Electrophysiological Testing After Myocardial Infarction

A Paradigm for Assessing the Incremental Value of a Diagnostic Test

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Richards et al in this issue of Circulation contribute interesting data to the debate on the value of programmed ventricular stimulation, but I believe it would be very premature to base clinical management on their report. At issue is not whether a test provides information, but whether it supplies incrementally valuable information and how it should be applied to routine patient care.

The ideal way to evaluate a medical treatment is a double-blind, randomized clinical trial. Randomization should distribute risk factors, both measurable and unmeasurable, equally in the two groups. Double blinding will eliminate any potential bias in the ascertainment of outcome. Multivariate analyses can control for imbalances remaining after randomization, and cost-effectiveness analysis can determine whether any incremental expense is warranted by incremental benefits.

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Unfortunately, the methodology of the double-blind, randomized clinical trial has rarely, if ever, been used to evaluate the incremental value of a diagnostic test. Nevertheless, the same scientific principles apply. The new test could be randomized. If double blinding is not possible, a standardized follow-up protocol could be used, and ascertainment of the outcome could be made by investigators who were unaware as to whether the patient had the new test. If the test's results are believed to warrant further evaluation or specific treatment, this care could be a standardized part of the intervention. Outcome could be compared in patients with and without the test, and the cost effectiveness of the test or test-directed therapy could be measured.

Richards et al conclude that inducible ventricular tachycardia by electrophysiological testing is the single best predictor of spontaneous ventricular tachycardia and sudden death after myocardial infarction. If such testing were to be performed at all hospitals on patients with a low ejection fraction but without uncontrolled cardiac failure or persistent myocardial ischemia, the investigators' experience suggests that about 55% of patients admitted with acute myocardial infarction would be eligible, which would translate to about 350,000 patients per year in the United States. At Brigham and Women's Hospital, this electrophysiological testing would generate incremental payments of about $3,500, including hospital and physician fees, just for the initial test. Even without considering repeated testing after drug therapy, $1.2 billion in annual expenditures may be generated, and a whole cadre of cardiologists would have to be trained to perform these tests.

Is Electrophysiological Testing of Incremental Prognostic Importance?

I am also concerned that Richards and colleagues have not proven that this test has significant, incremental prognostic value. To demonstrate my concern, consider the methodological principles that should guide studies of the incremental value of a test.14

Full Consideration of the History, Physical Examination, and Other Diagnostic Tests

To determine the incremental value of a new diagnostic modality, information obtainable from the history, physical examination, and other tests must be fully considered before the new test is performed.12 In the postinfarction patient, prognostic factors such as the severity of congestive heart failure, previous myocardial infarction, age, prior coronary revascularization, and acute thrombolysis are pertinent.

Each test's prognostic capabilities should be fully determined. When the ejection fraction is dichotomized as greater than 40% versus less than 40% or the Holter result as 6 or more versus less than 6 ventricular premature contractions per minute, the potential value of these tests may be diminished.
Similar problems arise from dichotomizing exercise test results only on the presence or absence of 2 mm or more of ST segment change, without considering other gradations of change, exercise capacity, exercise hemodynamics, or symptoms or arrhythmias provoked by exercise. Based on extensive data in the literature, this approach could substantially underestimate the prognostic value of exercise testing, especially because some patients were receiving digoxin, which causes false-positive ST segment changes. Although Richards and colleagues considered many of the potential prognostic factors, I am concerned that several were simplified in ways that could seriously underestimate their true prognostic importance. As a result, the incremental value of electrophysiological testing could be overestimated.

**Appropriate Patient Spectrum**

It is vital to determine the spectrum of patients on whom a test is being evaluated. Richards and colleagues studied only the 55% of their patients who did not have heart failure uncontrolled by fluid restriction or furosemide, or postinfarction angina requiring regular therapy, and who were not receiving any cardioactive medications other than digoxin. These relatively low-risk patients had a reasonable 9% death rate at about 2 years, but their results cannot be extrapolated to other types of patients.

**Blinded Assessment of Outcome**

Just as investigators in a randomized trial should be unaware of the patient's therapy, so should investigators in a study of prognosis be unaware of the patient's results on diagnostic testing. Otherwise, unintended bias may arise in the rigor of follow-up or the interpretation of outcomes. Potential biases are independent of the investigators' best intentions and are especially relevant when multiple end points, such as myocardial infarction versus witnessed and un witnessed sudden death, are considered. Richards and colleagues did not specify a blinded outcome assessment in their report.

**Did the Patients Receive Appropriate Therapy?**

To assess whether a test has incremental value for predicting prognosis, patients should receive standard, state-of-the-art therapy. Less than 50% of the patients of Richards and colleagues received β-adrenergic receptor antagonists despite an overwhelming literature of double-blind, randomized trials showing that these medications reduce reinfarction and cardiac death and analyses indicating that they are cost effective in all risk groups. It is possible that electrophysiological testing is not predictive of a poor outcome when patients receive these medications.

**Could the “Prognostic Value” of the Test Be an Artifact of Associated Treatment?**

Richards et al used therapies that were guided by subsequent episodes of spontaneous arrhythmia. However, if the results of electrophysiological testing were ever used to guide therapy, the prognostic value of testing could be affected. If these therapies were beneficial, the true prognostic value of electrophysiological testing would be underestimated. If, however, the electrophysiological testing–guided therapies were actually harmful, the therapies themselves would be responsible for the adverse prognosis associated with an abnormal test result, and the apparent prognostic value of the test would be artifactual. Although such an artifact could be dismissed as very unlikely if the test-guided treatment were free of side effects, the results of the Cardiac Arrhythmia Suppression Trial emphasize the potential hazards of antiarrhythmic therapy and the potential for imputing nonexistent prognostic importance from tests that are associated with harmful treatment.

**What Are the Appropriate Statistical Methods for Demonstrating Incremental Significance and for Measuring Accuracy?**

If a test adds incremental statistically significant prognostic value, it should be an independent predictor after all information from the history, physical examination, and other less-invasive or less-expensive tests is considered. Thus, the “single best predictor” may not add significant incremental information after other, less-potent factors are considered in aggregate. These other factors should be included in a multivariate model before the new test is considered. Approaches such as the multivariate confounder score demonstrate how factors can be included that do not meet the standard criteria for statistical significance if they are of clinical relevance. The incremental information can be measured by several statistical techniques, such as the improvement in sensitivity and specificity or in a variety of scores of prediction. For a test with continuous as opposed to dichotomous results, diagnostic value can be compared by assessing the area under a receiver operating characteristic curve. Richards and colleagues have not presented statistical models in which all other data are included before the new test is considered.

The value of a new test may equal or exceed the predictive value of standard clinical signs and symptoms. Thus, there is no reason why the positive predictive value of testing strategies cannot exceed the predictive value of spontaneous arrhythmia.

**Routine Electrophysiological Testing in Postinfarction Patients?**

Because there are no data indicating that treatment of inducible ventricular tachycardia will prolong life in postinfarction patients without arrhythmia-related symptoms, I strongly recommend against routine testing except in the context of a controlled clinical trial. The Cardiac Arrhythmia Suppression Trial has emphasized how treatment of a known adverse prognostic factor may worsen rather than improve outcome. The use of antiarrhythmic agents...
to treat another asymptomatic arrhythmia, namely inductible ventricular tachycardia, could have the same adverse effect.

Furthermore, as emphasized by existing guidelines,28 electrophysiological testing is not a simple procedure that should be performed in a nonstandardized fashion by literally thousands of unsupervised cardiologists with little training in the technique. If the test proves to be of more value than I suspect, an extensive national training program would be required.

Coronary artery disease remains the leading cause of death in the United States, where its annual direct and indirect costs are over $100 billion.29 Cost-effective modalities to improve prognostic stratification and to guide beneficial treatment are critically needed. I do not argue with the suggestion of Richards et al that patients who are at high risk for sudden arrhythmic death should be candidates for controlled trials of potential strategies to improve their clinical outcomes. In the meantime, I contend that a substantial literature demonstrates that predischarge exercise testing and β-adrenergic receptor antagonists should be used routinely in all postinfarction patients, unless there are contraindications.

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