Despite recent advances in cardiac imaging technology, morphological assessment of coronary anatomy tends to overestimate coronary narrowing that is not necessarily related to functional myocardial ischemia and outcomes.1 Recent multicenter studies clearly show that invasive therapeutic strategy based on coronary stenosis without initial assessment of myocardial ischemia does not necessarily improve prognosis in stable coronary artery disease (CAD) patients2-5 and that functional ischemia detection using stress myocardial perfusion imaging (MPI)6,7 or fractional flow reserve has demonstrated close correlations between the severity of myocardial ischemia and cardiac events and ischemia-based benefits of invasive and medical treatments. In this issue of the Journal, Petretta et al8 demonstrate the effects of the degree of stress-induced ischemia and post-stress left ventricular ejection fraction (LVEF), both of which were assessed by stress-gated MPI, on the prognostic benefits of revascularization in 2,059 patients with suspected or known CAD during 61 months. Despite its retrospective nature, the results derived from this large, long-term follow-up study are relevant given the strengthened recognition of the prognostic implications of functional ischemia in patients with stable CAD. Before these results can be put into clinical perspective, however, there are several issues to be recognized.

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Firstly, the stress MPI results were not blinded to the treating physicians who made the decision. Cardiologists select a more invasive strategy when patients are stable clinically without serious complications, symptomatically resistant to standard medical treatment and at high risk based on stress MPI and/or coronary lesions. This is clinically acceptable and the presented findings are biologically tenable. There, however, were apparently differences in the clinical and ischemic backgrounds between the groups treated with and without revascularization, and selection bias for indication of revascularization may have overestimated the therapeutic benefits in this study. Patients with smaller ischemic burden and preserved LVEF were treated without revascularization and had better outcomes, while revascularization was selected when patients had a larger ischemic burden and reduced LVEF (Table S1). Although the
event group treated with revascularization had a larger ischemic burden (summed difference score, SDS) than did the event group without revascularization (5.1±5.3 vs. 2.2±3.4, respectively), the cardiac event rates were nearly 3.8% following coronary revascularization and 9.5% without, strongly supporting the long-term prognostic benefits of revascularization. Secondly, an optimal cutoff of ischemic burden size for outcome prediction depends on post-stress LVEF; SDS cutoffs for effective revascularization were ≥6 in normal post-stress LVEF and ≥3 in reduced post-stress LVEF. Each percent ischemic myocardium was calculated as 8.8% for SDS 6 and 4.4% for SDS 3, respectively. Compared with cutoffs (10–12%) of ischemic burden size for differentiating prognostic benefits of medical and revascularization treatments reported previously, 7–9 the former (8.8%) is nearly identical but the latter (4.4%) is much lower. Percent myocardial ischemia was a powerful prognosis determinant and predictor of benefits from revascularization in patients with preserved post-stress LVEF. In patients with reduced post-stress LVEF, however, these findings were not necessarily evident and SDS was not a significant independent predictor of major cardiac events. The Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT (J-ACCESS) investigation of 4,031 patients with suspected or known CAD 10–11 reported the similar results; the major cardiac event rate was significantly related to reduced LVEF, and stress-induced myocardial perfusion abnormality further increased unfavorable outcomes in LVEF ≥45% but not in LVEF <45%. At variance with an increase in survival benefit from invasive therapy in parallel with ischemia grade, how did revascularization improve outcomes when myocardial ischemia was minimal, or conversely why did revascularization fail to show a corresponding reduction in hazard ratio when SDS was predominant in patients with reduced post-stress LVEF in this study? Revascularization may have been incomplete but effective enough to improve cardiac outcomes by abating critical myocardial ischemia in this study. Because of the lack of data on repeated stress-gated MPI, it remains to be clarified how revascularization improved post-stress LVEF and SDS in correlation with outcomes. Finally, although gated stress MPI is well established for the prediction of major cardiac events in patients with known or suspected CAD and for the selection of therapeutic strategy, the diagnostic value of this method in the prediction of ischemia-related heart failure remains to be explored. The value of gated stress MPI is suggested in patients with stress-induced LV dysfunction and myocardial perfusion abnormality, because of the ability of this technique to simultaneously evaluate myocardial viability, functionally reversible ischemia and cardiac function. 12 The J-ACCESS sub-study of 3,835 patients demonstrated that gated stress MPI has potential to identify patients at increased risk for new-onset heart failure in combination with stress-induced myocardial perfusion abnormality, kidney function and end-systolic volume (Figure). This feasibility of gated stress MPI in the risk-stratification and prognosis-prediction of heart failure or ischemic cardiomyopathy could contribute to the determination of therapeutic strategy such as optimal medical treatment, preventive coronary intervention or surgical LV reconstruction.

Despite these limitations, this study has clinically important messages to be noted: the long-term prognosis and effects of revascularization on cardiac outcomes depend on both the functional ischemia burden size and post-stress LVEF, and an appropriate selection of therapeutic strategy based on these functional parameters can contribute to predicting prognostic benefits of the treatment in CAD patients. Future comparative studies are needed to explore long-term, ischemia-based effects of optimal drug treatment and percutaneous coronary intervention, as well as surgical revascularization, on improvement in LVEF, functional ischemia and ultimately clinical outcomes.

Disclosures
T.N. and K.A. have no conflicts of interest to be declared.

References