using a scripted interview and examination of the patients' medical records as previously described.[12]

Baseline characteristics according to eGFR subsets were compared using chi-square test, Fisher's exact test, or Student's *t* test as appropriate. Initial visual assessment of histograms, scatterplots, and tests for normality showed that CACS and eGFR were both non-normally distributed and best transformed toward normality. Furthermore, residual analysis via residuals versus fitted values also showed the relation between CAC and eGFR to be nonlinear. Thus, we fit a fractional polynomial model, which allows for nonlinear associations, to examine the relation between CACS and eGFR.[19] We calculated the incidence of MACE per 1,000 person-years by dividing the number of MACE events by the absolute number of person-years at risk according to the category of CACS in each eGFR subset. We constructed Cox proportional hazards models to calculate the hazard ratios and associated 95% confidence intervals for the risk of MACE in each category of CACS, eGFR, and FRS. Covariates were included in a multivariable based on a priori clinical knowledge. Model 1 was adjusted for age and gender, and Model 2 was further adjusted for the remaining individual FRS factors including hypertension, diabetes, dyslipidemia, and current smoking. In additional analyses, we tested for possible effect modification between eGFR and CACS with MACE by using an interaction term in the fully adjusted model. To compare the risk of MACE between different categories of CACS, we used the Kaplan-Meier method and compared differences with log-rank tests for equality. Discriminatory ability was assessed by estimating the C-statistic in a model containing FRS, and separately FRS with CACS added. Areas under the receiver-operating characteristic curves (AUC) with 95% CI were then compared to evaluate model discrimination for the prediction of MACE according to eGFR subsets. We then assessed category-free net reclassification improvement (cNRI) for predicting MACE among those with renal impairment based on an eGFR <90 ml/min/1.73 m^2, 60 to 89 ml/min/1.73 m^2, and <60 ml/min/1.73 m^2. In a sensitivity analysis, we examined the association between CACS and MACE, excluding late revascularization from the combined end point. All statistical analyses were performed using STATA version 14 (StataCorp LP, College Station, TX), and a two-tailed p value less than 0.05 was considered statistically significant.

Results

Overall, the study population consisted of 9,563 participants; 52.8% were male; mean age of the cohort was 56 ± 12 years; and median follow-up duration was 24.5 months (interquartile range 16.9 to 41.1). Baseline characteristics of the study population according to eGFR subsets are shown in Table 1. Among the study cohort, 2,312 (24.2%) had eGFR ≥90 ml/min/1.73 m^2, 6,122 (64.0%) had eGFR 60 to 89 ml/min/1.73 m^2, and 1,129 (11.8%) had eGFR <60 ml/min/1.73 m^2. A total of 222 (2.3%) of patients had eGFR <45 ml/min/1.73 m^2. Patients with decreased renal function were generally older and had a higher prevalence of hypertension, diabetes, and dyslipidemia. Information regarding FRS was available among 9,378 (98.1%) patients. Among them, patients with decreased renal function also had higher FRS as compared with those with normal eGFR (p <0.001). The prevalence of obstructive CAD (as defined by stenosis severity >50% and >70%) in the cohort was 12% and 4.4%, respectively.

Overall, 54.5% of the study population had CACS 0, whereas 25.3% had CACS 1 to 100, 13.1% had CACS 101 to 400, and 7.1% had CACS >400. Overall, men had a higher prevalence of CAC than women in each eGFR subset (not shown). The relation of CACS with renal function is displayed in Figure 1. That is, with a decline in renal function, there was an increase in CACS. The frequency of CACS in each eGFR subset is displayed in Figure 1. Patients in the lowest eGFR subset (<60 ml/min/1.73 m^2) had the lowest prevalence of zero CACS (43.5%) and the highest frequency of CACS >400 (8.7%).

Figure 2 demonstrates the incidence of MACE per 1,000 person-years according to CACS and eGFR subsets. The incidence of MACE increased with higher CACS across each eGFR category. Notably, the lowest incidence of MACE was observed among those with a zero CACS and eGFR ≥90 ml/min/1.73 m^2 (3.9 per 1,000 person-years), whereas those with a CACS >400 and eGFR <60 ml/min/1.73 m^2 had the highest incidence of MACE (95.1 per 1,000 person-years). Among the 5,215 (54.5%) participants with a zero CACS, the overall incidence of MACE was 4.8 per 1,000 person-years. Among participants with a zero CACS, declining renal function was associated with an increase in the rate of MACE (e.g., 3.9, 4.4, and 10.0 per 1,000 person-years for eGFR ≥90, 60 to 89, and <60 ml/min/1.73 m^2, respectively).

Overall, MACE was observed in 261 patients (2.7%) during follow-up, which included 74 cases of ACM (28.4%), 39 (14.9%) nonfatal MI or unstable angina, 124 (47.5%) late revascularization, 5 (1.9%) concurrent ACM with nonfatal MI/unstable angina, 17(6.5%) concurrent nonfatal MI/unstable angina with late revascularization, 1 (0.4%) concurrent ACM with late revascularization, and 1 (0.4%) case of 3 concurrent components of MACE (0.4%). Among the total 1,129 patients with an eGFR <60 ml/min/1.73 m^2, a total of 63 (5.6%) experienced MACE. Supplemental Table 1 shows univariate associations between clinical risk factors, CACS, eGFR, and MACE. Increasing CACS was associated with an increased risk of MACE (HR for CACS >400 9.86 95% CI 6.97 to 13.95).

Table 2 demonstrates unadjusted and adjusted HRs for MACE in each CACS categories by subsets of eGFR. Following adjustment, increasing CACS categories increased the risk of MACE across all subsets of renal function. The presence of CACS >400 increased the risk of MACE by 4.46 (95% CI 1.68 to 11.85), 6.63 (95% CI 4.03 to 10.92), and 6.14 (95% CI 2.85 to 13.21) in patients with eGFR ≥90, 60 to 89, and <60 ml/min/1.73 m^2, respectively. Of

Table 1
Baseline characteristics

Variable	All patients (n = 9,563)	eGFR (ml/min/1.73 m^2)			p Value
		≥90 (n = 2,312)	60-89 (n = 6,122)	<60 (n= 1,129)	
Age (years)	56 ± 12	50 ± 12	57 ± 10	63 ± 10	<0.001
Men	5,049 (52.8%)	1,299 (56.2%)	3,290 (53.7%)	460 (40.7%)	<0.001
Body mass index (kg/m^2)	27.3 ± 5.3	27.8 ± 5.6	26.9 ± 4.9	28.2 ± 6.1	<0.001
Creatinine (mg/dl)	0.9 ± 0.6	0.7 ± 0.1	0.9 ± 0.2	1.4 ± 1.5	<0.001
Current smoker	1,336 (14.1%)	413 (18.1%)	789 (13.1%)	134 (11.9%)	<0.001
Hypertension	4,447 (47.4%)	871 (38.5%)	2,865 (47.7%)	711 (63.3%)	<0.001
Diabetes mellitus	1,248 (13.2%)	235 (10.3%)	810 (13.4%)	203 (18.0%)	<0.001
Dyslipidemia	5,236 (55.4%)	1,043 (45.9%)	3,521 (58.2%)	672 (59.8%)	<0.001
Family history of coronary artery disease	2,438 (26.2%)	715 (32.5%)	1,439 (24.1%)	284 (25.5%)	<0.001
White	3,846 (46.0%)	1,291 (62.7%)	2,114 (39.6%)	441 (45.5%)	<0.001
East Asian	3,635 (43.5%)	512 (24.9%)	2,769 (51.9%)	354 (36.5%)	
Black and other	882 (10.6%)	256 (12.4%)	452 (8.5%)	174 (18.0%)	
Framingham risk score	10.9 ± 8.3	8.9 ± 7.4	11.3 ± 8.2	13.1 ± 9.5	<0.001

eGFR = estimated glomerular filtration rate.

note, there was no significant interaction between eGFR subsets and CACS categories ($P_{interaction} = 0.98$). In Figure 3, Kaplan-Meier survival curves display the rate of incident MACE for increasing CACS according to each subgroup of eGFR (p <0.001 for log-rank test of equality, all). Overall, our findings remained consistent in a sensitivity analysis excluding late revascularization from the primary end point. CACS >400 was associated with an increased risk of MACE with HR of 3.98 (95% CI 1.13 to 14.05), 3.78 (95% CI 1.86 to 7.71), and 4.92 (95% CI 1.90 to 12.73) in patients with eGFR ≥90, 60 to 89, and <60 ml/min/1.73 m^2, respectively.

Among patients with impaired renal function (eGFR <90 ml/min/1.73 m^2), the addition of CACS significantly improved incremental utility above FRS alone for prediction (AUC: 0.70 vs 0.64, p <0.001) as well as reclassification (cNRI: 0.51, p <0.001) of MACE. The addition of CACS further improved discrimination and reclassification beyond FRS alone among those with an eGFR 60 to 89 ml/min/1.73 m^2 (AUC: 0.71 vs 0.66 p <0.001, and cNRI: 0.46, p <0.001) as well as an eGFR <60 ml/min/1.73 m^2 (AUC: 0.69 vs 0.55, p <0.001, and cNRI: 0.68, p <0.001).

Discussion

Using data from the CONFIRM registry, we sought to determine whether CACS improved risk stratification and prediction of future adverse cardiovascular events in patients with suspected CAD when stratified by subsets of renal function. Our findings demonstrated that CACS proved useful for risk prediction in patients irrespective of the level of renal function. The presence of any CAC was associated with a 3- to 4-fold increase in the risk of MACE among all eGFR categories with no evidence of effect

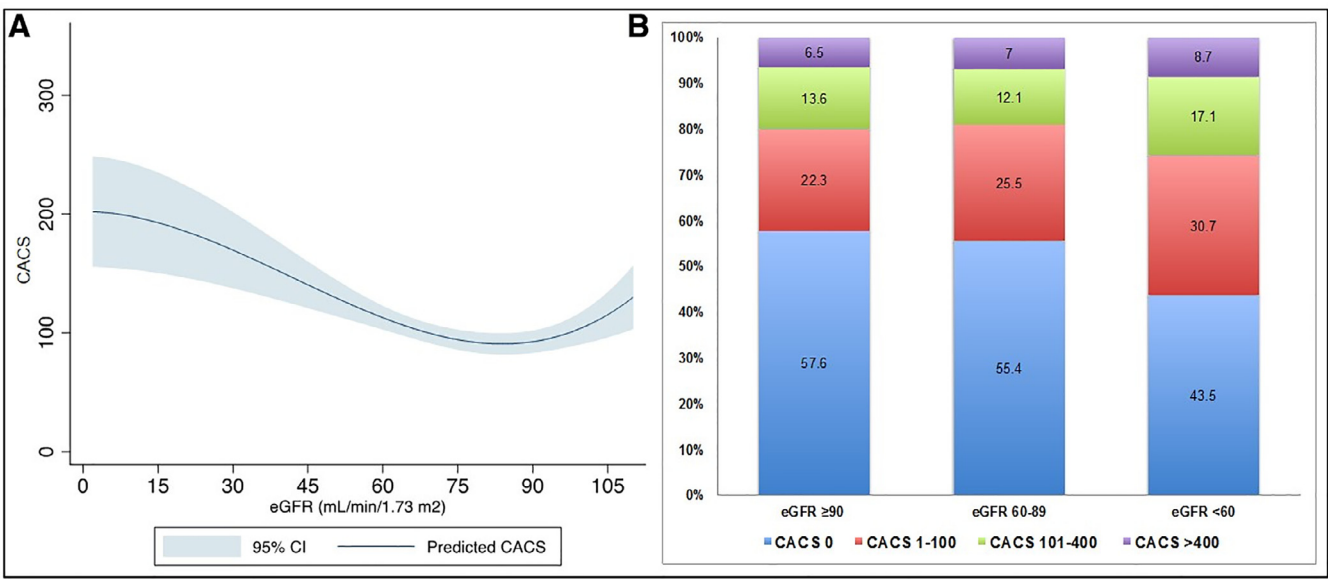
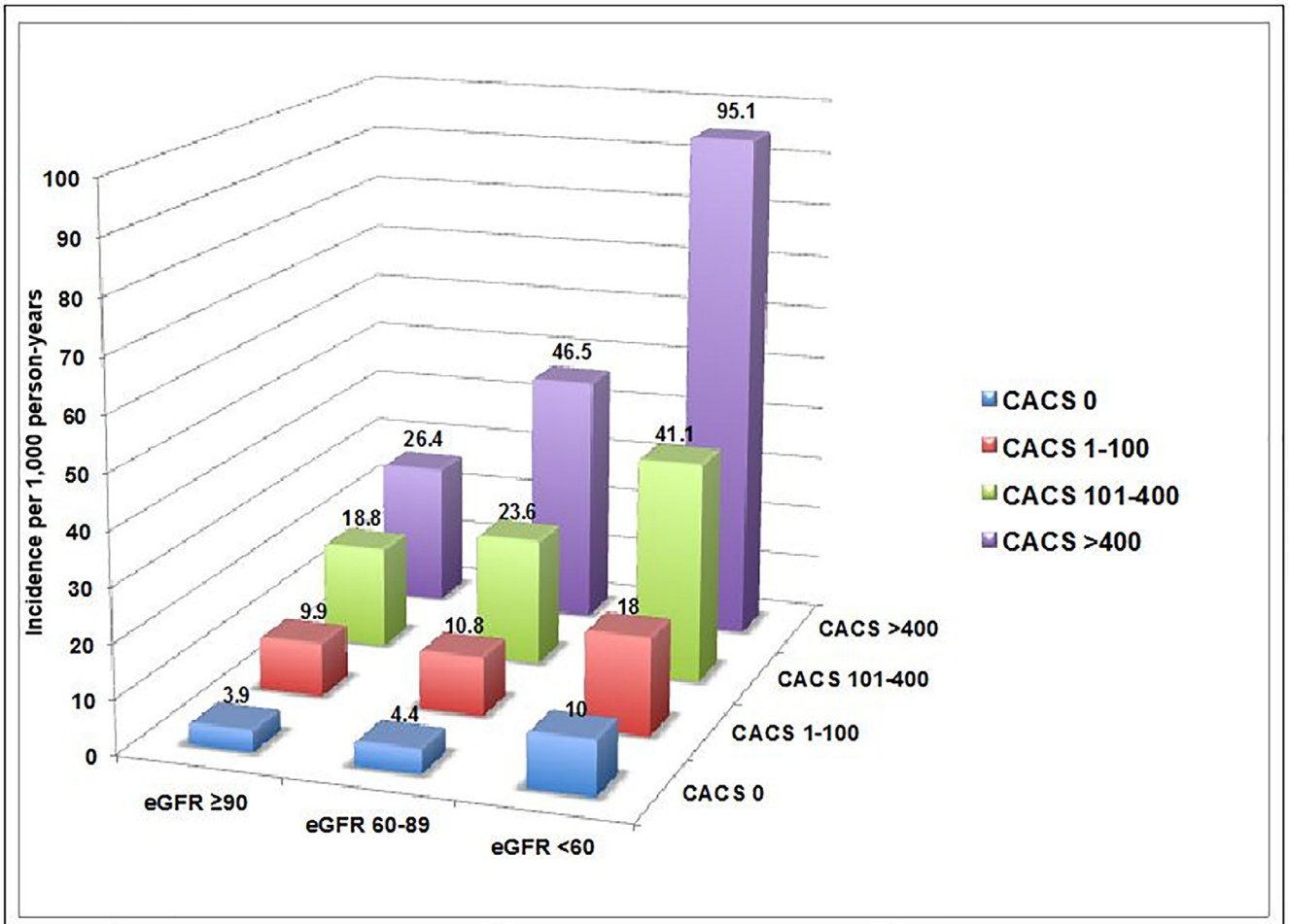


Figure 1. Association of CACS with renal function. (*A*) Fractional polynomial model demonstrating the pattern between CACS and eGFR; (*B*) distribution of CACS by subsets of eGFR. CACS = coronary artery calcium score; eGFR = estimated glomerular filtration rate (ml/min/1.73 m^2).



	eGFR ≥ 90				eGFR 60-89				eGFR <60			
CACS	0	1-100	101-400	>400	0	1-100	101-400	>400	0	1-100	101-400	>400
no. events/no. at risk (%)	11/1,332	10/515	10/314	7/151	39/3,392	41/1,557	39/742	41/431	12/491	15/347	17/193	19/98
	(0.8)	(1.9)	(3.2)	(4.6)	(1.2)	(2.6)	(5.3)	(9.5)	(2.4)	(4.3)	(8.8)	(19.4)

Figure 2. Incidence of MACE per 1,000 person-years according to CACS categories by subsets of eGFR. CACS = coronary artery calcium score; eGFR = estimated glomerular filtration rate (ml/min/1.73 m^2); MACE = major adverse cardiac events.

modification. Although any CAC increased the risk of MACE in this cohort regardless of renal function, the highest absolute risk of MACE was observed in the subgroup with CACS >400 and eGFR <60. Last, CAC screening provided further incremental value for predicting MACE over a traditional risk score for patients with mild-to-severely decreased renal function.

The prognostic utility of CACS screening has been well documented. However, there is a paucity of data related to the incidence, and prognostication of CACS in patients with CKD not receiving dialysis. Despite several small studies reporting conflicting findings between CACS and CKD, a recent set of cross-sectional studies have shown a graded relation between both parameters.[20,21] The Dallas Heart Study revealed an association between stage 3 to 5 CKD and increasing CACS, which was more prevalent among diabetic patients.[21] Likewise, Budoff et al showed a graded relation between severity of CKD and CACS that was independent of conventional risk factors.[20] The present study results are keeping with those findings as we have demonstrated an increased prevalence of CACS in patients with increasing renal dysfunction in a large international registry. Furthermore, deteriorating renal function was associated with an increased incidence of MACE even in patients with a zero CACS. This finding might be related in part to noncardiac causes of death, and possibly more frequent in patients with either moderate-to-severely decreased renal function or on dialysis. Indeed, our data showed increased rates of ACM according to deteriorating renal function (e.g., 11 [0.5%], 38 [0.6%], and 32 [2.8%] for eGFR ≥90, 60 to 89, and <60 ml/min/1.73 m^2, respectively), among those with zero CACS.

Table 2
Unadjusted and adjusted Cox proportional hazard ratios for MACE according to CACS categories by subsets of eGFR

Variable	Unadjusted		Model 1		Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
eGFR ≥90						
Any CACS	3.60 (1.78-7.29)	<0.001	2.71 (1.31-5.60)	0.01	2.55 (1.22-5.30)	0.01
CACS categories						
0	1 (ref)		1 (ref)		1 (ref)	
1-100	2.46 (1.04-5.80)	0.04	1.96 (0.82-4.67)	0.13	1.68 (0.68-4.14)	0.26
101-400	4.41 (1.95-10.5)	0.001	3.23 (1.33-7.85)	0.01	3.15 (1.29-7.66)	0.01
>400	6.31 (2.42-16.44)	<0.001	4.43 (1.66-11.8)	0.003	4.46 (1.68-11.85)	0.003
eGFR 60-89						
Any CACS	4.27 (2.97-6.13)	<0.001	3.24 (2.21-4.73)	<0.001	3.09 (2.08-4.59)	<0.001
CACS categories						
0	1 (ref)		1 (ref)		1 (ref)	
1-100	2.45 (1.58-3.80)	<0.001	2.07 (1.32-3.24)	0.002	2.01 (1.27-3.20)	0.003
101-400	5.25 (3.37-8.19)	<0.001	4.10 (2.57-6.53)	<0.001	4.03 (2.50-6.49)	<0.001
>400	10.10 (6.50-15.69)	<0.001	7.35 (4.57-11.84)	<0.001	6.63 (4.03-10.92)	<0.001
eGFR <60						
Any CACS	3.51 (1.87-6.58)	<0.001	2.73 (1.43-5.23)	0.002	2.54 (1.32-4.87)	0.01
CACS categories						
0	1 (ref)		1 (ref)		1 (ref)	
1-100	1.83 (0.86-3.91)	0.12	1.58 (0.73-3.40)	0.25	1.50 (0.69-3.25)	0.30
101-400	3.98 (1.90-8.35)	<0.001	3.16 (1.47-6.77)	0.003	2.85 (1.32-6.13)	0.01
>400	9.16 (4.44-18.89)	<0.001	6.93 (3.24-14.81)	<0.001	6.14 (2.85-13.21)	<0.001

CACS = coronary artery calcium score; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MACE = major adverse cardiac events.

Model 1 adjusted for age and gender. Model 2 further adjusted for individual Framingham risk factors including current smoking, hypertension, diabetes, and dyslipidemia.

Although CAC screening may generally provide valuable prognostic data, whether this tool can improve the risk stratification of patients with renal impairment remains a question. To date, there have been few studies examining the prognostic utility of CACS in patients with CKD.[10,11] The Multi-Ethnic Study of Atherosclerosis revealed that CAC screening was independently associated with global cardiovascular disease including CAD, and appeared to improve prediction of adverse cardiovascular outcomes in patients with CKD.[22] Our study results are congruent with these findings as we also demonstrated that increasing CACS severity increased the risk of MACE across varying degrees of renal impairment. Chaikriangkrai et al examined the prognostic implications of both CACS and renal function in symptomatic patients with suspected CAD and found that not only were CACS and renal function independent predictors of future adverse events, but both also provided incremental value to each other as well as beyond the FRS and thrombolysis in MI (TIMI) risk score.[11] In keeping with these findings, our study demonstrated the prognostic utility of CACS for predicting MACE in patients with normal or mildly decreased renal function, as well as among those with moderate-to-severe renal dysfunction, thereby broadening the notion that CACS might further improve discriminatory ability and reclassification by forecasting

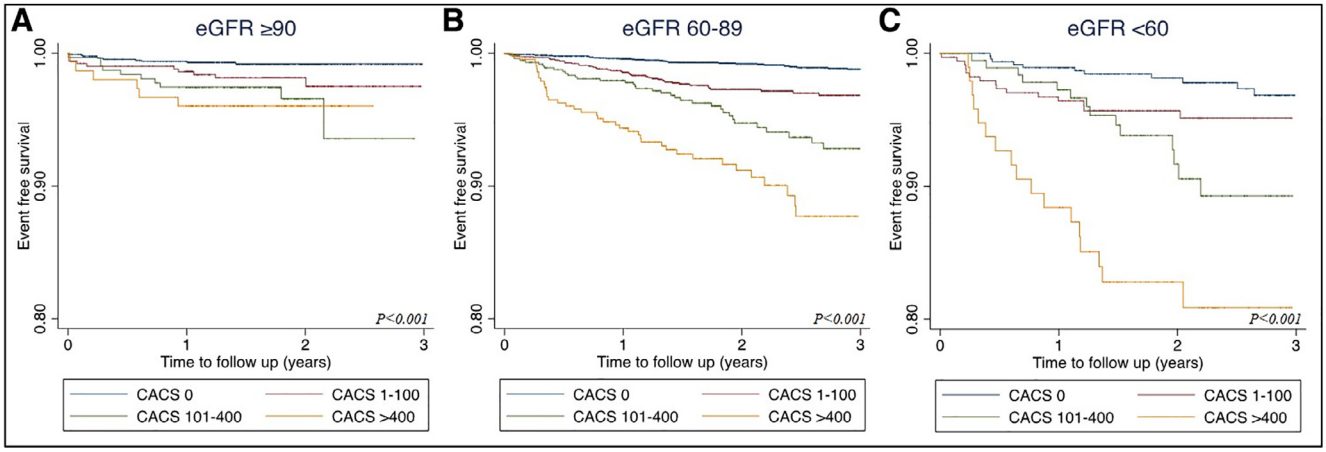


Figure 3. Kaplan-Meier survival curves for MACE according to CACS categories by subsets of eGFR. CACS = coronary artery calcium score; eGFR = estimated glomerular filtration rate (ml/min/1.73 m^2); MACE = major adverse cardiac events.

adverse outcomes in patients with mildly decreased renal function as well as in those with more advanced CKD.

In the general population, vascular calcification typically occurs at the intimal level, which is not only related to calcified atherosclerotic plaque in coronary vessels but also with ischemic cardiac outcomes such as acute coronary syndromes.[23] Conversely, in patients with CKD, calcification in a vessel can also occur at the medial level, resulting in vascular stiffness, left ventricular hypertrophy, and congestive heart failure.[24,25] These concomitant processes may both be at play in the relation between CACS and MACE in patients with CKD. Although, it remains challenging for cardiac CT to differentiate between these types of calcification,[26] both correlate with atherosclerotic and arteriosclerotic plaque and amplify adverse cardiovascular outcomes in patients with CKD. In light of this, the present study findings underscore the clinical usefulness of utilizing CAC screening in patients with varying renal function. CAC screening may be particularly valuable in planning primary prevention interventions in asymptomatic individuals. Current American Heart Association/American College of Cardiology guidelines for the management of cholesterol now consider it reasonable to use CAC screening in situations where a decision regarding statins is uncertain, including individuals who may have risk enhancing conditions such as CKD.[27]

This study has some limitations that bear mentioning. Despite our attempts to control for important confounders, given the observational nature of the present study, there remains the possibility of residual confounding and selection bias. The majority of patients presented with a mildly decreased eGFR level, hence, caution should be taken when attempting to extrapolate our findings to others with varying eGFR levels, including those with more advanced CKD, such as patients on dialysis. It is plausible that eGFR <60 ml/min/1.73 m^2 might include some patients on dialysis; therefore, other causes of mortality such as those related to dialysis-related complications might have played a role. Other markers of kidney damage necessary for defining CKD, such as albuminuria or urine sediment abnormalities, were not available in our registry. Also, we used a single-time point evaluation of eGFR, and cannot discount the possibility of sampling errors, which may have led to some misclassification in renal function categorization. We further cannot exclude the possibility of misclassification of patients due to the MDRD formula, originally derived from a population with CKD, and may have led to an underestimation of eGFR in those with a normal eGFR ≥90 ml/min/1.73 m^2.[28] To this end, a more recently developed CKD-Epidemiology Collaboration equation conferred less of an underestimation of eGFR in patients with normal renal function, and a more accurate classification for the risk of mortality as well as end-stage renal disease, when compared with the MDRD formula.[29,30] Also, the CONFIRM registry did not reflect a typical CAC screening population, since the current analysis largely includes symptomatic individuals. In addition, the majority of MACE events were late revascularizations, which may be reflective of the burden of obstructive disease. Therefore, caution should be taken in extrapolating our findings to an asymptomatic population undergoing CAC screening.

Disclosures

Dr. James K. Min receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare. Dr. Min serves on the scientific advisory board of Arineta and GE Healthcare, and has an equity interest in Cleerly. Dr. Gianluca Pontone is a member of the speakers' bureau for GE Healthcare, Bracco, and Medtronic. He also conducts research for GE Healthcare and Heartflow. Dr. Matthew Budoff receives grant support from GE Healthcare and the NIH. All other authors have no relevant disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2019.01.055.

1. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 2005;293:1737–1745.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–1305.
3. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol* 1998;31:126–133.
4. Chronic Kidney Disease Prognosis ConsortiumMatsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;375:2073–2081.
5. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308:788–795.
6. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007;71:438–441.
7. Fensterseifer DM, Karohl C, Schvartzman P, Costa CA, Veronese FJ. Coronary calcification and its association with mortality in haemodialysis patients. *Nephrology* 2009;14:164–170.
8. Shimoyama Y, Tsuruta Y, Niwa T. Coronary artery calcification score is associated with mortality in Japanese hemodialysis patients. *J Ren Nutr* 2012;22:139–142.
9. Matsuoka M, Iseki K, Tamashiro M, Fujimoto N, Higa N, Touma T, Takishita S. Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis. *Clin Exp Nephrol* 2004;8:54–58.
10. Chiu YW, Adler SG, Budoff MJ, Takasu J, Ashai J, Mehrotra R. Coronary artery calcification and mortality in diabetic patients with proteinuria. *Kidney Int* 2010;77:1107–1114.
11. Chaikriangkrai K, Nabi F, Mahmarian JJ, Chang SM. Additive prognostic value of coronary artery calcium score and renal function in patients with acute chest pain without known coronary artery disease: up to 5-year follow-up. *Int J Cardiovasc Imaging* 2015;31:1619–1626.
12. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah MH, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan KM, Chow B, Delago A, Hadamitzky M, Hausleiter J, Karlsberg RP, Kaufmann P, Maffei E, Nasir K, Pencina MJ, Raff GL, Shaw LJ, Villines TC. Rationale and design of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) Registry. *J Cardiovasc Comput Tomogr* 2011;5:84–92.
13. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–1847.

14. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology C. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007;53:766–772.
15. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int* 2014;85:49–61.
16. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2009;3:190–204.
17. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
18. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007;28:2525–2538.
19. Baneshi MR, Nakhaee F, Law M. On the use of fractional polynomial models to assess preventive aspect of variables: an example in prevention of mortality following HIV infection. *Int J Prev Med* 2013;4:414–419.
20. Budoff MJ, Rader DJ, Reilly MP, Mohler ER, 3rd LJ, Yang W, Rosen L, Glenn M, Teal V, Feldman HI, Investigators CS. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2011;58:519–526.
21. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. *J Am Soc Nephrol* 2005;16:507–513.
22. Matsushita K, Sang Y, Ballew SH, Shlipak M, Katz R, Rosas SE, Peralta CA, Woodward M, Kramer HJ, Jacobs DR, Sarnak MJ, Coresh J. Subclinical atherosclerosis measures for cardiovascular prediction in CKD. *J Am Soc Nephrol* 2015;26:439–447.
23. Haydar AA, Hujairi NM, Covic AA, Pereira D, Rubens M, Goldsmith DJ. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. *Nephrol Dial Transplant* 2004;19:2307–2312.
24. Moody WE, Edwards NC, Chue CD, Ferro CJ, Townend JN. Arterial disease in chronic kidney disease. *Heart* 2013;99:365–372.
25. Hruska KA, Mathew S, Lund R, Qiu P, Pratt R. Hyperphosphatemia of chronic kidney disease. *Kidney Int* 2008;74:148–157.
26. Gross ML, Meyer HP, Ziebart H, Rieger P, Wenzel U, Amann K, Berger I, Adamczak M, Schirmacher P, Ritz E. Calcification of coronary intima and media: immunohistochemistry, backscatter imaging, and x-ray analysis in renal and nonrenal patients. *Clin J Am Soc Nephrol* 2007;2:121–134.
27. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol. *Circulation* 2018, CIR0000000000000625. [Epub ahead of print].
28. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 2005;16:459–466.
29. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
30. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR, Levey AS. Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012;307:1941–1951.