The evolution of the prognostic value of regadenoson SPECT myocardial perfusion imaging

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Risk stratification for patients with known or suspected ischemic heart disease has the ability to alter patient management, with the goal of reducing subsequent cardiac events. Additionally, the clinical value of a “normal” noninvasive cardiac test, which suggests a low future incidence of a major cardiac event (MACE; cardiac death or acute myocardial infarction)¹ may decrease unnecessary downstream testing, thus benefiting patients and health care systems alike. Stress single-photon emission computed tomographic (SPECT) myocardial perfusion imaging (MPI) provides noninvasive physiologic information regarding the flow-limiting disease; semi-quantitative and quantitative measures of perfusion abnormalities have been shown to be of prognostic value in the prediction of major cardiac and non-cardiac event when performed in conjunction with either pharmacologic stress or exercise.²

Regadenoson, approved in 2008,³ has been integrated into nuclear cardiology laboratories and is currently the preferred pharmacological vasodilator stress agent in the USA, due to the simple logistics of administration (fixed dose, bolus injection, rapid onset/offset). The ADVANCE-MPI trials provided evidence

of the safety and diagnostic non-inferiority of regadenoson compared to adenosine.^{4,5} However, the prognostic yield of regadenoson has been largely imputed from outcome data of other pharmacological agents, dipyridamole, and adenosine, as there are limited outcome data with regards to regadenoson.

In this issue of the journal, Kattoor et al, add to the literature regarding the prognostic value of regadenoson SPECT MPI with a single-center retrospective cohort study of 10,275 consecutive patients, with a follow-up period of 2.4 ± 2.2 years. Remarkably, only 2.7% of patients were lost to follow-up. The data were collected for MACE, defined as cardiac death or myocardial infarction. The authors are to be congratulated for a job well-done with this large-scale and pragmatic evaluation of a commonly performed noninvasive test. This laboratory has published many reports of their real-world experience^{6,7} and those, along with the current study provide a unique evaluation, as the cohort is comprised largely of women.

The authors describe a direct correlation between parameters of abnormal stress imaging [summed stress score (SSS) and summed difference score (SDS)] with future risk of cardiac events, with a greater likelihood of MACE as the study becomes more abnormal. This has been noted in many trials, dating back to 1995 with dipyridamole⁸ and 2003 with adenosine.⁹ The current trial adds to the overall conclusion that irrespective of the mode or agent of stress, or the imaging methodology, the larger/more severe the perfusion abnormality, the worse the outcome. The incremental prognostic utility of regadenoson MPI using global Chi-square index was clearly demonstrated even after adjustment for other variables. However, this is somewhat an antiquated approach as it has been used since 1998.¹⁰ We applaud the authors of the current study to use a modern statistical

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approach, integrated discrimination improvement index, which is similar to net reclassification index but designed to evaluation improvement in risk prediction across a wide spectrum.

This study reports annualized event rate (AER) of a normal MPI, defined as a SSS ≤ 3 , to be 1.0% for cardiac death or myocardial infarction and 2.1% for a composite endpoint of MACE, which includes cardiac revascularization. The frequency of subsequent events is consistent with many articles, which demonstrate a higher AER for normal pharmacologic SPECT studies testing than noted with normal exercise tests^{11–14}; an abnormal pharmacologic stress SPECT study is also associated with a worse prognosis than with an abnormal exercise SPECT. The current trial reveals a high event rate, likely due to other factors, including a high prevalence of end-stage renal disease. Thus, an inability to perform maximal exercise is associated with a higher mortality risk (both cardiac and non-cardiac deaths).¹⁵ This is likely related to more advanced age as well as an increased incidence of comorbidities, such as diabetes and known coronary artery disease, which are more common in patients undergoing pharmacologic stress testing. Additionally, maximum “stress”, including the level of hyperemia, may not be equivalent between exercise and vasodilator stress testing.

Other investigators have also demonstrated the prognostic utility of regadenoson SPECT MPI. Hage et al¹⁶ demonstrated successful risk stratification in 1,400 patients, who were followed 46 ± 18 months. They also demonstrated a correlation of cardiac events with perfusion defect size. Comparably, Iqbal et al¹⁷ did a propensity match analysis of normal regadenoson vs. adenosine MPI studies with normal left ventricular ejection fraction (LVEF) with a resultant 505 patients in each group. The AER in the unmatched cohort for the primary outcome was 1.1% in the regadenoson group, and 1.7% in the adenosine group ($P = .09$) whereas in the matched cohort were 0.7% in the regadenoson group and 1.3% the adenosine group ($P = .26$), respectively. These authors noted a non-significantly lower event rate with a normal regadenoson study. The increased incidence of MACE and all-cause mortality noted in the unmatched cohort with regadenoson and adenosine, while not significant, raises a concern about whether this vasodilator promotes maximum hyperemia, as shown in a Rb-82 PET study where regadenoson was compared with dipyridamole.¹⁸ Nevertheless, the current study along with others solidifies the durable prognostic utility of regadenoson SPECT MPI.

Beyond the presence of abnormal perfusion and the size/severity of perfusion defects, SPECT MPI also provides additional markers of enhanced risk for MACE. Notably, a drop of stress LVEF by at least 5% compared

to rest (LVEF reserve) and a higher left ventricular end-diastolic volume post-stress have been associated with a poor prognosis.^{19–22} The authors of the current study also demonstrate an inverse correlation for stress left ventricular ejection fraction (LVEF), LVEF reserve, and future MACE risk with regadenoson. Additionally, transient cavity dilation with stress (AKA transient ischemic dilation or TID) has been shown to varying degrees to be a marker of high risk for subsequent cardiac events.^{23–25} Interestingly, the present study did not reveal increased incidence of MACE with an elevated transient ischemic dilatation (TID) ratio (≥ 1.31). Despite a high threshold value of 1.31, even a linear association of TID with MACE risk was unable to be established. The current study joins that by Golzar et al,²⁶ providing further uncertainty on the usefulness of TID with regadenoson stress testing to provide value for risk assessment. Regadenoson TID carries a high specificity for CAD diagnosis,²⁷ and there is substantial evidence of prognostic value with exercise SPECT MPI.^{28,29} However, in regards to risk assessment with vasodilator SPECT MPI, the TID ratio is not reliable, especially if no perfusion defects are present.

Other non-imaging markers also provide prognostic value when associated with regadenoson stress. ST segment changes are associated with worse outcomes, even in the absence of perfusion defects.³⁰ Also, a decreasing heart rate recovery (HRR) provides additional independent prognostic utility in patients undergoing regadenoson SPECT MPI.³¹ In fact, Hage et al³¹ demonstrated decreasing HRR to be associated with increasing mortality after adjusting for age, gender, diabetes mellitus, renal disease, & MPI findings. Neither ST segment changes nor HRR measurements were included in the current report.

A final note regarding stress SPECT MPI-exercise stress imaging remains the preferred modality for risk stratification,¹² with the AER for a normal exercise MPI 0.45% per year. With exercise, the Duke treadmill score utilizes an assessment of chest pain and ST segment changes to provide additional prognostic information, tools that are not available with regadenoson vasodilator stress imaging. It will likely be valuable to establish the prognostic power of a standardized tool integrating non-imaging parameters like HRR and ST changes, along with clinical factors, in risk reclassification of regadenoson SPECT perfusion studies, as has been reported with adenosine.³²

Regadenoson is well-established as a useful pharmacological stress agent, with attractive features that include ease of administration, no dose calculation, and a lower adverse event rate compared to adenosine and dipyridamole. It has demonstrated safety, diagnostic, and prognostic utility in a wide variety of subjects,

including vulnerable patient such as those with chronic pulmonary diseases³³ as well as in renal³⁴ and liver diseases.³⁵ The recent ischemia trial, however, gives us pause as to whether the presence or burden of ischemia is valuable, as this trial failed to demonstrate an association between ISCHEMIA and all-cause mortality.³⁶ However, this was a trial examining the potential value of patients with moderate to severe ischemia with regards to revascularization and was not designed to address the value in identifying low risk patients, such as has been demonstrated in the current study. In conclusion, the current study solidifies the role of regadenoson SPECT MPI as a prognostic tool in a real-world, diverse population and serves to reclassify risk for patients beyond standard clinical factors.

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