Prognostic Risk Stratification of Cardiac Events Evaluated by Aortic Calcification in Elderly Patients with Chronic Kidney Disease: Sub-analysis of a J-ACCESS 3 Study

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Abstract

Background: The relationship between myocardial perfusion imaging (MPI) and aortic calcification (AoC) in chronic kidney disease (CKD) patients remains unclear.

Methods: The Japanese Assessment of Cardiac Events and Survival Study by quantitative gated single-photon emission computed tomography (J-ACCESS 3) is a multicenter, prospective cohort study investigating the ability of MPI to predict cardiac events in 529 CKD patients. In J-ACCESS 3, the sum of myocardial perfusion defect score at stress (SSS) was a useful predictor of cardiac major events in CKD patients. However, aortic calcification was not examined. We examined the prognosis of patients with CKD according to the presence or absence of AoC using data from the J-ACCESS 3 cohort.

Results: There were 60 major cardiac events (three cardiac deaths, six sudden deaths, five non-fatal myocardial infarctions, 46 hospitalization cases for heart failure). In the univariate analysis, patients with AoC had a higher left ventricular (LV) ejection fraction, smaller LV volume, and lower SSS by MPI. Kaplan–Meier curves showed a significantly higher incidence of major cardiac events in the AoC group (P=0.0041). Patients were categorized into the following four groups: Group A (non-AoC and SSS<4; normal score of 0–3); Group B (AoC and SSS<4); Group C (non-AoC and SSS≥4); Group D (AoC and SSS≥4). Kaplan–Meier curves showed that the major cardiac events rates were A<B<C<D (P=0.002). The difference was most pronounced between the AoC and no-AoC groups with SSS<4.

Conclusions: The combination of SSS using MPI and AoC is a useful predictor of cardiac major events in CKD patients.

Keywords: Aortic calcification, Chest radiograph, Chronic kidney disease, Myocardial perfusion imaging, Summed stress scores

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With our aging society, there is a continuing increase in the number of chronic kidney disease (CKD) patients in Japan (1). Cardiovascular complications are known to be important for the long-term prognosis of dialysis patients (2, 3), because it is known there are a higher number of deaths by coronary artery disease (CAD) than death by end stage renal failure for CKD patients.

Although examination with a contrast agent is commonly used to investigate CAD, the incidence of contrast agent nephropathy has become a serious problem. It is important to develop a method of predicting cardiac events in CKD patients without renal deterioration.

Myocardial perfusion imaging (MPI) is a useful method for detecting CAD without renal deterioration in CKD patients. Quantitative gated single-photon emission computed tomography (SPECT), which is able to analyze the left ventricular...
volume and left ventricular function and is highly reproducible, was first developed by Germano et al., and is now used worldwide (4).

The Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT (J-ACCESS 3) is a multicenter, prospective cohort study investigating the ability of MPI to predict cardiac events in 529 patients with CKD but without definitive CAD (5, 6). In this study, a sum of the myocardial perfusion defect scores at stress (SSS) estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m², and a C-reactive protein (CRP) >0.3 (mg/dl) were associated with major cardiac events in CKD patients. SSS is a widely established prognostic predictor of cardiac events (7, 8).

There is also increasing evidence for the advancement of arteriosclerosis, especially artery calcification, in dialysis patients (9, 10). However, although the relation of cardiovascular disease of CKD patients and coronary calcification or aortic valve calcification is well known, the association of cardiovascular disease and atherosclerosis of aorta is not known in the patients’ group before dialysis.

Thus, the aim of the present study was to examine the relationship between cardiovascular calcification and outcomes, particularly aortic calcification observed in chest radiograph (CXR) used in general practice, in CKD patients using data from the J-ACCESS 3 study. We hypothesized that aortic calcification in CKD patients can be used as an indicator of cardiovascular events, and is correlated with nuclear medicine indices such as the SSS. In addition, we hypothesized that the combination of SSS and aortic calcification was a better predictor.

**Methods**

**Study population**

The principal design of the J-ACCESS 3 study was previously described (5, 6). In brief, 549 patients with an eGFR <50 ml/min/1.73 m² were registered. CKD cut-off values were determined in the original J-ACCESS 3. The inclusion criteria comprised of patients over 20 years of age, scheduled to undergo stress-rest ECG-gated MPI due to suspected ischemic CAD, and having at least one or more of the coronary risk factors for CAD, one or more of cardiac symptoms (e.g., patients with chest pain), and without a definitive diagnosis of CAD. Exclusion criteria from initial registration were end-stage renal failure, known ischemic heart disease and cardiomyopathy.

The 529 registered patients were followed-up for 3 years, with 75 showing aortic valve calcification, 17 showing mitral valve calcification in cardiac ultrasonography, and 105 showing aortic calcification in CXR. The aortic calcification was visually assessed using CXR (11). Eighty-two subjects were excluded as a CXR and echocardiography examination was not performed.

Four hundred and forty seven patients (mean age: 71.6 ± 10.9 years), which we could evaluate calcification were included in the final analysis (Figure 1).

**MPI procedure**

The patients underwent stress and rest myocardial perfusion SPECT using ⁹⁹mTc-tetrofosmin and Quantitative Gated SPECT with Quantitative Gated SPECT software (Cedars Sinai Medical Center, Los Angeles, CA, USA). Based on past
studies, one-day (96%) and two-day (4%) pharmaceutical stress MPI studies proceeded, which included adenosine (91%), dipyridamole (1%), adenosine-triphosphate (6%), and pharmaceutical agents combined with low-intensity exercise (2%). The average administered dose of 99mTc-tetrofosmin for the first and second studies were 312 and 689 MBq, respectively, and gated MPI was started at 35 ± 17 and 59 ± 45 minutes, respectively, after injection.

The SPECT images were normally divided into 17 segments, and visual perfusion of 99mTc-tetrofosmin uptake in each segment was scored as follows: score 0 = normal; 1 = mildly reduced; 2 = moderately reduced; 3 = severely reduced; and 4 = absent. An image interpretation committee objectively evaluated defect scores including SSS, summed rest scores (SRS), and summed deference score (SDS), calculated based on the stress and rest findings with the 17-segment model. SRS represented the sum of the myocardial perfusion defect score at rest, while SDS represented the difference between SSS and SRS.

Follow-up

Four hundred forty-seven participants were followed-up for 3 years after registration. The major cardiac events were defined as cardiac death, sudden death, nonfatal myocardial infarction, and heart failure (HF) hospitalization.

Statistical analysis

Continuous variables are presented as a mean ± standard deviation, while categorical data are presented as proportion. We applied the χ² test or the Wilcoxon rank sum test to compare the results from patients with and without cardiac events, and the chi-square test was used for categorical data. The association of selected variables with outcomes was assessed using the Cox proportional hazard model with univariate analysis and stepwise multivariable procedures. Kaplan–Meier cumulative survival was analyzed using the threshold values of SSS and cardiac risk factors. P<0.05 was considered statistically significant. All statistical calculations were performed with statistical software (SPSS v.9.1.3 Service Pack 2 and JMP 12.2; SPSS, Cary, NC, USA).

Results

Characteristics of the patients

The baseline characteristics of the 447 patients with or without aortic calcification are shown in Table 1. Traditional risk factors of age, sex, smoking, hypertension, dyslipidemia, and diabetes were compared between the two groups. Patients with aortic calcification were older (77.1 ± 8.7 years vs 70.3 ± 10.7 years, respectively; P<0.0001), predominantly women (male ratio=54.3% vs 72.2%, respectively; P=0.0009), had a higher prevalence of dyslipidemia (59.0% vs 44.7%, respectively; P=0.014), and had lower hemoglobin (11.1 ± 1.8 g/dl vs 11.7 ± 2.0 g/dl, respectively; P=0.0099) compared with patients without aortic calcification.

MPC findings

Patients with aortic calcification had a higher left ventricular ejection fraction (LVEF) at rest (63.8% ± 15% vs 60.1% ± 15%, respectively; P=0.038), smaller LV end-diastolic volume (EDV) (81.7 ± 38 ml vs 95.2 ± 40 ml, respectively; P=0.0005), smaller LV end-systolic volume (ESV) (LVESV; 33.9 ± 28 ml vs 42.4 ± 32 ml, respectively; P=0.0022), lower SSS (1.2 ± 3.0 vs 2.1 ± 3.9, respectively; P=0.0018), lower SRS (0.6 ± 2.5 vs 1.1 ± 3.0, respectively; P=0.025), and lower SDS (0.5 ± 1.3 vs 1.0 ± 2.0, respectively; P=0.012) in MPI findings (Table 1).

Cardiac events

Sixty major cardiac events occurred during the 3-year follow-up, including cardiac death (n=3), sudden death (n=6), nonfatal myocardial infarction (n=5), and HF hospitalization (n=46). A cardiac event was based on one event of one case, and when a complex event occurred, the initial event was adopted as the cardiac event. Complex events cases were cardiac death and myocardial infarction (n=1), cardiac death and HF hospitalization (n=3), and nonfatal myocardial infarction and HF hospitalization (n=2). The numbers of major cardiac events for patients with or without aortic calcification were 20 (19%) and 32 (9%), respectively.

For identification of major cardiac events including HF hospitalization in patients with aortic calcification, univariate Cox proportional hazard analysis showed that the usage rate of β blockers (χ²=4.401, P=0.03) and ST-T abnormalities of ECG (χ²=3.770, P=0.05) was a significant variable (Table 2). The traditional risk factors of age, sex, smoking, hypertension, diabetes, and dyslipidemia were not different in the patients with calcification.

Survival curves

The Kaplan–Meier curves for event-free survival at the end of the 3-year follow-up are shown in Figures 2 and 3. The event-free rates of cardiac major events were 0.79 and 0.90 for patients with or without aortic calcification, respectively (P=0.004; Figure 2). Particularly focusing on HF hospitalization with the largest number in the cardiac major events, the event-free rates of HF hospitalization were 0.83 and 0.91 for patients with or without aortic calcification, respectively (P=0.016; Figure 3). The Kaplan–Meier curves for event-free survival rates according to the combined SSS and aortic calcification in CKD patients is shown in Figure 4. Patients were categorized into the following groups: Group A (non-aortic calcification and SSS<4; normal score, 0–3), Group B (aortic calcification...
and SSS<4), Group C (non-aortic calcification and SSS≧4), and Group D (aortic calcification and SSS≧4). The Kaplan–Meier curves showed the cardiac events rate was lower in the order of A<B<C<D (P=0.002). The prognosis of patients with non-aortic calcification and SSS<4 had an excellent prognosis. The difference was most pronounced between the aortic calcification and no calcification groups with an SSS<4.

**Potential predictors of cardiac events**

There were no significant factors in the univariate Cox proportional hazard analysis for patients with aortic calcification. To identify the independent variables for cardiac events, we then used multivariate logistic regression modeling with the stepwise method to examine the association of cardiovascular events with some modulator which the probability of reported risk factors (eGFR, CRP, SSS, LVEF, ESV, EDV) and aortic calcification. These indicators were established in the J-ACCESS study and currently used broadly with software named ‘Heart Risk View’ to estimate the cardiac events (12–15). Because this present study was a sub-analysis of J-ACCESS 3, the analysis was performed using the numerical values from the original J-ACCESS 3 study.

ESV at rest (P=0.0008), EDV at rest (P=0.0007) and aortic calcification (P=0.0423) were significantly and independently associated with cardiac major events (Table 3).

**Discussion**

The aim of the present study was to examine the potential

| Characteristic                  | Aortic calc (+) n=105 | Aortic calc (-) n=342 | P Value |
|--------------------------------|-----------------------|-----------------------|---------|
| Age (years)                    | 77.1 ± 8.7 (50-89)    | 70.3 ± 10.7 (34-92)   | <.0001  |
| Sex (male) (%)                 | 54.3                  | 72.2                  | 0.0009  |
| BMI (kg/m2)                    | 23.8 ± 4.6            | 24.3 ± 4.0            | 0.088   |
| Systolic blood pressure (mmHg) | 145 ± 27.8            | 144.5 ± 27.0          | 0.984   |
| Smoking (%)                    | 3.81                  | 7.60                  | 0.256   |
| Hypertension (%)               | 94.3                  | 90.9                  | 0.374   |
| Diabetes (%)                   | 38.1                  | 43.8                  | 0.351   |
| Dyslipidemia (%)               | 59.0                  | 44.7                  | 0.014   |
| PAD (%)                        | 10.5                  | 7.6                   | 0.463   |
| Atrial fibrillation (%)        | 13.4                  | 9.9                   | 0.499   |
| SSS                            | 1.2 ± 3.0             | 2.1 ± 3.9             | 0.0018  |
| SSS>4 (%)                      | 12.3                  | 21.6                  | 0.050   |
| SRS                            | 0.6 ± 2.5             | 1.1 ± 3.0             | 0.025   |
| SDS                            | 0.5 ± 1.3             | 1.0 ± 2.0             | 0.012   |
| LVEF (%) at rest               | 63.8 ± 15             | 60.1 ± 15             | 0.038   |
| LVEDV (ml) at rest             | 81.7 ± 38             | 95.2 ± 40             | 0.0005  |
| LVESV (ml) at rest             | 33.9 ± 28             | 42.4 ± 32             | 0.0022  |
| Hemoglobin (g/dl)              | 11.1 ± 1.8            | 11.7 ± 2.0            | 0.0099  |
| CRP (mg/dl)                    | 0.5 ± 1.3             | 0.4 ± 0.8             | 0.084   |
| Creatinine (mg/dl)             | 2.0 ± 1.1             | 2.2 ± 1.3             | 0.252   |
| eGFR (ml/min/1.73m²)           | 28 ± 12.1             | 28.6 ± 12.5           | 0.674   |
| LDL-C (mg/dl)                  | 104 ± 34              | 110 ± 42              | 0.410   |
| HDL-C (mg/dl)                  | 49 ± 16               | 46 ± 14               | 0.224   |
| HbA1c (%)                      | 5.9 ± 1.3             | 5.9 ± 1.1             | 0.088   |
| ACE-I (%)                      | 11.4                  | 13.4                  | 0.663   |
| ARB (%)                        | 66.7                  | 62.9                  | 0.686   |
| β blocker (%)                  | 24.7                  | 32.4                  | 0.134   |
| Statin (%)                     | 45.7                  | 39.5                  | 0.364   |

Aortic calc: aortic calcification, ACE-I: angiotensin-converting inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, CRP: C-reactive protein, LVEF: left ventricular ejection fraction, eGFR: glomerular filtration rate, HbA1c: hemoglobin A1c, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, PAD: peripheral artery disease, SDS: summed difference score, SRS: summed rest score, SSS: summed stress score.
predictors of cardiac major events in CKD patients. Our main findings showed a significant difference in the major event rate because of the presence or absence of aortic calcification in patients with an SSS < 4, aortic calcification was independently associated with HF hospitalization, and aortic calcification of CKD patients may be useful for predicting the risk of HF preserved ejection fraction (HFpEF).

It is well established that dialysis patients have a higher risk of cardiovascular events (2, 3). Furthermore, epidemiological studies suggest that the risk of cardiovascular events in patients with impaired renal function can increase before the initiation of dialysis (16, 17). At any rate, their involvement with patients with an eGFR < 50 ml/min/1.73 m² has not been reported. In the J-ACCESS 3 study examining patients with an eGFR < 50 ml/min/1.73 m², a lower eGFR, a higher CRP, and a higher SSS using MPI was a strong predictor of prognosis in CKD patients (6). Based on the J-ACCESS study, SSS was also the most useful predictor for cardiac events in the Japanese population (12–14). In the present study, moderate to severe transient ischemia (SSS > 8) predicted cardiac events.

Table 2  Hazard ratios based on univariate Cox proportional hazard analysis to predict major cardiac events in aortic calcification group

| Predictor                          | Wald χ² | Hazard Ratio | Lower 95% | Upper 95% | p Value |
|-----------------------------------|---------|--------------|-----------|-----------|---------|
| Age, per year                     | 0.081   | 0.993        | 0.946     | 1.042     | 0.77    |
| Male (vs female)                  | 0.005   | 0.966        | 0.400     | 2.332     | 0.93    |
| BMI (kg/m²)                       | 0.486   | 0.961        | 0.860     | 1.075     | 0.48    |
| Smoking                           | 0.0001  | 0.000        | 0.00      | -         | 0.99    |
| Hypertension                      | 1.008   | 0.473        | 0.110     | 2.040     | 0.31    |
| Diabetes                          | 0.027   | 0.925        | 0.369     | 2.319     | 0.86    |
| Dyslipidemia                      | 1.955   | 2.059        | 0.748     | 5.665     | 0.16    |
| PAD                               | 0.048   | 1.179        | 0.273     | 5.094     | 0.82    |
| Atrial fibrillation               | 1.370   | 1.933        | 0.641     | 5.826     | 0.24    |
| ST-T abnormalities               | 3.770   | 2.985        | 0.990     | 9.001     | 0.05    |
| SSS                               | 0.877   | 1.050        | 0.948     | 1.163     | 0.34    |
| SSS>4                             | 1.287   | 1.888        | 0.630     | 5.656     | 0.25    |
| SRS                               | 0.18    | 1.029        | 0.905     | 1.169     | 0.66    |
| SDS                               | 2.010   | 1.204        | 0.932     | 1.556     | 0.15    |
| at rest LVEF                      | 2.511   | 0.978        | 0.952     | 1.005     | 0.11    |
| at exercise LVEF                  | 0.140   | 0.993        | 0.959     | 1.029     | 0.70    |
| at rest ESV                       | 1.647   | 1.008        | 0.996     | 1.021     | 0.19    |
| at exercise ESV                   | 3.289   | 1.008        | 0.999     | 1.017     | 0.06    |
| at rest EDV                       | 2.867   | 0.988        | 0.974     | 1.002     | 0.09    |
| at exercise EDV                   | 0.081   | 1.002        | 0.988     | 1.016     | 0.93    |
| Hemoglobin (g/dl)                 | 1.843   | 0.840        | 0.654     | 1.080     | 0.77    |
| CRP (mg/dl)                       | 0.204   | 1.062        | 0.819     | 1.376     | 0.65    |
| Creatinine (mg/dl)                | 0.121   | 1.068        | 0.737     | 1.549     | 0.72    |
| eGFR (ml/min/1.73m²)              | 0.122   | 0.994        | 0.958     | 1.030     | 0.72    |
| LDL-C (mg/dl)                     | 2.867   | 0.988        | 0.974     | 1.002     | 0.09    |
| HDL-C (mg/dl)                     | 0.001   | 1.000        | 0.973     | 1.027     | 0.97    |
| HbA1c (%)                         | 0.001   | 0.994        | 0.702     | 1.408     | 0.97    |
| ACE-I, user vs nonuser            | 2.158   | 2.274        | 0.760     | 6.807     | 0.14    |
| ARB, user vs nonuser              | 0.442   | 0.732        | 0.292     | 1.836     | 0.50    |
| ß blocker, user vs nonuser        | 4.401   | 2.570        | 1.064     | 6.205     | 0.03    |
| Aspirin, user vs nonuser          | 0.338   | 1.299        | 0.538     | 3.136     | 0.56    |
| Statin, user vs nonuser           | 0.481   | 1.366        | 0.566     | 3.297     | 0.48    |

ACE-I: angiotensin-converting inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, CRP: C-reactive protein, ESV: end-systolic volume, EDV: end-diastolic volume, LVEF: left ventricular ejection fraction, eGFR: glomerular filtration rate, HbA1c: hemoglobin A1c, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, PAD: peripheral artery disease, SDS: summed difference score, SRS: summed rest score, SSS: summed stress score
We also found differences in the prognosis depending on the presence or absence of aortic calcification for patients with SSS < 4. Therefore, we also examined the HF hospitalization in cardiac major events and found a small but significant increase in rates of HF hospitalization in patients with aortic calcification compared with those without aortic calcification (P = 0.016).

Patients with aortic calcification were older, predominantly women, had higher LVEF (mean LVEF 63.8%), a lower LV volume, and a lower SSS in MPI findings. Hypertension, LV hypertrophy, aging, and gender are well known as factors of HFpEF (18). However, there was no significant difference in the prevalence of hypertension or peripheral arterial pressure between patients with or without aortic calcification. Although it is inferred as the relation between aortic calcification and HFpEF, changes in central blood pressure are correlated with organ failure (19, 20). As such, aortic calcification is more likely to reflect changes in central blood pressure. In arteriosclerosis (calcification), the pressure wave that occurs during systole is increased. Thus, the reflected wave from the periphery returns earlier than normal. Augmentation of late systolic pressure (i.e., central arterial pressure) is triggered by this reflected wave, which causes increased afterload and HF. Reddy et al. also reported that arterial stiffening and reduced arterial reserved are specific to the HFpEF phenotype (21).

Coronary artery calcium scoring using non-contrast computed tomography provides a clinically useful noninvasive...
estimate of CAD burden (22). Both coronary artery calcium scoring and the SSS score of SPECT provide the same predictor of CAD. Even with the same calcification, the contents of cardiac events between coronary artery calcium scoring and aortic calcification were different. These phenomena may be attributed to the difference between Moenckeburg’s arteriosclerosis found in the medium and large artery and atherosclerotic calcification found in the coronary artery.

Thus, the combination of SSS and aortic calcification is a more useful predictor of cardiac events in patients with CKD. In the present study, the univariate Cox proportional hazard analysis showed that the use of a β blocker and ST-T abnormalities of ECG was associated with a major cardiac event. In the J-ACCESS 3 study, about half of patients had cardiac symptoms or ECG abnormalities. Although the use of a β blocker may be related to cardiac symptoms or ECG abnormalities, there was no significant difference in SSS
between the two groups. The multivariate Cox proportional hazards analysis showed the utility of ESV and EDV. ESV was also a useful predictor for cardiac events in the Japanese population (12, 23). However, as for the limitations of our study, the present study showed a gender difference between the AoC group and the non-AoC group. Usually, EDV or ESV is lower in females, so the gender difference may have affected the result. Because this present study was a sub-analysis of J-ACCESS 3, it was difficult to examine this point in further detail.

Additionally, there are some further limitations of our study. Severe HF was reported to be the main cause of cardiac events in Japanese patients with or without CKD (24). In the present study, approximately 77% of cardiac events involved HF, with a potential involvement of volume retention following renal failure. It is possible that the volume retention may have contributed to HF. We also examined the aortic valve calcification group in the present study, with event-free rates of major cardiac events of 0.92 and 0.82 for the groups with or without aortic valve calcification, respectively (data not shown). These findings were unexpected, but may relate to the exclusion of patients with hemodialysis, with the remaining patients having relatively fewer cardiac events.

Additionally, in this study, the ratio of HFrEF and HFpEF could not be clarified. It was because there was no data at the research design stage in the original J-ACCESS 3. As for future tasks, in multicentre collaborative trial, it will be desirable to analyse the heart failure events by dividing them into HFrEF and HFpEF.

Conclusion
We found a clear difference in the incidence of cardiac events between patients with and without aortic calcification compared with patients with SSS<4. Aortic calcification in CKD patients may be useful for predicting the risk of HFpEF. Aortic calcification combined with MPI abnormalities provides more information than that for each marker alone.

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Disclosures
The authors declare that there is no conflict of interest.

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References
1. Japan Nephrology Society. Evidence-based Clinical Practice Guidebook for CKD (article in Japanese) 2018, TOKYO IGAKUSHI
2. Lindner A, Charra B, Sherrard DJ, et al. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974; 290: 697–701.
3. Collins AJ, Kasiske B, Herzog C, et al; United States Renal Data System. Excerpts from United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis 2005; 45: 176–8.
4. Germano G, Kavanagh PB, Slomka PJ, et al. Quantitation in gated perfusion SPECT imaging: the Cedars-Sinai approach. J Nucl Cardiol 2007; 4: 433–54.
5. Joki N, Hase H, Kawano Y, et al. Myocardial perfusion imaging for predicting cardiac events in Japanese patients with advanced chronic kidney disease: 1-year interim report of the J-ACCESS 3 investigation. Eur J Nucl Med Mol Imaging 2014; 41: 1701–9.
6. Nakamura S, Kawano Y, Nakajima K, et al. Prognostic study of cardiac events in Japanese patients with chronic kidney disease using ECG-gated myocardial perfusion SPECT imaging: Final 3-year report of the J-ACCESS 3 study. J Nucl Cardiol 2017; 24: 319–30.
7. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998; 97: 535–43.
8. Valeti US, Miller TD, Hodge DO, et al. Exercise single-photon emission computed tomography provides effective risk stratification of elderly men and elderly women. Circulation 2005; 111: 1771–6.
9. Ibels LS, Alfrey AC, Huffer WE, et al. Arterial calcification and pathology in uremic patients undergoing dialysis. Am J Med 1979; 66: 790–6.
10. Nakagawa K. A study of aortic calcification in uremia (article in Japanese). Jpn J Nephrol 1997; 39: 135–41.
11. Bohn E, Tangri N, Gall B, et al. Predicting risk of mortality in dialysis patients: A retrospective cohort study evaluating the prognostic value of a simple chest X-ray. BMC Nephrol 2013; 14: 263.
12. Nishimura T, Nakajima K, Kusuoka H, et al. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. Eur J Nucl Med Mol Imaging 2008; 35: 319–28.
13. Matsuo S, Nakajima K, Horie M, et al; J-ACCESS
Investigators. Prognostic value of normal stress myocardial perfusion imaging in Japanese population: a study based on the J-ACCESS study. Circ J 2008; 72: 611–7.

14. Ueshima K, Yamashina A, Usami S, et al. Prognostic value of myocardial perfusion SPECT images in combination with the maximal heart rate at exercise testing in Japanese patients with suspected ischemic heart disease: a sub-analysis of J-ACCESS. Ann Nucl Med 2009; 23: 849–54.

15. Segawa C, Ogino M, Okabayashi A, et al. Basic investigation of software named “Heart Risk View” to estimate the probability of cardiac events, for the purpose of evaluating the availability in clinical practice (article in Japanese). Kaku Igaku 2009; 46: 21–7.

16. Kono K, Fuji H, Nakai K, et al. Composition and plaque patterns of coronary culprit lesions and clinical characteristics of patients with chronic kidney disease. Kidney Int 2012; 82: 344–51.

17. Milliner DS, Zinsmeister AR, Lieberman E, et al. Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int 1990; 38: 931–6.

18. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009; 119: 3070–7.

19. McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: current evidence and clinical importance. Eur Heart J 2014; 35: 1719–25.

20. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension 2007; 50: 197–203.

21. Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2017; 70: 136–48.

22. Villines TC, Hulten EA, Shaw LJ, et al; CONFIRM Registry Investigators. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT angiography evaluation for clinical outcomes: An international multicenter) registry. J Am Coll Cardiol 2011; 58: 2533–40.

23. Muramatsu T, Nishimura S, Yamashina A, et al; J-ACCESS Investigators. Relation between prognosis and myocardial perfusion imaging from the difference of end-point criterion for exercise stress testing: a sub-analysis of the J-ACCESS study. J Cardiol 2010; 56: 51–8.

24. Nakajima K, Matsuo S, Okuyama C, et al. Cardiac event risk in Japanese subjects estimated using gated myocardial perfusion imaging, in conjunction with diabetes mellitus and chronic kidney disease. Circ J 2012; 76: 168–75.