EDITORIAL

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Coronary artery disease in diabetes: Which (if any) test is best?

On exercise testing, ST changes are not the strongest predictors of risk

IN THE CURRENT ISSUE of the *Cleveland Clinic Journal of Medicine*, Dr. Wackers presents a scholarly and persuasive review arguing for frequent use of stress myocardial perfusion imaging (MPI) in patients with diabetes.[1]

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Dr. Wackers' argument is based on two points, both worthy of careful consideration. First, diabetes is associated with a marked increase in cardiovascular risk. Second, clinicians caring for patients with diabetes are faced with a number of diagnostic and prognostic testing options, including exercise testing, stress MPI, and stress echocardiography. MPI may have greater incremental prognostic value than exercise testing and is less technically difficult to perform than stress echocardiography. Indeed, there is an extensive literature from many institutions, including ours, showing that MPI is a powerful predictor of risk.[2–4]

PRE-TEST AND POST-TEST RISK

A fundamental principle of diagnostic and prognostic reasoning is that testing is most useful when baseline risk of disease is considered. Classic Bayesian thinking argues that a diagnostic test is valuable only when pre-test risk is intermediate or close to intermediate.

More recent work on the value of noninvasive tests when used for prognostic purposes has focused on targeting risk: that is, when combining pre-test risk with test findings, a test is useful only if post-test risk is high enough that aggressive treatment might arguably reduce risk.[5] Thus, if pre-test risk is very low, even a floridly abnormal test is unlikely to increase post-test risk to a level high enough that therapy should be changed.[2]

SENSITIVITY OF TESTS OVERRATED

With these concepts in mind, let us examine the issue of noninvasive testing in diabetes, particularly in the absence of symptoms or history of coronary events. Diabetes is now classified as a "coronary disease equivalent," meaning that the risk of subsequent cardiac events in asymptomatic patients with diabetes is no lower than in a patient with known coronary disease but no history of diabetes.[6] Hence, baseline risk in diabetes is high enough that an abnormal noninvasive test would be clinically relevant. Although there is overwhelming evidence that diabetes is associated with a markedly increased cardiovascular risk, it is interesting that recent epidemiological reports have suggested that the risk may not be as high as once thought.[7]

Given that patients with diabetes are at increased risk for having cardiovascular disease or for experiencing subsequent cardiovascular events, clinicians caring for these patients are faced with considering referral for noninvasive tests, either for establishing a diagnosis of coronary disease or for assessing risk. Although the reported sensitivity of MPI is very high in diabetes (see **FIGURE 1** of Dr. Wackers' article),[8] one must realize that the reported sensitivity, exceeding 85% is almost certainly biased, because not all patients referred for noninvasive testing subsequently

Dr. Lauer is supported by grant HL-66004 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

undergo coronary angiography. A number of groups have shown that failure to account for this "workup bias" leads to a marked inflation of sensitivity and deflation of specificity.[9–12] Once workup bias is accounted for, the true sensitivity of MPI falls to the range of 65%.[11]

Similarly, exercise testing and stress echocardiography also have poor sensitivity for the diagnosis of coronary disease after accounting for workup bias.[10,12]

MARKERS OF RISK ON EXERCISE TESTING

The true clinical value of noninvasive testing is its ability to prognosticate, particularly with regard to fatal events.[13] Which test is best for initial evaluation? Although MPI has been shown to be a stronger predictor of risk than exercise testing, most literature comparing the two tests has only considered ST-segment changes as the exercise-test marker of risk. Recent work based on large cohorts from several institutions has demonstrated that there are much stronger predictors of all-cause and cardiovascular death than ST-segments; namely, exercise capacity,[14] chronotropic response,[15] heart rate recovery,[16] and exercise-associated ventricular ectopy.[17] In one comparison with coronary angiography,[14] exercise capacity emerged as a much stronger predictor of death than angiographic extent of disease!

Will testing prevent premature death or myocardial infarction?

Data derived from general and clinical populations have been shown to apply to patients with diabetes, as well. One recent study of a large cohort of asymptomatic men with diabetes found that exercise capacity and heart rate recovery were strong risk predictors.[18]

WHEN IS IMAGING APPROPRIATE?

Given that exercise testing, when properly interpreted, is a very powerful predictor of risk, when is imaging, such as that afforded by echocardiography or MPI, appropriate?

Current guidelines recommend imaging when exercise testing suggests an intermediate risk for coronary events.[19] This recommendation is supported by data from contemporary cohort studies, in which imaging provided relevant prognostic information over and above exercise testing only when the exercise test suggested an intermediate or higher risk.[2]

Among patients for whom imaging is appropriate, two questions face the clinician: should stress be induced by exercise or pharmacologically, and which type of imaging is appropriate? With the possible exception of patients with left bundle-branch block,[19] it is probably preferable to use exercise to induce stress, since that yields additional important prognostic information from measurement of exercise capacity, heart rate responses, and exercise-associated ventricular ectopy. Direct head-to-head comparisons of MPI and stress echocardiography are few, but current data suggest similar test performance when in good hands.[20,21]

If a physician is faced with a patient with diabetes who has no coronary history and has an interpretable electrocardiogram, it is reasonable to choose to send the patient for an exercise test. Should that exercise test reveal a high risk, such as an impaired exercise capacity or an abnormal heart rate recovery, referring the patient for stress MPI or stress echocardiography is appropriate.

A final, and arguably the most critical, component of the analysis of noninvasive testing in asymptomatic patients, with or without diabetes, is whether or not testing improves outcome. Abnormal findings on imaging may subsequently lead to invasive procedures. Despite all the work that has been done to evaluate test performance, we simply do not know whether or not acquiring any of this information actually helps the patient. From the patient's point of view, the key question is whether premature death or myocardial infarction can be prevented or delayed. The only way to know definitively would be to perform a properly designed and powered randomized trial.

To date, no such trial has been performed.[22] That is why most current guidelines do not enthusiastically recommend any kind of noninvasive testing for screening, even in patients with diabetes.[13,19] However, thanks to work by Wackers and colleagues, we may soon have some real evidence to work with. As Wackers mentions in his article, he has successfully completed enrollment of a randomized trial of patients with diabetes in which testing and no-testing strategies are being compared (Detection of Ischemia in Asymptomatic Diabetics, or DIAD).[1] The

results of DIAD will not known for several years. In the meantime, the optimal testing strategy in patients with diabetes will remain subject to lively, inferential debate.

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