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EDITORIAL COMMENT

Quantitative Instruments for Predicting Risk . . . and Benefit*

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Many studies have examined the information content that can be garnered from noninvasive stress testing to inform patient management. For exercise electrocardiography (ECG), optimal interpretation does not involve simply whether ST segment depression is present. Recent literature has examined factors such as post-exercise heart rate recovery (1) and the percent of heart rate reserve achieved (2) as prognostic factors. For stress myocardial perfusion imaging (MPI), numerous elements beyond the presence of a perfusion defect are important, such as the extent and severity of defects, lung uptake of tracer, and transient dilatation of the ventricle (3). Weighting all of these elements for test interpretation and a management strategy is challenging for the individual physician.

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One solution to this vexing problem is the use of "predictive instruments." These tools use data from thousands of patients with known outcomes to construct models to predict the probability of an outcome too complex for an individual clinician to accomplish (4). Clinicians tend to focus on familiar elements of a test, such as ST-segment depression on exercise ECG (which may or may not contain the most powerful data), and are influenced by their recent cases, experience, and interpretation of the literature (5). Predictive instruments theoretically overcome these limitations.

What constitutes a good predictive instrument? First, the outcome prediction must be calibrated to actual outcomes. This is accomplished by deriving the model in one dataset and applying the instrument to a separate validation dataset. Second, any instrument should be portable to a setting distinct from where it was developed (external validity). Finally, and perhaps most importantly, any predictive instrument must be acceptable to clinicians for actual use and should improve clinical care (6).

Perhaps the best-known predictive instrument is the Duke treadmill score (7), which incorporates exercise time, symptoms, and ECG changes to construct an outcome prediction. The instrument has been shown to be portable, in that patients referred for stress MPI were appropriately categorized (8) spatially distinct from where it was developed. Limitations have been reported in applying the score to older patients (9). This should not come as a total surprise, because the score was developed in a cohort that did not include a large number of elderly subjects (7). The Thrombolysis In Myocardial Infarction (TIMI) risk score for assessing outcome risk in acute coronary syndromes is another example (10).

In this issue of the *Journal*, Hachamovitch et al. (11) derive and validate an "adenosine prognostic score," combining multiple elements from pharmacologic stress MPI into an outcome prediction. Most studies examining stress MPI have focused on the perfusion data to demonstrate prognostic value (3) and also have shown that the perfusion data have incremental prognostic value once simpler data have been taken into account (12). However, although the evaluation of "incremental value" tells us about information content, that does not speak to risk prediction for individual patients in terms of combining all of the testing elements and weighting them appropriately. This limitation is overcome by incorporation into a predictive instrument.

Pharmacologic stress responses have been challenging for clinicians to incorporate, as vasodilator stress is physiologically distinct from exercise (13). Blood pressure and heart rate responses reflect in part direct vasodilator actions as well as reflex responses, incorporating the integrity of the autonomic nervous system. The present study is the first to use a large database with known patient outcomes to model all of the elements occurring during a pharmacologic stress MPI study into an outcome prediction. A complex model is presented that lends itself to future incorporation into now widely available software programs. Moreover, the authors present a simplified score that clinicians can incorporate for immediate use. These data extend what has been generally an intuitive incorporation of risk stratification into a more quantitative format.

PREDICTING TREATMENT BENEFIT

Another very important feature in the article by Hachamovitch et al. (11), not highlighted enough in our opinion, is the use of the same data to predict potential benefit from revascularization. Of the voluminous literature on risk stratification, virtually all studies report prediction of risk. The usually unstated assumption is that higher risk patients should be referred for catheterization and revascularization, an assumption that has not been rigorously tested.

Hachamovitch et al. (14) have recently reported that the survival benefit of revascularization in outpatients referred for stress testing was evident only in patients with >12% of the left ventricle ischemic on single-photon emission computed tomography (SPECT) MPI. Moreover, the benefit increased as the magnitude of ischemia increased, suggesting that SPECT MPI data not only predicted natural

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history risk but also the potential benefit of revascularization. The current study extends those observations to a large group of patients undergoing pharmacologic stress, who are generally older, more likely women, and at generally higher risk than patients referred for exercise testing. The revascularization term within the prognostic score indicates that the prognostic score predicts a lower risk level when revascularization is performed as a function of the magnitude of potential ischemia.

The provision of quantitative data on outcome risk and the benefit of a treatment strategy is an important advance for noninvasive testing that has been developed in other areas. Selker et al. (15) developed, validated, and prospectively tested the "Thrombolytic Predictive Instrument," which, in the setting of ST-segment elevation myocardial infarction, incorporates demographic data and the ECG findings to create a 30-day mortality prediction for patients treated with or without thrombolytic therapy, along with the probability of treatment complications. In a 1,197-patient randomized controlled trial, the provision of prediction of benefit increased the use of thrombolytic therapy and its use within 1 h for patients with inferior myocardial infarction, for women, and for hospitals without on-site emergency department physicians (15). Thus, that instrument was developed, validated, and tested for its effect on clinical care. The TIMI risk score appears to provide guidance as to the potential benefit of platelet inhibitors in acute coronary syndromes (10), on the basis of retrospective application to clinical trials.

The next important step will be to determine whether the adenosine prognostic score has external validity in the current therapeutic era, as a proportion of the patients in this report were studied more than 10 years ago, before the widespread use of statins and other contemporary preventive and interventional therapies. Moreover, patients were presumably managed based on the treating physician's assessment of benefit, influenced in part by the imaging data. Thus, the differences in outcomes from the two therapies may reflect the astuteness of selection for revascularization by the treating physicians at a very sophisticated cardiac center. In previous studies, Hachamovitch et al. (14) have attempted to correct for this selection bias through the use of propensity analysis, although it does not appear that this approach was used in this dataset. Hence, the true impact of revascularization may well be quantitatively different from that presented by the current model. It would be ideal, though challenging, to test the impact of the prognostic score in a randomized controlled trial format, where patients are randomized to have the full information provided to their clinicians, or not, with outcomes compared between the two groups. If favorable impact on decision-making is shown, that would be a major advance.

The Thrombolytic Predictive Instrument provides a glimpse of how a predictive model based on perfusion imaging could be used to guide revascularization decisions. In fact, just as the weather forecaster's predicted probability of rain is most helpful for the overcast day, previous evidence (15) suggests that it is for the patient for whom the decision might be less clear, or the need for treatment less obvious, for whom such decision support is most helpful. In studies examining patterns of referral to catheterization, it is of interest that only approximately 60% of patients with "high-risk" MPI finding are referred to catheterization (16). The likely explanation for this apparent paradox is that clinicians are taking into account factors such as diabetes, renal function, age, and so on, and deciding that the risk of proceeding with intervention are simply too high on the basis of the inferred benefit. This qualitative judgment might be well informed by an instrument that can incorporate numerous complex elements of risk and benefit. A potentially very important direction in this area would be to incorporate data on the risks of revascularization from sources such as the National Heart, Lung, and Blood Institute registries (17) or the Northern New England group (18) so that a more comprehensive analysis of risk and benefit given extensive demographic and clinical data can be truly assessed in a real-life manner, an exciting direction for this field. In the future, we as a community will be dealing with patients presenting for consideration of revascularization at a later age with more comorbidities than we have dealt with in the past. Prediction tools that can incorporate large amounts of information, such as the risks predicted from noninvasive test results and the potential benefits and risks of revascularization on the basis of clinical and demographic factors, would be uniquely important for physicians in the future. The study by Hachamovitch et al. (11) is an important step in that direction.

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