Assessing the Prognostic Value of Cardiovascular Imaging
A Statistical Exercise or a Guide to Clinical Value and Application?

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Cardiovascular imaging has become the focus of attention from both physicians and payers. The former see the potential of newer modalities to permit new and exciting insights into the diagnosis and management of coronary artery disease (CAD), that, in turn, may result in enhanced patient care strategies and new efficient clinical algorithms. On the other hand, payers have understandable concerns about the excessive use and enormous costs associated with cardiovascular imaging. These concerns have been exacerbated by the rapid expansion of the imaging devices used for the assessment of patients with known or suspected CAD. Cardiovascular stress imaging has long been the domain of stress single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) and stress echocardiography wall motion studies. At present, stress positron emission tomography (PET) MPI, cardiac computed tomography coronary angiography (CTA) (and, possibly, stress CT MPI), as well as cardiac magnetic resonance imaging (CMR) MPI and wall motion studies are utilized in daily practice. Whether all of these modalities will be reimbursed in the future is uncertain, but little doubt remains that their rigorous validation will be compulsory.

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Cardiac magnetic resonance imaging is an evolving technique with growing indications within the clinical cardiology setting. Whereas late gadolinium enhancement (LGE) has gained acceptance as an accurate approach for viability assessment, CMR stress imaging use is increasing as well. Nonetheless, stress CMR techniques are in their relative infancy, and evidence is only now beginning to accumulate justifying their use. Whereas several studies have examined the diagnostic accuracy of stress CMR, only recently have sufficient numbers of patients been collected to assess the prognostic value of this approach1-5 (Table).6 The validation of stress CMR is more complex than that of previous modalities, inasmuch as a routine study would include rest function and structure, stress perfusion, and viability images (as well as, potentially, rest perfusion). In this issue of Circulation, Steel and colleagues6 report on the complementary prognostic values of stress myocardial perfusion and LGE imaging using stress perfusion CMR in 254 patients with known or suspected CAD who were followed up for a mean of 1.4 years. This study examined 2 primary end points: the combined end point of cardiac death and nonfatal myocardial infarction (CD/MI) and the composite end point of cardiac death, nonfatal MI, hospitalization for unstable angina, and late (>30 days after index CMR) revascularization. In their study, the risk of either end point increased with worsening test results, whether perfusion, left ventricular (LV) function, or LGE. The investigators found that the best model for prediction of CD/MI consisted of a history of prior cigarette smoking and LV end systolic volume index ($\chi^2$ 26), and the model most closely associated with their composite end point consisted of pre-CMR likelihood of CAD and reversible perfusion defects ($\chi^2$ 59). With respect to the prognostic complementarity of LGE and perfusion, the authors found that reversible perfusion defects and the presence of LGE were both associated with the end point of CD/MI in both univariate analyses and after adjustment for patient sex and age in a model inclusive of both of these CMR variables. This finding extends results from previous studies reporting the complementary nature of stress perfusion and viability7 to CMR, justifying the acquisition and reporting of both of these data elements.

Two significant potential weaknesses of this study merit discussion. First, the study cohort appears to have consisted of an unusual mix of patients. In comparison with other studies of stress imaging, the patients were relatively young (mean age 58 years), they had a low likelihood of CAD (29% mean probability of CAD) and normal LV function (mean EF 58%), they manifested a tachycardic response to vasodilator stress (average increase in heart rate of 29%, a marker of relatively low risk8), and only 22% had previously experienced MI. Yet these patients had a CD/MI rate of 7.9% per year, an event rate considerably higher than that generally reported with either stress SPECT, PET, or echocardiography in patients in stable condition. It was also a greater CD/MI rate than that reported in previous prognostic stress CMR studies (Table), including a study in patients with LV dysfunction.1 Hence, given the risk profile of these patients, the generalizability of results from this cohort is unclear.

The second issue is a common one: the combination of a relative small study size, a short follow-up interval, and—despite the relatively high event rate—an inadequate number of events, yielding suboptimal study power. The minimum number of variables that can be entered into a model in the performance of multivariable modeling is a function of the number of events accrued in the study. Generally, 1 variable per 10 events is strongly recommended, and 1 variable per 20 events is preferred.9 In the current study, the authors would have been limited to 2 to 3 variables in any model of CD/MI.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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occurring. Inasmuch as 35 of the 49 events were related to when 1 of the composite end points is the principal event and other events, and the challenge of reporting study results influenced outcomes (eg, revascularization, hospitalization) in assessment of risk homogeneity among the component events, it is insufficient in light of the many other potential confounders. Consequently, the authors’ ability to model their data—the basis of all the results in this study—are quite limited, and overfitting is inevitable.

Interestingly, the central analysis of this study—the assessment of the complementarity of LGE and stress perfusion—appears to be underfitted in that the models examined do not consider variables of likely importance, thus leading to potential overestimation of the value of the modeled data. It is insufficient to assess whether LGE and perfusion add incrementally to each other; it is necessary to determine whether they do so incrementally to all other known data. Thus, to adjust only for sex and age in this analysis was insufficient in light of the many other potential confounders of the relationship between CMR measures and outcomes.

In the current study, the small number of events necessitated the use of composite end points. The use of composite end points increases the number of events and lowers accrual time but has numerous limitations. They include the assumption of risk homogeneity among the component events, differences in treatment response between physician-influenced outcomes (eg, revascularization, hospitalization) and other events, and the challenge of reporting study results when 1 of the composite end points is the principal event occurring. Inasmuch as 35 of the 49 events were related to unstable syndromes (acute MI, unstable angina), whether the reported models are predictive of cardiac death or late revascularization is unclear.

However, it is critical to also understand that the CMR prognostic literature is in its infancy, and as centers continue to use this approach, larger and better-powered studies will be published in the future. The initial data thus far are promising, and stress CMR will accrue a body of evidence to support its use over time.

### What Clinical Lessons Can Be Taken From This Study?

To enable us to understand whether the study results indicate that stress CMR achieves adequate risk stratification, 2 questions must be addressed: Does a “normal” study identify low-risk patients, and do abnormal CMR results define strata of risk? In this study, patients without reversible defects had a 4.2% CD/MI frequency (3.0%/year); in the absence of prior MI, this was 3.8% (2.7%/year). Adding LGE as a “complementary” test reduced CD/MI frequency in patients with normal study results (no reversible perfusion defects or LGE) to a 1.9% annual CD/MI frequency. This suggests that even with the use of this combined imaging approach, CMR failed to identify a low-risk subset. Although a low-risk group was not identified, risk stratification was achieved in the sense that increasing test abnormality was associated with greater risk. Interestingly, this risk was more striking when the test result was considered as a dichotomous result rather than a continuous result. For example, the presence of a reversible perfusion defect had a hazard ratio of 6.88 (almost a 7-fold increase in risk); yet summed difference score had a hazard ratio of 1.05 (a 50% increase in risk per 10 summed difference score point increase). Finally, on the basis of the presented results, it is unclear how many patients were reclassified by normal studies as not needing further testing.

### Translating Prognostic Studies to Clinical Practice

Prognostic studies of cardiovascular imaging require statistical rigor, yet must convey to clinicians how the modality examined can be optimally applied in practice. How clinicians can translate published studies to their daily practice is challenging.

First, with respect to study end points, the question whether patient management and/or treatment to prevent these end points is driven or altered by the use of stress imaging must be asked. The prevention of CAD progression, unstable syndromes, acute MI, and other related outcomes is the realm of medical management and lifestyle modifications. There is no evidence to support the use of stress imaging as a means of targeting disease, guiding treatment, or tracking its success with respect to these end points. The domain of stress MPI, whether performed by SPECT, PET, CMR, or CT, is the detection and assessment of obstructive CAD. Hence, its clinical role is more likely to be in the identification of patients with sufficient disease burden that they may benefit from an interventional strategy. Thus, although the prognostic literature for all cardiovascular imaging modalities is replete with composite end points, they are at best a temporary analytic approach for a modality awaiting larger data sets.

Second, and of greater importance, is the metric by which testing is assessed. The focus of prognostic studies has centered on patient risk. With the development of larger imaging databases, study power has increased, permitting larger, better-powered studies. In turn, this has allowed studies to use cardiac death alone as an end point (enhancing clinical relevance) and to analytically deconstruct imaging results (eg, modeling ischemia and scar as separate MPI components). This has resulted in more recent prognostic

### Table. Results of Previous Prognostic Stress CMR Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Events</th>
<th>Hard Events*</th>
<th>Mean Follow-Up (Years)</th>
<th>Hard Events/yr</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dall’Armellina et al</td>
<td>200</td>
<td>35</td>
<td>35</td>
<td>5</td>
<td>3.5%</td>
<td>Patients with reduced LV function</td>
</tr>
<tr>
<td>Jahnke et al</td>
<td>513</td>
<td>19</td>
<td>19</td>
<td>2.3</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Bodi et al</td>
<td>420</td>
<td>41</td>
<td>23</td>
<td>1.2</td>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td>Pilz et al</td>
<td>218</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0.0%</td>
<td>Normal adenosine stress CMR</td>
</tr>
<tr>
<td>Steel et al</td>
<td>254</td>
<td>49</td>
<td>28</td>
<td>1.4</td>
<td>7.9%</td>
<td></td>
</tr>
</tbody>
</table>

LV indicates left ventricular; CMR, cardiac magnetic resonance imaging.

*Cardiac death + nonfatal myocardial infarction.
studies identifying factors such as scar, LVEF, and LV volumes as the predominant predictors of cardiac death, whereas ischemia has been found to be a poor or borderline predictor of this end point. Thus, the more recent MPI literature indicates that the prediction of cardiac death, the most relevant clinical end point, is in the domain of scar and LV function, and ischemia is a secondary consideration in the identification of the high-risk patient.

What does this mean for referring clinicians? Despite the predictive value of scar, LV volumes, and EF, post-MPI resource utilization is driven predominantly (>80% to 90%) by inducible ischemia and to a lesser extent by anginal symptoms, ischemic ECG response, and likelihood of CAD.9,10 Thus, paradoxically, the literature suggests that risk assessment is best performed by the use of a set of variables that are not primarily considered by physicians in formulating decisions related to referral to catheterization, revascularization, and medical management. These decisions are based on data elements that are at best mediocre predictors of risk. However, although MPI-assessed ischemia is not a predominant predictor of risk, it has been found in observational studies to be the only predictor of which patients may accrue a survival benefit with revascularization versus medical therapy.10,11 Hence, identification of patient risk and identification of potential patient benefit are not analogous. As the latter represents added value for patients and helpful information for their physicians, future evaluations of cardiovascular imaging must incorporate this essential endpoint.

In the current healthcare climate, the criteria for a modality to gain acceptability has become increasingly demanding, not only for newer technologies (PET, CMR, CT) but for older previously “validated” techniques as well. Although this process was previously based on an incremental, risk-based approach, more recently calls for value-based healthcare assessment have increased,12 and payment for performance-based reimbursement has become a possibility.13 The ability of an ischemia-based patient management algorithm to identify enhanced patient status—a demonstration of patient value—may play a key role in the future of cardiovascular imaging.

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References

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