Acute chest pain evaluation: Is there too much stress on the system?

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See related article, pp. 1002–1012

Those who have followed the literature regarding the evaluation of patients with acute chest pain over the last two decades are aware of these commonly repeated facts: Over 100 million patients present to the emergency department (ED) each year, of whom approximately 6%-8% are related to chest pain or other symptoms suggestive of myocardial infarction (MI).¹ The missed acute coronary syndrome (ACS) rate is estimated at 2%-4%^{2,3} (although recent studies are lacking), with substantially worse outcomes than those who are recognized.² The cost related to chest pain evaluation is significant, estimated to be in the tens of billions of dollars,⁴ which has likely increased since these estimates. This high cost is in part related to the low threshold for evaluation, owing to a conservative practice to avoid litigation related to missed MI,⁵ one of the largest sources of ED malpractice awards.⁶

In response, a variety of strategies have been developed for rapid assessment to exclude MI,⁷⁻¹⁰ followed by provocative testing to exclude ischemia, and more recently imaging to identify significant coronary artery disease (CAD).^{11,12} The goal of this “secondary” evaluation is to identify the few remaining high risk patients among the many low risk patients (at times analogous to finding a needle in a haystack). Multiple studies have demonstrated that using a standardized protocol that included serial biomarkers and subsequent testing could reduce overall costs with similar or improved outcomes compared to standard care for

evaluating low risk chest pain patients.¹³⁻¹⁵ As a result, this approach has become the standard of care and is often carried out in the ED or Observation Unit.

Secondary testing can take numerous forms. Although exercise stress testing alone has been shown to be effective,^{8,16} the use of imaging, either myocardial perfusion imaging (MPI),¹⁷ echocardiography,^{18,19} or more advanced protocols using cardiac MRI²⁰ is frequently used as an alternative. Recently, evaluation with cardiac computed tomographic angiography (CTA) has emerged, in which coronary anatomy can be defined with high accuracy in a rapid fashion.^{11,12}

This frequent use of imaging may in part be related to the proportion of patients who cannot exercise, have uninterpretable ECGs, or possibly the perception that the increased sensitivity added by imaging is important.²¹ All of these tests have the goal of excluding myocardial ischemia as a potential cause for the patient’s symptoms, although the optimal test for evaluation remains unclear.

Only a few randomized studies have been performed that compare different types of testing, and most have included relatively small numbers of patients,^{12,18,19} with a few notable exceptions.^{11,13} In this regard, the current study by Lim et al²² is timely. The authors compare stress MPI to a standard evaluation process of ED patients presenting with possible myocardial ischemia. Patients underwent clinical assessment with subsequent exclusion of MI using both CKMB and troponin (Tn). All patients who developed significant ST segment changes of ischemia or infarction or those who had biomarkers indicative of MI were admitted. The remainder were randomized in a 2:1 ratio to stress MPI (n = 1,004) or routine clinical assessment (n = 504).

Participants randomized to routine clinical assessment (standard care) were assessed, and those considered to be at high or intermediate risk for ACS were admitted. Patients in the study arm (stress MPI) were admitted if their test was abnormal (defined as a defect $\geq 5\%$ of the left ventricle, or LVEF $\leq 50\%$ with associated wall motion abnormalities).

The authors found that patients randomized to stress MPI had a significantly lower admission rate, 10.2% vs 18.5% [RR 0.56 (95% CI 0.43-0.72), $P < .005$]. Cardiac events were low in both arms at 30 days and were not significantly different: MPI 0.40% vs standard care 0.79% [RR 0.50 (95% CI 0.13-2.0)], and remained low

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J Nucl Cardiol 2013;20:960–2.

1071-3581/\$34.00

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doi:10.1007/s12350-013-9782-3

at 1 year (MPI 0.70% vs standard care 0.99%) [RR 0.70 (95% CI 0.22–2.2)].

As expected, subsequent evaluations were higher in the standard care arm in which all types of testing (rest and stress echo, stress MPI) were used more frequently. Coronary angiography (11.1% vs 7.3%, $P < .02$) and subsequent revascularization (6.2% vs 4.8%, $P = .28$) were also more common in the standard care arm.

A number of points deserve consideration. The patients were relative young, as is typical of most low risk chest pain observation populations. Consistent with the selection of a low risk population, prior CAD was very low, present in $<5\%$, with only 1% having a history of MI. Both the stress MPI and standard care arms had low event rates that were not significantly different, indicating that either pathway appeared to safely provide similar outcomes. The primary difference in the two arms was the number of patients who were hospitalized, the rate of subsequent testing (both of which can be considered a surrogate for cost), and the rate of detection of CAD. The higher rate of subsequent testing in the standard care arm is not unexpected, particularly considering that all patients in the stress MPI arm had their secondary test at the outset. Despite the increased testing, the rates of coronary angiography were significantly lower in the stress MPI arm. This is in contrast to trials using CTA, which have usually found higher rates of subsequent coronary angiography and revascularization,²³ which is one of the largest drivers of cost.

The study has a number of limitations. One of the most important limitations is failure to include a cost analysis. Given the relatively similar outcomes between the two arms, cost becomes critical to defining an optimal protocol. In addition, the relative distribution of costs in the standard of care arm would be interesting to see. As previously seen, there is likely to be a much higher variation in costs related to differing degrees of testing in the standard care arm.¹⁵

The few clinical events that occurred limit the ability to provide firm conclusions in a more heterogeneous population that includes intermediate risk. Given that treadmill testing without imaging was effective in this study, inclusion of a third arm in which patients were randomized to exercise treadmill testing alone would have been valuable.

Another limitation, which is common to most such studies, is using of detection of CAD as a surrogate for identifying patients with unstable angina (UA). Given the increase sensitivity of current ED chest pain protocols in identifying ACS, routine stress testing is much more likely to identify patients who have stable CAD, rather than those with UA for whom such protocols were originally studied. As there is no long-term advantage of revascularization in patients with stable CAD, routine

secondary testing can lead to excessive downstream costs, with increased use of coronary angiography and revascularization, as has been seen in CTA trials,²³ without improving outcomes. It has been recently suggested that routine stress testing in this low risk group leads to more harm than good.^{24,25}

The very low event rate seen in this patient population brings into question whether there is value in routine secondary testing of all patients once MI is excluded.^{24,25} It is important to remember that the rationale for performing such testing was derived in an era of relatively insensitive (by current standards) cardiac injury markers, and less standardized clinical risk stratification. In contrast, successive generations of Tn assays, in conjunction with more standardized clinical assessment tools²⁶ have improved the ability to identify higher risk patients, resulting in a much larger group of patients who are at very low risk (often $<1\%$). It may be that biomarker analysis using more sensitive Tns may negate the need for subsequent stress testing in the lowest risk group. Recent studies have demonstrated that such a strategy can be applied safely,²⁷ particularly in specific low risk patient populations (i.e., <40 years old,²⁸ or with a low TIMI risk score and negative Tn²⁹). As the sensitivity of Tn assays improve, it may render the diagnosis of UA extinct.³⁰ Recent ED chest pain evaluation studies have begun to demonstrate the feasibility of a marker alone protocol, without need for subsequent provocative testing.³¹

An important potential “downside” to more sensitive Tns is the detection of elevations that are a result of chronic underlying cardiovascular disease rather than ACS. In contrast to low risk patients, it may be this patient population in whom provocative testing is required. Increasingly sensitive Tn assays, currently used in Europe (but not yet in the US), are likely to exacerbate this issue. It is possible that in the future we will see the current evaluation process inverted, in which Tn negative patients are directly discharged and those with low level Tn elevations undergo additional testing for evaluation.

In conclusion, it appears that a strategy of stress MPI offers benefits over standard of care evaluation, leading to reduced admissions and a low risk for subsequent clinical events. Whether this reduces costs compared to other types of imaging, or treadmill testing without imaging, remains unclear, particularly in an era of high sensitivity Tns, and should be addressed in future studies.

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