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Association of Estimated Glomerular Filtration Rate and Proteinuria With Lipid-Rich Plaque in Coronary Artery Disease

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Background: Estimated glomerular filtration rate (eGFR) and proteinuria are both important determinants of the risk of cardiovascular disease and mortality. The aim of the present study was to investigate the independent and combined effects of eGFR and proteinuria on tissue characterization of the coronary plaques of culprit lesions.

Methods and Results: Conventional intravascular ultrasound and 3-D integrated backscatter intravascular ultrasound (IB-IVUS) were performed in 555 patients undergoing elective percutaneous coronary intervention. They were divided into 2 groups according to the absence or presence of proteinuria (dipstick result ≥1+). Patients with proteinuria had coronary plaque with significantly greater percentage lipid volume compared with those without (43.6±14.8% vs. 48.6±16.1%, P=0.005). Combined analysis was done using eGFR and absence or presence of proteinuria. Subjects with eGFR 45–59 ml/min/1.73 m^2 and proteinuria were significantly more likely to have higher percent lipid volume compared with those with eGFR >60 ml/min/1.73 m^2 without proteinuria. After multivariate adjustment for confounders, the presence of proteinuria proved to be an independent predictor for lipid-rich plaque (OR, 1.85; 95% CI: 1.12–3.06, P=0.016).

Conclusions: The addition of proteinuria to eGFR level may be of value in the risk stratification of patients with coronary artery disease. (*Circ J* 2015; **79:** 2263–2270)

Key Words: Coronary artery disease; Integrated backscatter intravascular ultrasound; Lipid-rich plaque; Proteinuria

Chronic kidney disease (CKD) is an established risk factor for adverse cardiovascular outcomes in various clinical presentations.[1–3] It is now widely accepted that both renal filtration function and proteinuria are independent predictors of cardiovascular disease (CVD).[4–6] In addition, it has been reported that these patients have more vulnerable coronary plaques as estimated glomerular filtration rate (eGFR) decreases.[7,8] Few studies, however, have examined the relationship between coronary plaque composition and proteinuria.

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The recent development of integrated backscatter intravascular ultrasound (IB-IVUS) has enabled analysis of the tissue components of coronary plaque.[9,10] Recent studies have suggested that lipid-rich plaque detected on IB-IVUS is more frequently seen in patients with acute coronary syndrome (ACS), increased insulin resistance and reduced eGFR.[11–13] In addition, it has been reported that lipid-rich plaque may predict future coronary events and major adverse clinical events after percutaneous coronary intervention (PCI).[14,15]

The aim of the present study was to investigate the independent and combined effects of eGFR and proteinuria on tissue characterization of coronary plaque, using IB-IVUS.

Methods

Subjects

This observational study included 823 patients who were successfully treated with PCI between September 2008 and March 2014 at Nagoya University Hospital. Exclusion criteria were

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eGFR<15 ml/min/1.73 m^2 (n=22, including 11 hemodialysis patients), ACS (n=239; CKD, n=112; non-CKD, n=127), and failing to pass IVUS catheter to the severe calcified culprit lesions (n=7; CKD, n=5; non-CKD, n=2). After exclusion of these patients, a total of 555 patients were evaluated in the present study. All patients had stable angina pectoris and documented myocardial ischemia. This study was approved by the research and ethics committees, and was conducted in accordance with 1975 Declaration of Helsinki. Written informed consent was obtained from all patients before any procedures were conducted.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current anti-hypertensive medication. Diabetes mellitus was defined as the use of anti-hyperglycemic medication, current diagnosis of diabetes, fasting plasma glucose concentration >126 mg/dl, or glycosylated hemoglobin concentration ≥6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, triglycerides ≥150 mg/dl, or current lipid-lowering medication. Smoking habit was defined as current habit or discontinuation ≤6 months before PCI.

Laboratory Findings

Various lipid and inflammatory profiles were measured by commercial radioimmunoassay kit and assays. For this purpose, blood samples were collected from all patients before PCI after 12-h overnight fast. Serum creatinine was measured using the isotope-dilution mass spectrometry traceable enzymatic method. eGFR was calculated according to the new Japanese equation: eGFR (ml/min/1.73 m^2)=194×serum creatinine−1.094×age−0.287×0.739 (female).[16] Patients were classified into one of 4 categories (eGFR ≥60, 45–59, 30–44, or 15–29 ml/min/1.73 m^2) according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.[5] Reduced eGFR was defined as <60 ml/min/1.73 m^2. Proteinuria (−, ±, 1+, or ≥2+) was assessed using a dipstick test for spot-urine (Uropaper αIII; Eikenkagaku, Japan). Proteinuria was defined as present if the dipstick result was ≥1+.

QCA and IVUS Analysis

All patients had received dual antiplatelet therapy with aspirin and thienopyridine derivatives before PCI. In addition, any statins had been administered for ≥1 month before PCI. Intracoronary infusion of isosorbide dinitrate was used to achieve maximum vasodilatation before angiography for quantitative coronary angiography (QCA) and IVUS. We analyzed the culprit lesion, defined as the most stenotic of the lesions responsible for clinical symptoms and abnormalities on echocardiography and/or myocardial scintigraphy. Coronary angiograms were obtained before PCI. The projection showing the maximum degree of stenosis was selected for QCA, which was analyzed using a contour detection minimum cost algorithm (QCA-CMS version 3.0; MEDIS, Leiden, Netherlands), and we defined lesion type according to the American Heart Association/American College of Cardiology (AHA/ACC) classification as previously described.[17] A commercially available IVUS imaging system (View It; Terumo, Tokyo, Japan) was used to perform IVUS. After insertion of the guidewire into the PCI-treated coronary artery, the IVUS catheter was advanced 10 mm distal to the lesion, and images were obtained inside the coronary artery up to 10 mm proximal to the lesion. The images were obtained at a rate of 0.5 mm/s with a motored pull-back device and a commercial scanner. IB-IVUS was not performed when patients had severe calcification lesions that were difficult to cross with the IVUS catheter.

The cross-sectional area (CSA) of the external elastic membrane (EEM) was measured by tracing the leading edge of the adventitia. The plaque plus media CSA was calculated as the EEM–lumen CSA. The plaque area percentage was defined as (EEM area−luminal area)/EEM area×100. The plaque volume percent was calculated as (EEM volume−luminal volume)/EEM volume.[18] Coronary stents were implanted with or without pre-dilation. The operator, who was blinded to patient characteristics and treatment, selected the position and length of the angioplasty and stent implantation according to angiography and conventional IVUS findings.

IB signals were obtained with a commercially available system connected to the IVUS imaging system (IB-IVUS; YD, Nara, Japan). The IB value for each tissue component was calculated as an average power of the ultrasound backscattered signal from a small volume of tissue using a fast Fourier transform, measured in decibels (dB). The definition of the IB value was determined for each of 3 histologic categories: fibrous area, lipid area, and high-signal area (calcification on the inner surface). The percentage of fibrous volume (%FV; FV/plaque volume), percentage of lipid volume (%LV; LV/plaque volume), and high-signal volume (high-signal volume/plaque volume) were calculated automatically. For the analysis of 3-D IVUS images, LV, FV, and high-signal volume were calculated as the sum of fibrous, lipid, and high-signal areas, respectively, in each CSA at 1-mm axis intervals. The cut-off point for lipid-rich plaque was defined as %LV=54%, which was the 75th percentile for %LV in this study population.[9,19]

Statistical Analysis

Continuous variables are expressed as mean±SD. Categorical variables are expressed as percentages. Student's t-test was used to compare continuous variables, and the chi-squared or Fisher exact test was used to compare categorical variables. To identify independent predictors of lipid-rich plaque, multivariate logistic regression analysis was performed, adjusting for age, gender, body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking status and eGFR level. Two-sided P<0.05 was considered to indicate statistical significance. SPSS version 18.0 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analysis.

Results

The clinical characteristics according to the presence or absence of proteinuria are summarized in Table 1. Patients with proteinuria were significantly older, more likely to have diabetes, and more likely to have a current smoking habit compared with patients without proteinuria. Glycosylated hemoglobin concentration was significantly higher and eGFR was significantly lower in patients with proteinuria compared with those without, but other risk factors and lipid profiles were similar between the 2 groups.

The correlation of %LV and %FV measured by 2 physicians who conducted IB-IVUS measurements independently was r=0.950 (P<0.001) and r=0.933 (P<0.001), respectively. QCA and IVUS findings are presented in Table 2. There were no significant differences in the culprit lesion characteristics on QCA between the 2 groups. For IVUS, various parameters were similar between the 2 groups. On 3-D IB-IVUS, however, patients with proteinuria had plaque with significantly higher %LV and significantly lower %FV compared with

Table 1. Patient Characteristics vs. Urinary Protein Level

Variable	Urinary protein		P-value
	(–) or +/– (n=471)	≥1+ (n=84)	
Demographics			
Male	368 (78)	71 (85)	0.19
Age (years)	68.5±9.8	71.0±9.3	0.026
BMI (kg/m²)	23.6±3.5	23.8±3.9	0.60
Hypertension	327 (69)	65 (77)	0.15
Diabetes	185 (39)	54 (64)	<0.001
Dyslipidemia	356 (76)	59 (70)	0.34
Current smoker	122 (26)	31 (37)	0.046
Laboratory data			
Hemoglobin (g/dl)	13.2±1.8	12.4±2.0	0.001
LDL-C (mg/dl)	103.7±30.9	101.3±32.2	0.54
HDL-C (mg/dl)	46.1±13.2	45.3±12.7	0.61
Triglycerides (mg/dl)	132.4±67.1	142.8±66.9	0.20
Hemoglobin A1c (%)	6.3±1.0	7.1±1.5	<0.001
C-reactive protein (mg/dl)	0.11 (0.04–0.35)	0.17 (0.04–0.81)	0.43
Blood urea nitrogen (mg/dl)	17.1±5.9	19.2±8.7	0.007
Creatinine (mg/dl)	0.9±0.7	1.1±0.6	0.009
eGFR (ml/min/1.73 m²)	67.5±18.8	58.1±22.6	<0.001
eGFR levels (ml/min/1.73 m²)			<0.001
eGFR ≥60	314 (67)	38 (45)	
45≤eGFR<60	104 (22)	24 (29)	
30≤eGFR<45	45 (9)	12 (14)	
15≤eGFR<30	8 (2)	10 (12)	
Medications			
ACEI or ARB	251 (53)	38 (45)	0.34
Ca channel blocker	161 (34)	43 (51)	0.003
β-blocker	138 (29)	28 (33)	0.52
Statins			0.56
Pravastatin	81 (17)	21 (25)	
Rosuvastatin	103 (22)	11 (13)	
Atorvastatin	146 (31)	26 (31)	
Pitavastatin	141 (30)	26 (31)	
Anti-diabetes drugs	131 (28)	44 (52)	0.001

Data given as mean±SD, n (%) or median (IQR). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

patients without proteinuria (48.6±16.1% vs. 43.6±14.8%, P=0.005; and 48.8±14.8% vs. 53.6±22.8%, P=0.048, respectively). Table 3 lists IB-IVUS analysis stratified by level of kidney function and dipstick urinary protein. The proportion of patients according to eGFR ≥60, 45–59, 30–44, and 15–29 ml/min/1.73 m², was 63.4%, 23.1%, 10.3%, and 3.2%, respectively. The %LV was highest in patients with eGFR 45–59 ml/min/1.73 m² (43.0±14.8%, 48.7±14.8%, 44.1±15.8%, and 40.9±17.4%, respectively). The proportion of patients according to dipstick urinary protein level was as follows: – in 70.3% of patients, ± in 14.6%, 1+ in 9.5%, and ≥2+ in 5.6%. Figure 1 shows the combined analysis using eGFR category and absence or presence of proteinuria on dipstick urine test. For eGFR 45–59 ml/min/1.73 m², subjects with proteinuria were significantly more likely to have higher %LV compared with those with eGFR >60 ml/min/1.73 m² without proteinuria. After multivariate adjustment for cardiovascular risk factors, the presence of proteinuria proved to be an independent predictor for lipid-rich plaque (OR, 1.85; 95% CI: 1.12–3.06, P=0.016; Table 4).

Representative conventional and IB-IVUS of coronary artery plaques is given for patients with (Figure 2A) or without (Figure 2B) proteinuria. The %LV and %FV were 64.7% and 34.4% in Figure 2A, and 40.0% and 56.1% in Figure 2B, respectively.

Discussion

Previous data on the prevalence of proteinuria have been reported in several clinical populations. In a large Japanese community-based study, the prevalence of proteinuria was 5.2%,[20] and 10.5% in patients with diabetes.[21] In the present study, 15.1% of patients had proteinuria. Furthermore, because we excluded patients with ACS and patients with eGFR <15 ml/min/1.73 m², it is possible that the prevalence of proteinuria was higher in the patients with coronary artery disease (CAD). In the present study, a positive proteinuria test result had a strong predictive value for the presence of lipid-rich

Table 2. Lesion Characteristics vs. Urinary Protein Level

Variable	Urinary protein		P-value
	(–) or +/– (n=471)	≥1+ (n=84)	
Culprit lesion location			0.55
LAD	202 (42.9)	34 (40.5)	
LCX	110 (23.4)	23 (27.4)	
Right coronary artery	150 (31.8)	27 (32.1)	
Left main trunk	9 (1.9)	0 (0.0)	
AHA/ACC type B2C	202 (42.9)	30 (35.7)	0.23
QCA			
Reference vessel diameter (mm)	2.5±0.6	2.6±0.5	0.20
Minimal lumen diameter (mm)	0.69±0.34	0.66±0.32	0.59
Percentage diameter stenosis (%)	72.2±12.6	74.5±10.9	0.15
Lesion length (mm)	12.5±6.3	12.7±6.3	0.82
Gray-scale IVUS			
EEM volume (mm^3)	199.5±160.0	234.4±177.9	0.072
Lumen volume (mm^3)	68.1±71.1	71.0±51.6	0.72
Plaque volume (mm^3)	131.0±106.0	158.8±127.1	0.032
Percentage plaque volume (%)	64.3±10.9	65.3±12.1	0.46
IB-IVUS			
Fibrous volume (%)	53.6±22.8	48.8±14.8	0.048
Lipid volume (%)	43.6±14.8	48.6±16.1	0.005
High-signal volume (%)	3.4±3.7	2.6±2.6	0.036

Data given as mean±SD or n (%). AHA/ACC, American Heart Association/American College of Cardiology; EEM, external elastic membrane; IB, integrated backscatter; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; QCA, quantitative coronary angiography.

Table 3. IB-IVUS Parameters vs. Kidney Function and Urinary Protein

	eGFR (ml/min/1.73 m^2)			
	≥60	45–59	30–44	15–29
n	352	128	57	18
Fibrous volume (%)	54.4±24.2	48.5±12.9**,†	52.6±14.0	56.8±16.3
Lipid volume (%)	43.0±14.8	48.7±14.8**,†	44.1±15.8	40.9±17.4
High-signal volume (%)	3.6±3.9	2.9±2.7	3.1±3.3	2.2±1.8*,†
	Dipstick urinary protein			
	(–)	+/–	1+	≥2+
n	390	81	53	31
Fibrous volume (%)	53.5±24.4	54.3±11.9	48.6±14.1	49.0±16.2
Lipid volume (%)	43.9±14.9	42.4±14.5	48.8±15.4	48.3±17.6
High-signal volume (%)	3.4±3.8	3.9±3.3	2.5±2.7	2.7±2.3
	eGFR≥60, P(–)	eGFR≥60, P(+)	eGFR<60, P(–)	eGFR<60, P(+)
n	314	38	157	46
Fibrous volume (%)	54.6±26.2	52.3±14.7	51.7±13.3	45.8±14.4**,††
Lipid volume (%)	42.8±14.6	44.6±16.2	45.2±15.2	51.9±15.5**,††
High-signal volume (%)	3.6±4.0	3.0±2.7	3.1±2.9	2.3±2.5

Data given as mean±SD. *P<0.05, **P<0.01, ***P<0.001. †vs. eGFR ≥60 ml/min/1.73 m^2; ††vs. eGFR ≥60 ml/min/1.73 m^2+P. P, proteinuria. Other abbreviations as in Table 1.

plaque in patients with stable angina pectoris. These findings suggest that the dipstick urine test is also useful for cardiovascular risk stratification of high-risk populations.

Recent autopsy studies have demonstrated that CKD is closely associated with the severity of coronary atherosclerosis and the vulnerability of coronary plaques.[22,23] In such studies, frequencies of advanced atherosclerotic coronary lesions (AHA types IV–VI)[17] increase gradually as eGFR decreases. Given that prevalence of calcified coronary lesions (type V and VI) was significantly higher in individuals with eGFR <30 ml/min/1.73 m^2 compared with those with eGFR>60 ml/min/1.73 m^2, proportion of AHA type IV atherosclerotic lesion was higher for eGFR 30–59 ml/min/1.73 m^2, therefore LV was highest for eGFR 45–59 ml/min/1.73 m^2. Similar findings have also been noted for carotid atheroma progression.[24] There are limited data, however, on the histology of coronary plaque in

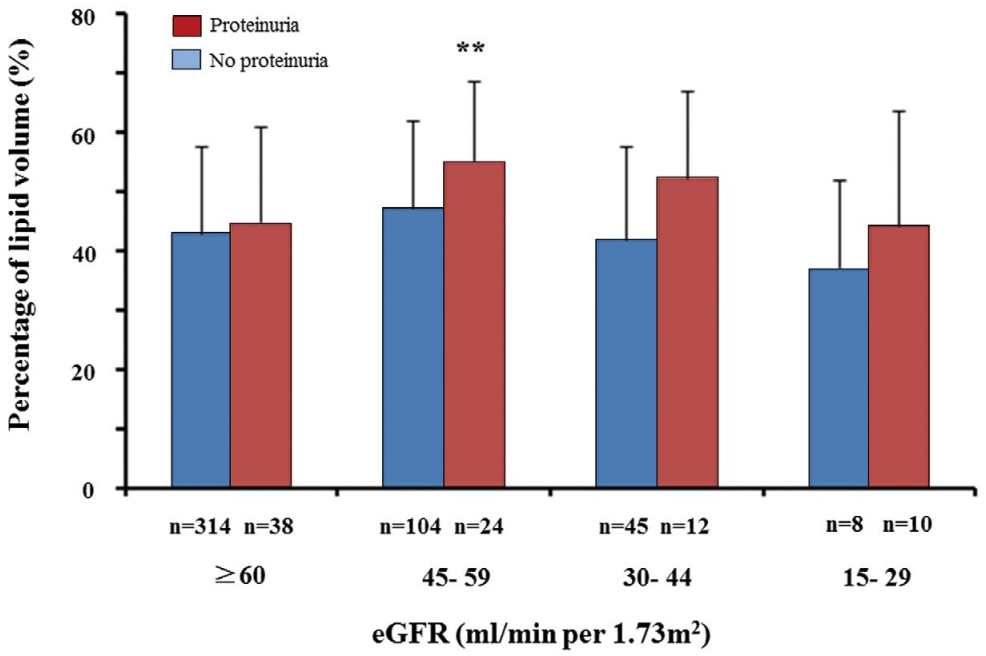

Figure 1. Three-dimensional integrated backscatter intravascular ultrasound analysis. Combined analysis based on estimated glomerular filtration rate (eGFR) and absence or presence of proteinuria on dipstick urine test. For eGFR 45–59 ml/min/1.73 m², subjects with proteinuria were significantly more likely to have higher percent lipid volume compared with those with eGFR >60 ml/min/1.73 m² without proteinuria. **P<0.05.

Table 4. Multivariate Indicators of Lipid-Rich Plaque (%LV 75th Percentile)

Variables	Simple regression			Multiple regression		
	OR	95% CI	P-value	OR	95% CI	P-value
Male	2.40	1.38–4.17	0.002	2.28	1.29–4.00	0.004
Age (years)	1.01	0.99–1.03	0.29			
BMI (kg/m²)	1.00	0.95–1.06	0.99			
Hypertension	1.18	0.77–1.80	0.45			
Diabetes mellitus	1.19	0.81–1.74	0.37			
Current smoking	1.57	1.04–2.36	0.031	1.38	0.91–2.11	0.13
HDL-C (mg/dl)	0.99	0.98–1.01	0.87			
LDL-C (mg/dl)	0.99	0.99–1.00	0.42			
Reduced eGFR (<60 ml/min/1.73 m²)	1.87	1.27–2.75	0.001	1.76	1.18–2.61	0.006
Presence of P (≥1+)	2.21	1.36–3.58	0.001	1.85	1.12–3.06	0.016

%LV, percentage of lipid volume. Other abbreviations as in Tables 1,3.

living patients with various degrees of renal function. In the present study, we showed that a mild degree of renal dysfunction (eGFR 45–59 ml/min/1.73 m²) was significantly associated with lipid-rich plaque among patients with CAD. The present findings may partially explain why patients with mild renal dysfunction are at risk of vulnerable coronary plaque and are likely to develop ACS.

Many cross-sectional and prospective studies have recently reported the value of proteinuria to identify patients at high risk of stroke and several acute cardiovascular events, including myocardial infarction.[25,26] A positive correlation between the degree of proteinuria and the severity of the event has been documented.[27] In addition, recent studies have found that patients with both proteinuria and reduced eGFR are at the highest risk for cardiovascular outcomes in a general population.[4,28] These findings support the idea that proteinuria is a predictor of adverse cardiovascular events independent of eGFR, suggesting that there are distinct mechanisms underlying the cardiovascular risks associated with proteinuria and reduced eGFR.[29] In the present study, patients with proteinuria had a significantly higher lipid plaque volume compared with those without. Therefore, the presence of proteinuria in CAD patients is an indicator of more vulnerable coronary plaque. Moreover, the addition of proteinuria to kidney function was associated with an increased prognostic value of lipid-rich plaque, suggesting that proteinuria provides additional prognostic

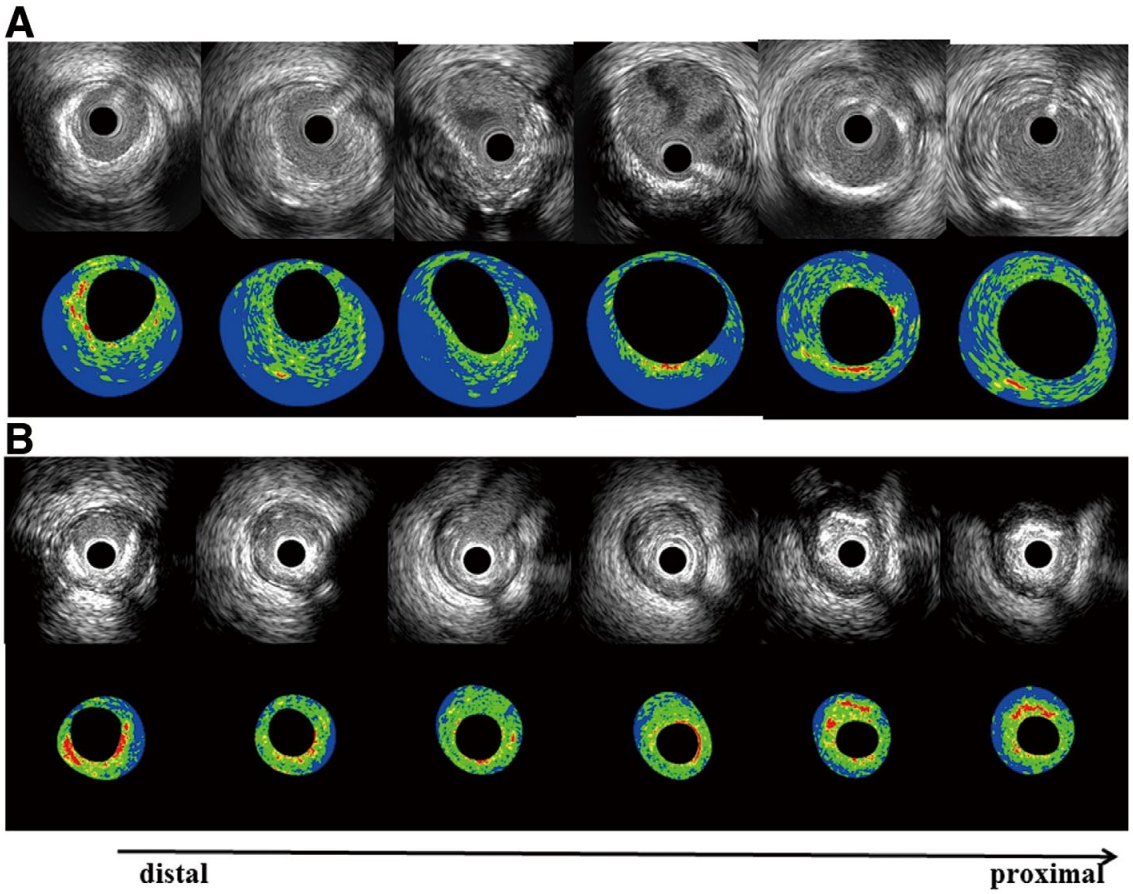

Figure 2. Representative conventional and integrated backscatter intravascular ultrasound of coronary artery plaque in patients (**A**) with or (**B**) without proteinuria. The percentage of lipid and fibrous volume were (**A**) 64.7% and 34.4% and (**B**) 40.0% and 56.1%. Blue, lipid lesion; green and yellow, fibrous lesion; red, high-signal lesion.

information beyond eGFR alone. This suggests that assessments of both proteinuria and eGFR, in particular eGFR 45–59 ml/min/1.73 m^2, are needed to better identify patients with high-risk coronary plaque and to initiate appropriate preventive measures earlier.

A number of plausible mechanisms have been proposed for the atherogenic effects of proteinuria. First, a close relationship has been found between the degree of proteinuria and several inflammatory biomarkers such as C-reactive protein.[30] Second, a strong association has been reported between proteinuria and vascular endothelial dysfunction. Vascular endothelial dysfunction as assessed on flow-mediated dilatation has been shown to be impaired in individuals with proteinuria.[31] Although a direct pathological connection between proteinuria and clinical atherosclerosis has not been fully established, there is some indication that presence of proteinuria could relate to the development of cardiovascular outcomes.[6,32] To the best of our knowledge, the present study is the first to indicate the predictive role of proteinuria for lipid-rich plaque in patients with CAD. Further large studies are required to confirm the present findings, and proteinuria may be a useful therapeutic target for cardiovascular risk reduction in these patients. Furthermore, proteinuria has been associated with several other risk factors that may themselves be linked with atherosclerosis, including diabetes, hypertension, and insulin resistance.[33–35] In the present study, however, even after adjustment for these factors, the presence of proteinuria remained strongly associated with lipid-rich coronary plaque.

This study has several limitations. First, this was a single-center study involving a relatively small number of advanced CKD patients (stage IV, n=18; stage V, n=22); and patients with severe calcified lesions that were difficult to pass and evaluate using the IVUS catheter, were excluded. Recently, a significant correlation was reported between coronary artery calcification score and cardiovascular events in CKD patients,[36] but there was no significant association between intracoronary calcification and renal function in the present study. For this reason, we excluded patients with severe calcified lesions, and those with advanced CKD. A recent autopsy study had suggested that coronary calcification is significantly increased in more advanced CKD.[22] Therefore we must review the selection bias. Second, single-spot urine test for measuring dipstick proteinuria and serum creatinine may cause misclassification of the true prevalence of CKD. Third, urinary protein excretion was analyzed on dipstick urine alone, and not with a quantitative and/or semi-quantitative method to detect albuminuria. High false-positive rates emphasize the need for laboratory confirmation of positive dipstick results (>1+). A

negative dipstick result (<trace), however, has a high negative predictive value with minimal risk of missed diagnosis of macroalbuminuria.[37] Fourth, we obtained no information on the duration of statin treatment, statin dose, pre-LDL-C level and the plaque characteristics of non-culprit lesions.[38–40] Therefore, we must review the influences of statin status on coronary plaque characteristics. Finally, it is generally accepted that the Modification of Diet in Renal Disease (MDRD) study equation and CKD-Epidemiology Collaboration (CKD-EPI) equation are used to evaluate eGFR in Caucasian subjects, but this is not feasible for Japanese subjects, mainly due to their smaller body muscle mass compared with Caucasian subjects. Therefore, Japanese Society of Nephrology recommends using the Japanese eGFR equation to evaluate eGFR among Japanese patients.

Conclusions

Reduced eGFR and the presence of proteinuria were significantly associated with the presence of lipid-rich plaque in patients with CAD. The identification of patients at greater risk of developing ACS is essential for the timely implementation of appropriate prevention strategies. The addition of proteinuria to eGFR may be of value in the risk stratification of patients with CAD.

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Disclosures

All authors declare no conflicts of interest related to this manuscript. All authors sufficiently contributed to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; and agreed with the final version of the manuscript.

References

1. Shroff GR, Frederick PD, Herzog CA. Renal failure and acute myocardial infarction: Clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease: A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. *Am Heart J* 2012; **163:** 399–406.
2. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators: Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; **113:** 671–678.
3. Minakata K, Bando K, Tanaka S, Takanashi S, Konishi H, Miyamoto Y, et al. Preoperative chronic kidney disease as a strong predictor of postoperative infection and mortality after coronary artery bypass grafting. *Circ J* 2014; **78:** 2225–2231.
4. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. 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. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. *Kidney Int* 2011; **80:** 17–28.
6. Chronic Kidney Disease Prognosis Consortium, van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality: A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; **79:** 1341–1352.
7. Kono K, Fujii H, Nakai K, Goto S, Shite J, Hirata K, et al. Composition and plaque patterns of coronary culprit lesions and clinical characteristics of patients with chronic kidney disease. *Kidney Int* 2012; **82:** 344–351.
8. Baber U, Stone GW, Weisz G, Moreno P, Dangas G, Maehara A, et al. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. *JACC Cardiovasc Imaging* 2012; **5:** 53–61.
9. Kawasaki M, Takatsu H, Noda T, Sano K, Ito Y, Hayakawa K, et al. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. *Circulation* 2002; **105:** 2487–2492.
10. Okubo M, Kawasaki M, Ishihara Y, Takeyama U, Yasuda S, Kubota T, et al. Tissue characterization of coronary plaques: Comparison of integrated backscatter intravascular ultrasound with virtual histology intravascular ultrasound. *Circ J* 2008; **72:** 1631–1639.
11. Sano K, Kawasaki M, Ishihara Y, Okubo M, Tsuchiya K, Nishigaki K, et al. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2006; **47:** 734–741.
12. Amano T, Matsubara T, Uetani T, Nanki M, Marui N, Kato M, et al. Abnormal glucose regulation is associated with lipid-rich coronary plaque: Relationship to insulin resistance. *JACC Cardiovasc Imaging* 2008; **1:** 39–45.
13. Hayano S, Ichimiya S, Ishii H, Kanashiro M, Watanabe J, Kurebayashi N, et al. Relation between estimated glomerular filtration rate and composition of coronary arterial atherosclerotic plaques. *Am J Cardiol* 2012; **109:** 1131–1136.
14. Amano T, Matsubara T, Uetani T, Kato M, Kato B, Yoshida T, et al. Lipid-rich plaques predict non-target-lesion ischemic events in patients undergoing percutaneous coronary intervention. *Circ J* 2010; **75:** 157–166.
15. Uetani T, Amano T, Ando H, Yokoi K, Arai K, Kato M, et al. The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. *Eur Heart J* 2008; **29:** 1714–1720.
16. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
17. Ryan TJ, Bauman WB, Kennedy JW, Kereiakes DJ, King SB 3rd, McCallister BD, et al. Guidelines for percutaneous transluminal coronary angioplasty: A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutics Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 1993; **88:** 2987–3007.
18. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001; **37:** 1478–1492.
19. Amano T, Matsubara T, Uetani T, Nanki M, Marui N, Kato M, et al. Impact of metabolic syndrome on tissue characteristics of angiographically mild to moderate coronary lesions: Integrated backscatter intravascular ultrasound study. *J Am Coll Cardiol* 2007; **49:** 1149–1156.
20. Uchida D, Kawarazaki H, Shibagaki Y, Yasuda T, Tominaga N, Watanabe T, et al. Underestimating chronic kidney disease by urine dipstick without serum creatinine as a screening tool in the general Japanese population. *Clin Exp Nephrol* 2015; **19:** 474–480.
21. Yokoyama H, Kawai K, Kobayashi M; Japan Diabetes Clinical Data Management Study Group. Microalbuminuria is common in Japanese type 2 diabetic patients: A nationwide survey from the Japan Diabetes Clinical Data Management Study Group (JDDM 10). *Diabetes Care* 2007; **30:** 989–992.
22. Nakano T, Ninomiya T, Sumiyoshi S, Fujii H, Doi Y, Hirakata H, et al. Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: The Hisayama study. *Am J Kidney Dis* 2010; **55:** 21–30.
23. Nakano T, Ninomiya T, Sumiyoshi S, Onimaru M, Fujii H, Itabe H, et al. Chronic kidney disease is associated with neovascularization and intraplaque hemorrhage in coronary atherosclerosis in elders: Results from the Hisayama Study. *Kidney Int* 2013; **84:** 373–380.
24. Rigatto C, Levin A, House AA, Barrett B, Carlisle E, Fine A. Atheroma progression in chronic kidney disease. *Clin J Am Soc Nephrol* 2009; **4:** 291–298.
25. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Impact of microalbuminuria on incident stroke: A meta-analysis. *Stroke* 2010; **41:** 2625–2631.

26. Schiele F, Meneveau N, Chopard R, Descotes-Genon V, Oettinger J, Seronde MF, et al. Prognostic value of albuminuria on 1-month mortality in acute myocardial infarction. *Am Heart J* 2009; **157:** 327–333.
27. Turaj W, Słowik A, Wyrwicz-Petkow U, Pankiewicz J, Iskra T, Rudzińska M, et al. The prognostic significance of microalbuminuria in non-diabetic acute stroke patients. *Med Sci Monit* 2001; **7:** 989–994.
28. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, et al; ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009; **20:** 1813–1821.
29. Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: A mechanistic viewpoint. *Kidney Int* 2008; **74:** 22–36.
30. Tsioufis C, Dimitriadis K, Chatzis D, Vasiliadou C, Tousoulis D, Papademetriou V, et al. Relation of microalbuminuria to adiponectin and augmented C-reactive protein levels in men with essential hypertension. *Am J Cardiol* 2005; **96:** 946–951.
31. Agrawal V, Marinescu V, Agarwal M, McCullough PA. Cardiovascular implications of proteinuria: An indicator of chronic kidney disease. *Nat Rev Cardiol* 2009; **6:** 301–311.
32. Park SK, Moon SY, Oh CM, Ryoo JH, Park MS. High normal urine albumin-to-creatinine ratio predicts development of hypertension in Korean men. *Circ J* 2014; **78:** 656–661.
33. Redon J, Rovira E, Miralles A, Julve R, Pascual JM. Factors related to the occurrence of microalbuminuria during antihypertensive treatment in essential hypertension. *Hypertension* 2002; **39:** 794–798.
34. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG; DEMAND investigators. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: A global perspective. *Kidney Int* 2006; **69:** 2057–2063.
35. Mykkänen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: The insulin resistance atherosclerosis study. *Diabetes* 1998; **47:** 793–800.
36. Matsushita K, Sang Y, Ballew SH, Shlipak M, Katz R, Rosas SE, et al. Subclinical atherosclerosis measures for cardiovascular prediction in CKD. *J Am Soc Nephrol* 2015; **26:** 439–447.
37. White SL, Yu R, Craig JC, Polkinghorne KR, Atkins RC, Chadban SJ. Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community. *Am J Kidney Dis* 2011; **58:** 19–28.
38. Ishii M, Hokimoto S, Akasaka T, Fujimoto K, Miyao Y, Kaikita K, et al; Kumamoto Intervention Conference Study (KICS) Investigators. Differential effects of strong and regular statins on the clinical outcome of patients with chronic kidney disease following coronary stent implantation: The Kumamoto Intervention Conference Study (KICS) Registry. *Circ J* 2015; **79:** 1115–1124.
39. Natsuaki M, Furukawa Y, Morimoto T, Nakagawa Y, Ono K, Kaburagi S, et al; CREDO-Kyoto PCI/CABG registry cohort-2 investigators. Intensity of statin therapy, achieved low-density lipoprotein cholesterol levels and cardiovascular outcomes in Japanese patients after coronary revascularization: Perspectives from the CREDO-Kyoto registry cohort-2. *Circ J* 2012; **76:** 1369–1379.
40. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol* 2015; **65:** 1273–1282.