Stress myocardial perfusion imaging: Can we tell the results without doing the test?

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Despite an overall decrease in the number of deaths annually over the past decade, coronary artery disease (CAD) remains the leading cause of mortality in the USA. Of the available modalities for testing for CAD, single photon emission computed tomography myocardial perfusion imaging (MPI) is by far the most commonly employed modality with over 2 million studies performed on Medicare beneficiaries alone in 2017.¹ There is a wealth of data supporting the use of MPI for diagnosing CAD and for risk stratification.

The estimated annual costs for the treatment of stable CAD and acute myocardial infarctions represent two of the ten most expensive conditions at \$9.0 and \$12.1 billion, respectively, and are expected to increase 100% over the next 10 years.² These considerations stress the importance of prudent and cost-conscious evaluation of patients presenting with symptoms concerning for CAD. If a provider is capable of predicting with reasonable accuracy which patient will have an abnormal MPI, then risk-benefit and cost-effective considerations would preclude the performance of the test in most patients (MPI may still be useful for risk stratification since some abnormal tests may be in low risk while others in high risk). Further, a careful characterization of the pretest probability of CAD is of utmost importance as the benefit of non-invasive diagnostic testing is highest among those patients at an intermediate risk of the disease.³ Multiple studies in the USA have demonstrated a progressive decline in the

percentage of abnormal studies over the past two decades despite a concomitant increase in the prevalence of cardiovascular risk factors of those referred.^{4–6} This dichotomy forces the careful evaluation of the methods used in estimating risk in the referred population.

In 1979, Diamond and Forrester proposed a model for estimating the pretest probability of obstructive CAD in stable chest pain patients using three basic variables: age, gender, and the character of chest pain (i.e., anginal, atypical anginal, or non-anginal).⁷ They derived the risk using the observed prevalence of obstructive CAD defined as lesions > 50% visualized by invasive coronary angiography or autopsy. They went even further by applying Bayes theorem and estimating the post-test probability of the disease using various diagnostic methods of the time; however, even at the time of publication, Diamond and Forrester recognized the limitations of their dataset and suggested that their model be updated as more data and information become available. This original classification of Diamond and Forrester represented an effective gatekeeper for cardiac testing and remains part of the recommended strategy for estimating the pretest probability of obstructive CAD 40 years after its development based on the most recent US guidelines for stable ischemic heart disease, a testimony to its rigor.³

In 2011, Genders et al. as part of the CAD Consortium heeded the advice of Diamond and Forrester, reevaluating their model and updating it utilizing a more modern dataset with the same basic variables of age, sex, and type of chest pain.⁸ This included an extended model which expanded the age range to include patients beyond the ages of 30–69, a limitation of the original. Their findings demonstrated an overall overestimation of the pretest probability of obstructive CAD using the original model, particularly among women. The updated and extended models demonstrated robust c-statistics of 0.79 (95% CI 0.77–0.81) and 0.82 (95% CI 0.80–0.84), respectively. Shortly thereafter, the CAD Consortium developed additional models which in addition to the

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basic clinical variables included clinical variables consisting of cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, and smoking.⁹ An extended model was also developed which in addition to the clinical model added computed tomography (CT) based coronary calcium scoring. When compared against the basic model, the clinical model improved the c-statistic from 0.77 to 0.79 and the extended model improved upon this even further with a c-statistic of 0.88. These findings suggested that modern datasets and the addition of clinical variables, including cardiovascular risk factors, could significantly improve the accuracy of risk prediction models for obstructive CAD.

Following the publication of the updated Diamond and Forrester model by the CAD Consortium, the European guidelines adjusted their recommendations for the pretest risk stratification in stable ischemic heart disease.¹⁰ Over the past several years, numerous centers have demonstrated overall reductions in the number of abnormal SPECT MPI studies despite a more sensitive and specific risk prediction strategy.⁴⁻⁶ This led to the speculation that even these updated risk prediction models were overestimating the burden of obstructive CAD. In 2018, Reeh et al. performed a retrospective analysis of a relatively unselected group of patients presenting with symptoms concerning for angina.¹¹ Their population consisted of 3,903 patients without known CAD of which the majority were female and most presented with non-anginal chest pain (59%). Invasive coronary angiography was not required, and the initial diagnostic tests were mostly non-invasive CT coronary angiography (41%) or MPI (31%). Using the updated Diamond and Forrester model, the mean predicted prevalence of obstructive CAD was 31.4%; however, the observed prevalence of obstructive CAD was only 7%. This reduction in observed prevalence may in part be due to their differing definition of obstructive CAD with lesions > 70% (as opposed to 50%) as well as those with fractional flow reserve < 0.8 or deemed needing revascularization being considered significant. Using this population, the investigators derived new risk prediction models including one with the same basic variables as the updated Diamond and Forrester model (chest pain character, age, gender) as well as a clinical model which included dyslipidemia, family history, and diabetes. The c-statistic of the basic model was 0.86 with the clinical model slightly higher at 0.88.

A limitation of these models is the use of anatomic disease by invasive coronary angiography as the gold-standard. While there is obvious correlation between coronary artery stenosis severity and hyperemic myocardial blood flow, there is great variability especially in the intermediate range of stenosis.¹²⁻¹⁴ We

have known for several decades that myocardial ischemia on imaging provides more robust prognostic information than anatomic information by invasive coronary angiography.¹⁵ More recently there has been increasing interest in INOCA (Ischemia and No Obstructive Coronary Disease), since patients with stable angina and normal or non-obstructive CAD have been shown to be at higher risk of cardiovascular events than those without angina.^{16,17} Therefore, there is multiple incentives to develop a clinical prediction tool to predict the presence of myocardial ischemia.

In this issue of the Journal, Megna et al.¹⁸ describe a novel model for the prediction of an abnormal SPECT MPI in a population without known CAD using similar variables to the models previously described for the prediction of obstructive CAD. Their population consisted of 5601 consecutive patients who underwent MPI at a single academic institution in Italy, of whom 1055 (19%) were abnormal. On multivariable analysis, age, male gender, anginal symptoms, diabetes, and smoking were independent predictors of abnormal MPI. The study employed two different prediction models: a basic model inclusive of age, gender, and anginal symptoms, as well as a clinical model which in addition to the basic model included the recognized cardiac risk factors of diabetes, hypertension, hypercholesterolemia, smoking, and a family history of CAD. The basic model was 75% sensitive and 45% specific for prediction of abnormal MPI yielding a c-statistic of 0.644. The clinical model added minimal benefit with a c-statistic of 0.647. While the model employed in this study performed better than the other models described above, all models had limited strength in discrimination of normal vs. abnormal MPI. However, it is notable that 89% of patients classified at low risk had a normal MPI. Decision curve analysis revealed high net benefit around threshold probabilities of 15-30% for both models. Selective referral of patients with pretest probabilities > 15% could therefore decrease unnecessary testing without sacrificing sensitivity. Since the study did not assess appropriateness of testing according to published criteria,¹⁹ it is not possible to assess whether using the developed model adds value to using Appropriate Use Criteria to curtail use of imaging in patients least likely to benefit; it is important to note that these criteria were derived using the original Diamond and Forrester model for risk stratification.

In a separate study, Duvall et al. described a model to predict a normal stress MPI in order to facilitate a 1-day stress/rest protocol.²⁰ They derived a risk score using clinical variables predictive of an abnormal study including age > 65, diabetes, typical chest pain, congestive heart, abnormal ECG, male gender, and documented CAD. Referral from the emergency department was negatively predictive of an abnormal

study. The derivation cohort included 1996 patients and the validation cohorts included 3435 patients. Use of their scoring system achieved a c-statistic ranging from 0.75 to 0.83 in the validation cohorts depending on the use of attenuation correction and traditional versus CZT cameras. Unlike the study of Megna et al.¹⁸, more than a third of the patients in this study had known CAD which likely improved the discrimination of the model and limits its applicability in predicting an abnormal MPI study in a population without known CAD.

These studies and others demonstrate the limited abilities of current clinical models to accurately predict the presence of myocardial ischemia without the use of imaging. It is possible that more complicated models, including ones developed by machine learning may improve on this in the future.²¹ For now, we are left with MPI to determine the presence of ischemia. Nevertheless, we should ensure that we are only testing appropriate patients. Appropriate Use Criteria and clinical models such as the one developed by Megna et al.¹⁸ may help identify patients that do not require any testing.

Disclosure

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