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EDITORIAL COMMENT

Updating Algorithms for Predicting Pre-Test Likelihood of Coronary Artery Disease

A Cure for Inappropriate Testing?*

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Despite profound ongoing technological advances in cardiovascular imaging, evidence of persisting inappropriate referral to noninvasive testing (NIT) persists. Although approximately two-thirds of patients undergo NIT prior to elective invasive coronary angiography (ICA), most patients are found to have nonobstructive coronary artery disease (CAD) (1). The failure of NIT to identify patients with a significant prevalence of obstructive CAD is attributable to several factors. First, cardiovascular mortality rates have fallen dramatically—between 1969 and 2013, the age-standardized death rate per 100,000 for heart disease decreased from 520.4 to 169.1 (2). As most of the risk reductions were due to medical therapies and prevention rather than to interventions, the baseline risk of patients undergoing NIT was reduced (3). This is consistent with the observed shift the results of cardiovascular imaging; the prevalence of abnormal single-photon emission computed tomography studies fell from 40.9% in 1991 to 8.7% in 2009 (4). Finally, the increased use of expensive imaging has been out of proportion with underlying patient age and characteristics (5).

Historically, patient selection for NIT has been informed by clinicians' determination of pre-test likelihood of CAD. Guidelines and appropriate use criteria advise that in symptomatic patients with adequate suspicion of CAD to justify cardiac evaluation, physicians "should make a probability estimate of the likelihood of CAD prior to selecting testing" based on several available approaches (6). The assessment of CAD likelihood is meant to serve as a gatekeeper for NIT that would, in turn, serve as a gatekeeper to ICA. The failure to optimally refer the "right" patients to cardiovascular imaging is due, in part, to guideline recommendations of relatively outdated approaches for estimation of CAD likelihood. Hence, these scores lack information on coronary calcium scoring, biomarkers (e.g., high-density lipoprotein, low-density lipoprotein, troponin), and other newer risk factors that would likely enhance likelihood of CAD estimates.

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In this issue of *iJACC*, Genders et al. (7) use data from the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial (8), a comparison of initial strategies of anatomic versus functional testing with respect to outcomes in symptomatic patients with suspected CAD, to externally validate predictive scores for the presence of obstructive CAD previously derived and validated by Genders et al. (9,10). These models included a basic model (age, sex, type of chest pain), a clinical model (basic model plus cardiovascular risk factors), and an extended model (clinical model plus coronary artery calcium [CAC] scoring).

The authors identified 3,468 patients assigned to the anatomic testing strategy, of whom 99.6% underwent CTA. Importantly, 3,016 of these patients (87%) did not have ICA data, the primary endpoint of the study. In 910 of these patients, the authors assumed absence of CAD based on a normal CTA. In the remaining 2,106 (61%) ICA data were imputed. In this cohort, the 3 models demonstrated moderate-good discrimination with superior

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discrimination after the addition of CAC data. Model calibration revealed that typical chest pain and diabetes were less predictive, and CAC score more predictive, than was suggested by the models. The application of the clinical model to PROMISE trial data identified a low-likelihood group (31% of the cohort) for whom the prevalence of CAD was 7% whereas the enhanced clinical model identified 48% of patents as low risk (observed prevalence of 2%). Hence, these previously derived and validated models appear able to identify a significant proportion of symptomatic—ostensibly intermediate likelihood—patients as having low likelihood of CAD.

The Genders et al. (7) study addresses central issues that challenge NIT today. This question is important in an era requiring restraint in NIT referrals. Although identification of appropriate patients using pre-test likelihood have long been encouraged, accurate, up-to-date scores have been unavailable. Today, prediction tools can be readily interfaced with electronic medical records to inform medical decision-making at the point of care. Further, although parsimony versus robustness in development of scores has been a point of debate in the past, in an electronic medical records-centric era robust, complex scores with the potential for enhanced accuracy are readily applicable.

The current study's major strength is weighting predictive algorithms based on modern patient cohorts. Guidelines, for purposes of simplicity and parsimony, based Diamond-Forrester estimates of pretest CAD likelihood on only 3 data elements—patient age, sex, and symptoms (11). However, these estimates were originally based on a more robust algorithm using a Bayesian analysis of information, later from multiple noninvasive tests (12), and in 1 iteration 8 covariates of proven value in formulating a robust likelihood estimate (11). The failure of this and other older algorithms to be predictive in the current era is due to the evolution of therapeutics, the changing profile of patients presenting for evaluation, and the emphasis on parsimonious predictive scores. As stated by Diamond and Forrester (12), these approaches should be open to updates as newer data necessitate; they would have applauded the efforts by Genders et al. (7).

What is CAD? The question posed to the test by the physician defines the NIT's value. Patient selection for testing, efficacy metrics, and post-test strategies are driven by this question. The term CAD is usually left undefined; are we referring to obstructive epicardial stenoses, nonobstructive atherosclerosis, or both? Referral to CTA and stress imaging poses the question: does sufficient obstructive disease exist that ICA may help define targets for revascularization? Hence, these tests should be limited to patients with proven atherosclerosis. In current practice, patients are often referred for advanced imaging when a test of atherosclerosis (e.g., CAC) may have identified them as low risk or low likelihood. Indeed, the results of both studies deriving or validating scores from the PROMISE trial include CAC as part of the score (7,13). Our inability to understand which question needs asking results in increasing inappropriate test use. Because of this, and the reasons outlined previously, a valid, reproducible, precise score to exclude low-likelihood patients is an important contribution for patient care.

Genders et al. (7) focused on the former despite issues of verification bias and incomplete ICA use. The presence of anatomic CAD does not necessarily track with patient risk. Indeed, appropriate use criteria and guidelines have emphasized risk and risk stratification over defining and acting on coronary anatomy. Fordyce et al. (13) recently used data from the PROMISE trial to develop a score for risk. Although not mentioned in the current study, by deriving and validating a score to identify low-risk patients based on pre-test and CAC data, inappropriate testing in lower risk patents could be deferred. This endpoint is more in line with current clinical strategies and subject to less bias than is the approach by Genders et al. (7). That said, statements of both likelihood of CAD and risk of untoward events may both be hypothetically useful in clinical decision making, the 2 types of information potentially complementary.

The most serious limitation of the current study is the failure of 87% of patients to undergo ICA, the primary endpoint of the study. Although imputation is an accepted and widely used statistical technique, the study used a combination of ICA, CTA results, and imputation to define the endpoint. Sensitivity of the imputed results is problematic due to the suboptimal positive predictive value of CTA and the limited number (and referral bias associated with) patients undergoing ICA. It is unclear why the authors did not focus their efforts on the excellent negative predictive value of CAC or CTA results (to identify low-likelihood patients) and ignore the incomplete and biased ICA data.

In an era of excess NIT use, valid clinical scores permit accurate estimates of likelihood of CAD, potentially permitting physicians to make more informed and appropriate decisions regarding the use of NIT. The methodological challenge remains

how to derive such a score given the biases involved with the traditional approach of ICA-based endpoint. The availability of highly accurate atherosclerosis imaging may be the key for future success.

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