

REVIEW ARTICLE—INTERNATIONAL CORNER

J-ACCESS: Japanese Multicenter Prognostic Study of Coronary Artery Disease Using Myocardial Perfusion SPECT

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Abstract

J-ACCESS was the first database created in Japan to assess prognosis of patients with coronary artery disease (CAD) using myocardial perfusion imaging and its quantitation. Four J-ACCESS studies have been completed since 2001, and 4,629 patients who were diagnosed with or suspected of having CAD were registered in the initial study. The J-ACCESS investigations of prognostic databases after stress myocardial perfusion single-photon emission computed tomography (SPECT) between 2004 and 2018, which included patients with diabetes mellitus (J-ACCESS 2), chronic kidney disease (J-ACCESS 3) and coronary revascularization (J-ACCESS 4), uncovered novel findings. Myocardial perfusion defects and left ventricular function were identified as determinants of major cardiac events, and the clinical variables of diabetes and chronic kidney disease (or estimated glomerular filtration rate) were selected as independent predictors of cardiac events. Multivariable risk models can estimate major event risk, and thus stratify patients according to the likelihood of being at low, intermediate, or high risk for CAD.

Keywords: Cardiac events, Chronic kidney disease, Diabetes mellitus, Japanese database, Myocardial perfusion imaging, Risk stratification

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The Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated single-photon emission computed tomography (SPECT) (J-ACCESS) was the first nation-wide database specifically created to determine the ability of myocardial perfusion SPECT to assess patients who were diagnosed with or suspected of having coronary artery disease (CAD). Outcomes were analyzed using the quantitative gated SPECT analytical software, QGS (Sinai Medical Center, Los Angeles, CA, USA) (1). Table 1 outlines the J-ACCESS investigations, which included 4,629 patients for J-ACCESS and approximately 500 patients each for J-ACCESS 2, 3 and 4. This article summarizes the major findings of these studies.

J-ACCESS

J-ACCESS included 4,629 consecutively registered patients who were diagnosed with or were suspected of having CAD at

117 institutions during 2001 (1). All patients were assessed by ^{99m}Tc-tetrofosmin stress-rest and gated SPECT and their data were analyzed using QGS software, which was highly precise for multicenter studies (2). Myocardial perfusion defects were analyzed using summed stress/rest/difference scores (SSS/SRS/SDS). Primary endpoints comprised the major events of cardiac death, non-fatal myocardial infarction, and heart failure severe enough to require hospitalization. The patients analyzed in J-ACCESS 1 to 3 were followed up for three years. These methods of data collection, processing and analysis were the same in all J-ACCESS studies.

Among 4,031 patients who were followed up for three years, 175 (4.3%) developed major cardiac events comprising cardiac death (n=45), nonfatal myocardial infarction (n=37) and heart failure requiring hospitalization (n=93). Although the rates of cardiac hard events were lower (by approximately 1/3) among the Japanese, than North American patients, event

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Table 1 J-ACCESS investigations

	Patient selection and purpose	Duration of entry and follow-up	Hospitals (n)	Patients (n)	Predictors of major cardiac events (multivariate analysis)	Major events/3 years
J-ACCESS	Consecutive registration, suspected CAD	2001.10-2002.3 3-y follow-up	117	4,629	Age, SSS, LVEF, ESV, LVEF	175/4031 (4.3%)
J-ACCESS 2	Type 2 diabetes asymptomatic for CAD	2004.06-2005.09 3-y follow-up	50	513	SSS, eGFR, current smoking	17/485 (3.5%)
J-ACCESS 3	Chronic kidney disease with eGFR <50 mL/min/1.73 m ²	2009.04-2010.9 3-y follow-up	62	549	SSS, eGFR, CRP	60/529 (11.3%)
J-ACCESS 4	CAD, Reduction of ischemia after revascularization or appropriate medications	2012.06-2013.12 At least 1-year follow-up	59	494	Comparison of patients with ≥5% and <5% ischemia	4/114 (3.5%)

CAD: coronary artery disease, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, ESV: end-systolic volume, LVEF: left ventricular ejection fraction, SSS: summed stress score

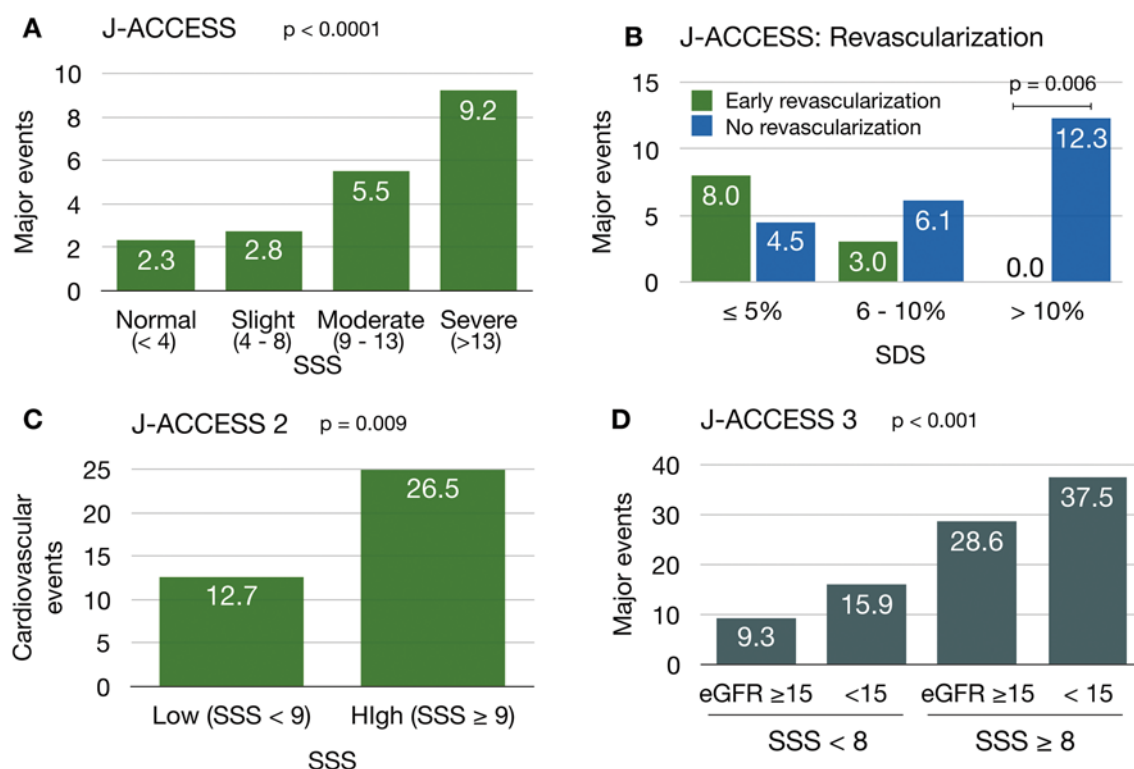


Fig. 1 Findings and cardiac events in J-ACCESS studies.

Major cardiac events (%/3 years) and summed stress scores (A). Cardiac event rates with and without early revascularization (B). Cardiovascular events and SSS in J-ACCESS 2 (C). Major cardiac events in J-ACCESS 3 (D). Graphs were created from original data in references 1, 7, 9 and 10, respectively. SSS, summed stress scores.

predictors were similar among several multicenter studies. Myocardial perfusion defects on stress SPECT images determined from SSS and lower left ventricular ejection fraction (LVEF) were major predictors of cardiac events (Fig. 1A). Patients with diabetes had a two-fold increase in major event risk. In addition, estimated glomerular filtration rates (eGFR) or chronic kidney disease (CKD) were significant independent predictors (3, 4). Normal ventricular function determined by myocardial perfusion SPECT was an indicator of a good prognosis (5). Perfusion abnormalities determined by myocardial perfusion SPECT had a significant additive value over coronary stenosis to predict cardiac events (6).

Propensity-score-matched analysis showed that early revascularization was more effective than medication for patients with >10% ischemia (Fig. 1B) (7). Although the study included a high proportion of patients with heart failure, CKD, higher SSS and higher end-systolic volumes conferred independent and additive value for predicting the risk of refractory heart failure in patients with known or suspected CAD (8).

J-ACCESS 2: Patients with type 2 diabetes

Since the risk of cardiovascular events was considered high among patients with type 2 diabetes, J-ACCESS 2 examined the prognosis of patients with diabetes who were asymptoma-

tic for CAD (9). Perfusion findings included myocardial ischemia and/or scar in 32% of these patients. During a three-year follow-up, 62 (13%) events comprised five cardiac deaths (sudden death, $n=3$; cardiac death, $n=2$) and 57 cardiovascular events comprising nonfatal acute coronary syndrome ($n=9$), heart failure requiring hospitalization ($n=3$), new onset of stable angina pectoris ($n=10$), cerebrovascular accident ($n=15$), and others (Fig. 1C). Multivariate Cox regression analysis selected SSS ≥ 9 , low eGFR, and being a current smoker as significant variables, indicating a need for active treatment strategies for patients with type 2 diabetes who are asymptomatic for CAD.

J-ACCESS 3: Patients with CKD

This prospective cohort study investigated the ability of myocardial perfusion SPECT to predict cardiac events in patients with CKD and an eGFR <50 mL/min/1.73 m² without definitive CAD (10). The event-free survival rate was lower among patients with kidney dysfunction and higher SSS (Fig. 1D). C-reactive protein ≥ 0.3 mg/dL was notably an independent predictor of cardiac events, suggesting that an inflammatory parameter should be included as a pathophysiological basis for the development of cardiovascular events.

J-ACCESS 4: Patients with coronary revascularization

Although cardiology guidelines include stress-induced myocardial ischemia as an indication for coronary revascularization in patients with chronic stable CAD, whether myocardial ischemia could be a target of coronary revascularization to reduce cardiac events in a Japanese population had not been verified (11). When patients were classified into groups based on a threshold of a 5% reduction in ischemia (5% corresponds to a score of 4/68 with a 17-segment model and 0 to 4 points for each segment), the prognosis was significantly better for those with $\geq 5\%$ improvement after revascularization.

J-ACCESS risk model

We proposed the risk stratification of patients based on multivariable logistic models derived from all J-ACCESS findings. The risk model included variables of age, SSS, LVEF, diabetes, and subsequently eGFR. One feature of the risk model was the direct calculation of major event rates in terms of %/3 years (12), and the model was validated by comparing predicted and actual outcomes between a new patient cohort in the APPROACH study (13) and the patients in J-ACCESS 3 (14). That study effectively stratified risk in the J-ACCESS models, whereas actual event rates were equally high across all risk groups among patients with eGFR <15 mL/min/1.73 m².

Risk stratification incorporating SPECT and clinical

variables allows the classification of patients into being at low, intermediate and high risk for cardiovascular events, thus providing useful information upon which to base decisions regarding medications and other treatments such as revascularization (15).

Conclusions

J-ACCESS has created a nationwide prognostic database of Japanese patients who have been followed up for three years. The prognostic evidence generated from Japanese patients with CAD assessed by myocardial perfusion SPECT can provide baseline information from which prognosis can be predicted, nuclear cardiology guidelines can be established, and most importantly, medical care can be appropriately personalized for patients considering degrees of risk.

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Conflicts of interest

None.

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References

1. 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.
2. Nakajima K, Nishimura T. Inter-institution preference-based variability of ejection fraction and volumes using quantitative gated SPECT with 99mTc-tetrofosmin: a multicentre study involving 106 hospitals. *Eur J Nucl Med Mol Imaging* 2006; 33: 127-33.
3. Hatta T, Nishimura S, Nishimura T. Prognostic risk stratification of myocardial ischaemia evaluated by gated myocardial perfusion SPECT in patients with chronic kidney disease. *Eur J Nucl Med Mol Imaging* 2009; 36: 1835-41.
4. Nakajima K, Matsuo S, Okuda K, et al. Estimation of cardiac event risk by gated myocardial perfusion imaging and quantitative scoring methods based on a multi-center J-ACCESS database. *Circ J* 2011; 75: 2417-23.

5. Matsuo S, Nakajima K, Horie M, et al. Prognostic value of normal stress myocardial perfusion imaging in Japanese population. *Circ J* 2008; 72: 611-7.
6. Momose M, Nakajima K, Nishimura T. Prognostic significance of stress myocardial gated SPECT among Japanese patients referred for coronary angiography: A study of data from the J-ACCESS database. *Eur J Nucl Med Mol Imaging* 2009; 36: 1329-37.
7. Moroi M, Yamashina A, Tsukamoto K, et al. Coronary revascularization does not decrease cardiac events in patients with stable ischemic heart disease but might do in those who showed moderate to severe ischemia. *Int J Cardiol* 2012; 158: 246-52.
8. Nakata T, Hashimoto A, Wakabayashi T, et al. Prediction of new-onset refractory congestive heart failure using stress/rest gated perfusion SPECT imaging in patients with known or suspected coronary artery disease: Sub-analysis of the J-ACCESS study. *JACC Cardiovasc Imaging* 2009; 2: 1393-400.
9. Yamasaki Y, Nakajima K, Kusuoka H, et al. Prognostic value of gated myocardial perfusion imaging for asymptomatic patients with type 2 diabetes: the J-ACCESS 2 investigation. *Diabetes Care* 2010; 33: 2320-6.
10. 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 imaging: Final 3-year report of the J-ACCESS 3 study. *J Nucl Cardiol* 2017 [Epub ahead of print] doi: 10.1007/s12350-017-0880-5.
11. Nanasato M, Matsumoto N, Nakajima K, et al. Prognostic impact of reducing myocardial ischemia identified using ECG-gated myocardial perfusion SPECT in Japanese patients with coronary artery disease: J-ACCESS 4 study. *Int J Cardiol* 2018 [Epub ahead of print] doi.org/10.1016/j.ijcard.2018.05.090.
12. 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.
13. Aburadani I, Usuda K, Sumiya H, et al. Ability of the prognostic model of J-ACCESS study to predict cardiac events in a clinical setting: the APPROACH study. *J Cardiol* 2018; 72: 81-6.
14. Nakajima K, Nakamura S, Hase H, Takeishi Y, Nishimura S, Kawano Y, et al. Risk stratification based on J-ACCESS risk models with myocardial perfusion images of patients with chronic kidney disease. *J Nucl Cardiol* 2018 [Epub ahead of print] doi.org/10.1007/s12350-018-1330-8.
15. Nakajima K, Nishimura T. Cardiovascular events in Japan. Lessons from the J-ACCESS multicenter prognostic study using myocardial perfusion imaging. *Circ J* 2012; 76: 1313-21.

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