EDITORIAL COMMENT

Noninvasive Risk Stratification After Myocardial Infarction

New Evidence, New Questions*

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This issue of the Journal contains 2 important papers by Mahmorian et al. (1,2). The first describes a prospective observational registry study involving the early use of adenosine myocardial perfusion imaging (MPI) for risk stratification after myocardial infarction (MI) (1). The entry criteria included a broad spectrum of patients who were almost equally divided between those with non–ST-segment elevation MI (NSTEMI) and those with ST-segment elevation MI (STEMI). All patients were enrolled within 10 days after MI without prior percutaneous coronary intervention (PCI) during this admission. These entry criteria undoubtedly led to a broad spectrum of coronary anatomy and occlusion, although only a minority of patients underwent angiography.

See pages 2448 and 2458

This was a demanding protocol. Among the patients enrolled in the United States, the majority underwent MPI within 2 days of hospital admission. The protocol restricted “clinician independence,” because it urged that patient management be based on the results of MPI. In the subset of patients with large total perfusion defects (>20% of left ventricle [LV]), ischemia (>10% of the LV), and reasonably preserved LV function (ejection fraction ≥35%), the protocol involved randomization to intensive medical therapy or revascularization and medical therapy. The second paper in this issue of the Journal (2) reports the results of that randomized trial.

The authors are to be congratulated on their completion of such a demanding protocol. At the start of this study, a group of investigators in the Mayo Cardiovascular Division reviewed the protocol. Although we were very impressed by its scientific quality, we declined to participate because the majority of our clinicians were unlikely to agree either to the restrictions on their decision making or to the randomization of patients in the high-risk subgroup to intensive medical therapy.

In the observational study, early MPI successfully risk-stratified patients. Low-risk patients with perfusion defects of <20% of the LV comprised nearly one-third of the study group. They were candidates for early hospital discharge and had very low subsequent event rates. The event rates progressively increased in the intermediate-risk and high-risk groups. In the randomized trial of high-risk patients, both intensive medical therapy and revascularization produced comparable reductions (and frequently elimination) of both total and ischemic perfusion defect sizes on later scans.

What are the implications of this successful multinational study? In hospitals without cardiac catheterization facilities, MPI can identify those patients who do not require transfer to another facility for cardiac catheterization and can be discharged safely at an early date. However, this strategy requires that the hospital have the capability to perform MPI, which is of uncertain likelihood in the absence of a cardiac catheterization laboratory. The use of adenosine stress in this study permitted earlier testing with greater safety and enrollment of patients who were unable to exercise. However, in patients who are able to exercise, clinicians may be reluctant to accept the absence of exercise data, which is of great value for both prognostication and rehabilitation.

In hospitals with cardiac catheterization facilities, we are concerned that these results may have little short-term impact. Established practice often favors early coronary angiography. In patients with STEMI, current guidelines (3,4) favor acute PCI as the preferred therapy, based on the demonstrated mortality benefit in several meta-analyses. In patients with NSTEMI, several randomized trials (5,6), which were reported after the present study was initiated, form the basis for the recommendations for an early invasive approach in current guidelines (7,8). Obviously, some patients with STEMI may present too late to undergo acute PCI, and the estimated risk of some patients with NSTEMI may be too low to mandate an early invasive strategy. However, in these subsets of patients, the existing reimbursement system in the U.S. rewards both hospitals and physicians for early catheterization, which has become the established practice when a catheterization laboratory is available (9). The noninvasive approach proposed here would likely extend the hospital stay of patients who are felt to still require angiography after MPI. Many clinicians will likely favor angiography for patients with ischemic defects of 10% of LV, because they may benefit from revascularization (10). It will likely require major structural health care reform in the U.S. to reverse these long-standing practice patterns and incentives.

In the present study, revascularization in low- and intermediate-risk patients appeared to have little benefit.
However, these data may not reduce the current rates of revascularization. The majority of low- and intermediate-risk patients who underwent coronary angiography in this study also underwent revascularization. The decision to proceed with revascularization in these patients after angiography is obviously multifactorial, reflecting patient symptoms, legal concerns, and the “oculostenotic reflex” (11). This reflex likely reflects existing incentives, as well as the widely held assumption that “more care is better,” despite evidence to the contrary (12,13).

The results of the randomized trial suggest that the heterogeneity of myocardial blood flow induced by adenosine (labeled by the authors as scintigraphic ischemia) can be suppressed in 4 out of 5 patients with intensive medical therapy. Although earlier observational studies have suggested that antianginal therapy could reduce the abnormality on pharmacologic MPI (14,15), this is the first evidence that the magnitude of this reduction is comparable to coronary revascularization. Although medical therapy has been known to potentially increase myocardial oxygen supply, the major symptomatic benefit of such therapy has been attributed to a reduction in myocardial oxygen demand. Successful elimination of adenosine-induced myocardial blood flow changes by intensive medical therapy in this trial suggests far greater effects on myocardial supply than previously recognized. These results, along with other studies (16,17), suggest the need for a reassessment of the pathophysiologic benefits of antianginal and lipid-lowering therapy. Because this randomized trial was underpowered with respect to subsequent cardiac events, we agree with the authors’ call for an adequately powered outcome trial in these patients. However, many clinicians may be reluctant to enroll patients with high-risk scans in such a trial without knowledge of coronary anatomy. The scientific support for such a trial may depend on the outcome of the recently completed COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (18), which compared intensive medical therapy to revascularization in patients with stable coronary artery disease.

This study was not without limitations. The number of patients who were eligible at the participating centers when these 728 patients were enrolled is not provided.

In addition, the effects of medical therapy and revascularization on perfusion defect size may have been confounded by the “natural recovery” of perfusion defects very early after MI. Myocardial stunning is known to affect resting defect size within 48 hours after MI (19) and could potentially affect stress defect size as well.

As already indicated, the randomized trial was underpowered for clinical events. There were a number of patient “drop-outs” and crossovers in the randomized trial, which is inevitable in such efforts. The mixed population of patients with both STEMI and NSTEMI limits the comparison of these randomized trial results to other randomized trials, which have typically enrolled either STEMI or NSTEMI patients only. It will likely also reduce the impact of these data on existing STEMI and NSTEMI clinical practice guidelines. Finally, we would question whether the authors’ application of the Thrombolysis In Myocardial Infarction (TIMI) STEMI risk score, which was developed in STEMI patients (20), and differs from the TIMI NSTEMI risk score (21), to their “mixed” population. There is a growing crisis in health care expenditures. The recent increase in stress imaging procedures far exceeds the increase in coronary artery disease or revascularization procedures (22,23). The increase in cardiac imaging has drawn increasing attention from third-party payers (24). The American College of Cardiology and the American Society of Nuclear Cardiology have published a series of appropriateness criteria to better define those circumstances in which imaging should and should not be performed (25). This study is an important contribution to the evidence in this area; it demonstrates the appropriateness of early MPI in patients after MI who have not undergone previous coronary intervention.

The medical and scientific community needs to lead the effort to make medical care more efficient. This principle of care, first proposed by the Institute of Medicine, is frequently discouraged by the inappropriate incentives in the existing system; great improvement is needed. This study is an important step in the right direction. It represents the latest contribution in a 16-year-old research effort using adenosine that was begun by the late Mario Verani, who was our friend and a mentor to John Mahmarian, the principal investigator of this study. We are certain that Mario would have been very proud of these 2 papers and this landmark study.

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REFERENCES


