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EDITORIAL COMMENT

Comparing Prognostic Value of Imaging Agents and Imaging Techniques*

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In the development trajectory of a new noninvasive imaging agent or technology, initial studies often focus on the ability of the modality to detect or rule out coronary disease, driven in part by regulatory considerations because regulatory approval often involves measures of diagnostic performance. Later in the life cycle of the modality, studies begin to appear that evaluate the prognostic performance of the technique.

See page 1014

The seminal studies of Brown et al. (1) and Ladenheim et al. (2) in the 1980s brought to the fore the concept of using noninvasive imaging data to assess prognosis. Since that time, there have been literally hundreds, if not thousands, of publications evaluating the prognostic implications of imaging findings. These papers span the gamut of all imaging modalities, as well as spanning across distinct techniques and patient groups within modalities. For example, the prognostic ability of radionuclide myocardial perfusion imaging (MPI) seems to hold no matter what tracer or stressor is used and seems to hold across both genders (3).

After those initial reports involving radionuclide imaging, the literature grew over the subsequent 15 years. In 2003, the American College of Cardiology/American Heart Association/American Society for Nuclear Cardiology guidelines for radionuclide imaging summarized studies involving >20,000 patients in which a normal stress myocardial perfusion study was associated with a subsequent event rate of <1% per year (3). In contemporary practice, the expectation of the community for such data has grown, and the speed with which data are gathered and published has increased as well. Relatively soon after multidetector computed tomography angiography (CTA) reached a stage in its technical development allowing widespread use and good diagnostic performance, multicenter studies involving >20,000 patients appeared documenting the prognostic power of this modality (4).

The general concepts involved in the literature in this area follow a stereotypical format. Some measure of the magnitude of abnormality of the imaging data is related to the risk of an untoward event over long-term follow-up. In the radionuclide MPI literature, this usually means that a semiquantitative or quantitative measure of the extent and/or severity of perfusion abnormality on the stress image relates to the risk of cardiac death or nonfatal myocardial infarction during follow-up. The more abnormal the perfusion during the test, the higher the risk (usually annualized) of a subsequent event (1,2). The abnormality on imaging could be the extent of wall motion abnormality on stress echocardiography (5), abnormal perfusion on stress cardiac magnetic resonance (6), or the extent of coronary disease on CTA (4).

A consistently important feature of all of these studies is the low event rate associated with a normal study result. As noted, this has been well documented for radionuclide MPI (3), for CTA (7), and indeed for all of the modalities, although less overall information exists at this time point for cardiac magnetic resonance. The reason such information is important clinically is that among all

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outpatients referred for noninvasive testing, the majority will have a normal study result. Knowing that this result is associated with very low risk assists clinicians in making a decision toward a conservative management strategy.

What underlies this consistent finding in the literature? Of course, many patients have normal study results because they do not have underlying coronary disease and thus are not at risk for cardiac events over the foreseeable future. However, the data showing that outcomes associated with a normal study are also relatively benign even among patients with known coronary disease (8) have suggested that the demonstration of normal stress perfusion is likely reflective of other factors that influence myocardial blood flow, such as preserved endothelial function and robust collateralization, which should also be protective against acute events. Thus, there are many reasons why clinicians desire this type of information about any new agent involved in noninvasive imaging of patients who have suspected or known coronary disease.

Regadenoson is a pharmacological stress agent that recently received regulatory approval and has quickly gained widespread use for radionuclide MPI, due in part to its more convenient method of administration compared with adenosine (i.e., bolus dosing instead of the requirement for an infusion pump) (9). In vivo studies support the belief that regadenoson is more selective for the adenosine A_{2A} receptor than adenosine (10), which in theory should make the adverse effect profile more favorable. The data on this point have been more mixed, with composite scores in trials showing some benefit over adenosine in that regard but prevalence of individual adverse effects revealing little difference (9). There is a growing literature on the safety of using regadenoson in patients with chronic pulmonary disease (11), which is clinically useful.

In this issue of *iJACC*, Iqbal et al. (12) report results of 1 of the initial large-scale outcomes studies on imaging with regadenoson; it is thus a paper of great interest. The investigators assembled a cohort of 1,000 consecutive patients from a single center who underwent pharmacological stress with this new agent and who also had normal perfusion images and normal left ventricular function. All patients were followed for 2 years after testing for the occurrence of any composite of events, including cardiac death, nonfatal myocardial infarction, or revascularization. The results show that the rate of the composite endpoint was low among these patients, and the rate of the "harder" endpoints of cardiac death or nonfatal myocardial infarction was also low and in the range of results reported in most other studies of noninvasive imaging modalities. This is important and clinically useful information.

Most papers reporting prognostic data for imaging tests are descriptive of only 1 modality. The paper by Iqbal et al. (12), however, also reports comparative data on outcomes associated with normal adenosine pharmacological stress MPI in another sample of 1,000 consecutive patients from the same center, albeit from an earlier era before the laboratory switched stress agents for everyday use. The results show that the regadenoson data are generally comparable to those of adenosine in terms of the low risk associated with a normal perfusion study result. This comparison is a major strength of the paper and is of great interest. Such an analytical approach brings with it significant challenges, however. As seen in Table 1 of the paper, there were substantial demographic and clinical differences between the 2 patient groups. Among the adenosine group, there was a much higher rate of inpatient testing, likely a marker of a sicker, higher-risk population. Among the regadenoson group, there was a much higher rate of referral for testing for pre-transplant evaluation, likely a marker of significant noncardiac morbidities. The investigators addressed this issue by using propensity scoring and matching, creating a subcohort of the 2 groups well matched for almost all characteristics, in which the outcomes were compared. This analysis also found that the prognostic value of a normal MPI study result was similar between the 2 agents, in a much "cleaner" comparison, albeit with fewer patients and events and thus with lower confidence in the estimates.

There are several strengths of this analysis (12). As noted, few papers directly compare outcomes associated with different imaging agents or techniques. The authors' use of propensity scoring and matching to attempt to address the baseline differences in the population samples clearly sets a standard for such analyses for the future.

There are also some important limitations to bear in mind. Although the total group of 2,000 patients reported seems large, by the time the groups are "whittled down" in the propensity-matched cohorts, there remains only approximately 500 patients per group, and, as noted earlier, the rate of events is low (12). This leads to wide confidence limits around the hazard ratio comparing regadenoson with adenosine, and thus leaves open the possibility that regadenoson is distinctly worse, or

better, than adenosine with regard to the outcome of interest, although that is not likely.

Moreover, reporting only outcomes associated with a normal MPI study result, while of interest and clinically useful, is an incomplete descriptor of the prognostic power of a technique. It would have been more informative to assemble cohorts of consecutive patients referred for testing and assessed outcomes associated with the entire range of MPI results, from normal to severely abnormal, as is usually done. If, for instance, it was found that outcomes associated with a mild or moderately abnormal regadenoson MPI were also low risk (i.e., "false positive" with regard to prognosis), this finding would have called into question the overall impact of using this agent. Again, that finding is not likely but remains an open question that needs to be addressed.

Hence, the study by Iqbal et al. (12) is a step forward in our knowledge of a new pharmacological stress agent. Their findings that outcomes associated with a normal regadenoson MPI study are indeed low risk is important knowledge for clinicians making decisions about patient management after testing. The use of propensity scoring and matching to allow a direct comparison between a well-established agent and a newer agent in this field sets a standard for future comparative studies. We will need to await future studies that assess the outcomes associated with a full range of MPI results with this agent and also involve large numbers of patients beyond a highly expert single center. The bar for outcomes studies is now very high, with multicenter studies involving many thousands of patients (7) becoming the norm.

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