Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 62, No. 9, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.04.065

EDITORIAL COMMENT

Stress Cardiac Magnetic Resonance Imaging

It Is Time to Trust the Magnetic Crystal Ball*

Raymond H. Chan, MD, MPH,†
Warren J. Manning, MD†‡
Boston, Massachusetts

There is increasing scrutiny regarding overutilization of diagnostic medical imaging tests due to both costs and potential morbidity (1). Noninvasive cardiovascular imaging has received considerable attention because its growth rate exceeds other physician services without a similar increase in disease prevalence (2). Thus, there is a need to thoroughly evaluate new imaging techniques before implementation of widespread clinical use and, perhaps from a more pragmatic perspective, before payers will provide reimbursement. With the development of each new imaging technique, the threshold of evidence required to demonstrate clinical utility above existing technology becomes higher, particularly if other modalities are more widely available and established.

See page 826

Numerous diagnostic tests are available for evaluating patients with suspected coronary artery disease (CAD). The natural evolution of this diagnostic developmental process follows a common pathway: 1) proof of concept in phantom and animal models; 2) small correlation studies in humans to verify accuracy; and 3) single and multicenter human studies to validate the results of the smaller studies. The ability of a test to provide prognostic data and to risk-stratify patients must then be assessed by examining patient outcomes in single-center and multicenter studies. Once these studies are done, the body of literature can then be evaluated via meta-analysis of such prognostic studies. The next step would be to examine whether this new diagnostic test in fact alters physician decision-making processes. Finally, to justify its role, cost-effectiveness of the new test would have to be demonstrated.

Why do clinicians order diagnostic tests during the evaluation process of patients with suspected or established CAD? In many instances, the purpose is to risk-stratify patients, such as before surgical procedures or after coronary events, and for management of symptomatic patients. Although radiographic coronary angiography can undoubtedly identify patients with high-risk anatomy (e.g., significant left main stenosis, triple vessel disease) or patients with normal coronary anatomy, its invasive nature makes it less than an ideal initial test. Furthermore, the atherosclerotic process begins in the vessel wall and cannot be fully characterized by invasive or noninvasive luminography. Therefore, luminal diameter may have little prognostic relevance unless we understand its physiological significance (3). Therefore, despite its clinical status as the gold standard for diagnosing CAD, invasive radiograph angiography is not likely to be the test of choice for most patients.

Therefore, in addition to making a correct diagnosis, a preferred test needs to accurately identify low-risk patients who will not benefit from downstream testing, in effect acting as a "gatekeeper" for other invasive and noninvasive tests and procedures. Furthermore, once results of the tests are negative, repeat testing in the near term should not be required. The test must also identify high-risk patients who would benefit from downstream invasive angiography and/or revascularization. To that end, although performance characteristics such as sensitivity and specificity against a gold standard (e.g., invasive angiography) are certainly relevant, it can be argued that the prognostic performance of a test is an even more important metric.

Over the past 2 decades, cardiac magnetic resonance imaging (CMR) has grown from a research curiosity to mainstream use at most medical centers. Previous meta-analyses of stress CMR have focused on its diagnostic performance in detecting CAD (4–7), while a recent trial showed multiparametric CMR to have superior diagnostic accuracy compared with myocardial perfusion imaging (MPI) (8). In this issue of the *Journal*, Lipinski et al. (9) elegantly summarize the evidence surrounding the prognostic value of pharmacological stress CMR (including dobutamine stress and vasodilator stress). Among 19 studies involving nearly 12,000 patients with suspected or established CAD followed up for a median of 25 months, a positive stress CMR had a much higher risk of the combined hard outcomes of cardiovascular death and myocardial infarction (MI), with a pooled odds ratio (OR) of 6.5; and higher annual rates of cardiovascular death (2.8% vs. 0.3%) and nonfatal MI (2.6% vs. 0.4%). When expressed in clinical terms, annualized event rates (AERs) were 4.9% versus 0.8% for patients with positive and negative stress

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Department of Medicine (Cardiovascular Division), Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; and the ‡Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts. Dr. Manning has received a research grant from Philips Medical Systems. Dr. Chan has reported that he has no relationships relevant to the contents of this paper to disclose.

CMR, respectively. Event rates were similar between those undergoing vasodilator stress and dobutamine stress. Furthermore, a subset of studies that reported results with late gadolinium enhancement (LGE) demonstrated a higher risk of adverse events when there was LGE present (OR: 3.82; AER of the combined outcome of cardiovascular death and MI: 4.6% vs. 1.4%). This body of evidence supports the excellent discriminatory ability of stress CMR with or without LGE to risk-stratify patients with known or suspected CAD.

The OR provides a convenient summary measure that quantifies the relative risks of the cumulative events at the end of follow-up, but this summary statistic does not give an indication of how risks may vary during the follow-up period. Despite these limitations, the estimated short-term AER for patients with a negative stress CMR seems consistent with the low event rates observed after a negative stress echocardiogram and stress radionuclide MPI (10). All have the ability to identify patients with sufficiently low risk for future events who can be managed medically, supporting a similar "watch and wait" strategy for patients with negative stress echocardiogram or MPI. These patients can safely avoid further downstream testing and interventions.

What is a clinician to do, therefore, with the results of a positive stress CMR? It remains to be resolved how the prognostic information from stress CMR should be applied to optimally guide patient management, particularly in an era in which novel strategies such as fractional flow reserve–guided revascularization show promise (3).

There are several limitations to this meta-analysis (9). There is heterogeneity between the study populations, with likely different pretest probabilities of CAD, baseline risk factors, and known CAD. These would influence event rates regardless of test results, in addition to their effects on the operating characteristics of the test itself. As recognized by the authors, there is a mixture of prospective and retrospective studies. The definition of a positive CMR was variable, and not all studies compared stress with rest images. Ischemia was also quantified as a dichotomous variable, rather than as a continuous variable (e.g., by extent of ischemia). Most studies focused on the prognostic value of the stress CMR or LGE portion of the examination, and few examined the relative incremental predictive value of combinations of various parameters obtained in a comprehensive stress CMR study.

Second, there are limitations to the generalizability of their data (9). All but 1 study involved single-center reports in which expert CMR readers interpreted the scans. Interpretation of stress CMR remains highly dependent on the skill and experience of the reader compared with more established and accepted imaging modalities (11,12). Misinterpretation by nonexpert readers in a real-world setting would likely cause the observed risk rates to regress toward the mean, thereby decreasing the prognostic discriminating ability of the test. About 30% of patients had known CAD, and the data need to be taken in this context. Previous studies using stress echocardiography or radionuclide MPI used slightly lower risk populations; however, the AER of patients with a negative CMR at 0.8% is comparably low. In a real-world setting, this may underestimate the true risk because many patients referred to a stress CMR would likely have inherently higher risk characteristics that made a CMR the test choice compared with echocardiography or MPI. However, the diagnostic yield, as reflected by the proportion of patients with a positive stress CMR, was 32%, suggesting that the study population was of intermediate pretest risk for CAD. The meta-analysis was also overwhelmingly based on 1.5-T imaging. Emerging data suggest that 3-T stress CMR has superior diagnostic performance (13).

CMR has the unique capability to provide a comprehensive cardiovascular evaluation in 1 session previously available only by combining multiple modalities. It offers superior spatial resolution in the assessment of ischemia and the function and structure of both ventricles and valves. It can also directly characterize whether ischemic tissue is viable or nonviable, thereby providing information as to whether a patient is likely to benefit from invasive catheterization and/or revascularization. Experimental CMR sequences that directly identify vulnerable plaques are also under active investigation (14). However, it remains to be proven whether the additional information gained from this comprehensive examination is of clinical utility. Indeed, studies have demonstrated that each component of a comprehensive CMR examination (i.e., stress perfusion, LGE, flow, left ventricular structure and function) add incremental prognostic information over each other (15), suggesting each component to be additive rather than redundant in predicting risk. Future studies are needed to clarify the role of the comprehensive cardiac examination.

What is the role of stress CMR, therefore, in the context of an era of overtesting? The next logical step would be the direct comparison of prognosis in similar populations using these 3 modalities, as well as comparing the cost-effectiveness of each test strategy (16,17). In a recent model-based analysis, Boldt et al. (17) demonstrated the superior cost-effectiveness of stress CMR compared with single-photon emission computed tomography in Germany for diagnosing suspected CAD in patients with low to intermediate pretest probability of CAD. Whether this analysis can be generalizable in other settings will require further validation. Using this information, appropriate-use criteria need to be carefully drafted to ensure the optimal use of these imaging technologies for the right clinical scenario in the right patient population, taking into account factors such as local expertise, current infrastructure, and support personnel. The ultimate goal is to avoid unnecessary testing.

In summary, we congratulate Lipinski et al. (9) for providing validation of the high negative predictive value of stress CMR in risk stratification of patients with established or suspected CAD. Those without ischemia on stress CMR have a very favorable intermediate-term prognosis, whereas

a positive test identifies high-risk patients. One cannot deny the attractiveness of a test that is free of ionizing radiation, accurate, and potentially cost-effective. There is now ample evidence to support the use of stress CMR as a prognostic tool, accurately differentiating between low-risk and high-risk patients. Although important questions remain unanswered with regard to the clinical utility of a comprehensive CMR examination, it is due time for the cardiology community to trust the magnetic crystal ball!

Reprint requests and correspondence: Dr. Warren J. Manning, Department of Medicine, Cardiovascular Division, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215. E-mail: wmanning@bidmc.harvard.edu.

REFERENCES

1. Pearlman AS, Ryan T, Picard MH, Douglas PS. Evolving trends in the use of echocardiography: a study of Medicare beneficiaries. J Am Coll Cardiol 2007;49:2283–91.
2. Lucas FL, DeLorenzo MA, Siewers AE, Wennberg DE. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993-2001. Circulation 2006;113:374–9.
3. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.
4. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. J Am Coll Cardiol 2007;50:1343–53.
5. Hamon M, Fau G, Née G, Ehtisham J, Morello R, Hamon M. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. J Cardiovasc Magn Reson 2010;12:29.
6. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012;59:1719–28.
7. De Jong MC, Genders TS, Van Geuns RJ, Moelker A, Hunink MG. Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. Eur Radiol 2012;22:1881–95.
8. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 2011;6736:1–8.
9. Lipinski MJ, McVey CM, Berger JS, Kramer CM, Salerno M. Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis. J Am Coll Cardiol 2013;62:826–38.
10. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007;49:227–37.
11. Lubbers DD, Kuijpers D, Bodewes R, et al. Inter-observer variability of visual analysis of "stress"-only adenosine first-pass myocardial perfusion imaging in relation to clinical experience and reading criteria. Int J Cardiovasc Imaging 2011;27:557–62.
12. Morton G, Jogiya R, Plein S, Schuster A, Chiribiri A, Nagel E. Quantitative cardiovascular magnetic resonance perfusion imaging: inter-study reproducibility. Eur Heart J Cardiovasc Imaging 2012;13:954–60.
13. Cheng AS, Pegg TJ, Karamitsos TD, et al. Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla. J Am Coll Cardiol 2007;49:2440–9.
14. Qian D, Bottomley PA. High-resolution intravascular magnetic resonance quantification of atherosclerotic plaque at 3T. J Cardiovasc Magn Reson 2012;14:20.
15. Bingham SE, Hachamovitch R. Incremental prognostic significance of combined cardiac magnetic resonance imaging, adenosine stress perfusion, delayed enhancement, and left ventricular function over preimaging information for the prediction of adverse events. Circulation 2011;123:1509–18.
16. Greenwood JP, Maredia N, Radjenovic A, et al. Clinical evaluation of magnetic resonance imaging in coronary heart disease: the CE-MARC study. Trials 2009;10:62.
17. Boldt J, Leber AW, Bonaventura K, et al. Cost-effectiveness of cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary artery disease in Germany. J Cardiovasc Magn Reson 2013;15:30.

Key Words: cardiac magnetic resonance imaging ■ prognosis ■ stress.