Editorial

Risk Stratification of Diabetics With Stress Testing
Can We Do Better?

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It is estimated that 9% of adults or 347 million people worldwide have diabetes mellitus, and cardiovascular disease including coronary artery disease (CAD), stroke, peripheral arterial disease, heart failure, and cardiomyopathy is estimated to account for between 50% and 80% of deaths in diabetics. Diabetes mellitus has been designated as a cardiovascular disease risk equivalent for both lipid and hypertension treatment goals, and risk factor modification is recommended in all diabetics. Nevertheless, as the number of diabetics is expected to grow, total deaths from diabetes mellitus are projected to increase by >50% in 10 years. CAD tends to be more severe and to occur at an earlier age in diabetics. In patients with diabetes mellitus and known CAD, the risk for future events is particularly high. Considering the magnitude of the problem of diabetes mellitus-related cardiovascular disease, stress testing of diabetics with known or suspected CAD would seem a reasonable approach to guide therapy, including intensive medical therapy and coronary revascularization. Stress testing, and subsequent intervention, might reduce patients’ risk of cardiovascular morbidity and mortality.

The study by Cortigiani et al in this issue of Circulation: Cardiovascular Imaging compared the use of stress echocardiography in predicting mortality in diabetics versus nondiabetics and sought to determine if the parameters related to outcome were different in the 2 groups. The study comprised an impressively large unselected population of 2835 diabetics and 11,305 nondiabetics referred for stress echocardiography for evaluation of known or suspected CAD at 2 Italian institutions during a 16-year period. There were few exclusion criteria and over a median follow-up of 30 months, only 2% were lost to follow-up. The mean age of the patients was 64 years, 63% were males, known CAD was present in 40%, and 37% were on antithrombotic therapy. Most (85%) patients underwent pharmacological rather than exercise stress echocardiography. Rest wall motion abnormalities were present in 41% and ischemic wall motion abnormalities in 24%; only 50% of tests were normal. Both the rest and ischemic wall motion abnormalities were significantly more frequent in diabetics.

During follow-up, 9% of patients died. The results of stress echocardiography were strongly and independently predictive of mortality in both diabetics and nondiabetics. Multivariable predictors of mortality in both the groups included age, rest wall motion abnormalities, and ischemia at stress echocardiography. In addition, in the nondiabetics, male sex, and anti-ischemic therapy at the time of testing, including β-blockers, calcium antagonists, or nitrates, were also predictors of mortality. Interestingly, among nondiabetic patients without ischemia, anti-ischemic therapy at the time of testing was associated with increased mortality both in patients with and without rest wall motion abnormalities. As this relationship was not significant in the smaller number of patients with diabetes mellitus, the investigators speculate that anti-ischemic therapy may be less effective in diabetics; such therapy may be less effective in attenuating ischemic responses to stress testing in diabetics.

As expected, the rates of coronary revascularization were higher in diabetics than in nondiabetics, both in patients with and without ischemia. Despite this, annual mortality was twice as high in diabetics as in nondiabetics. Mortality in diabetics was increased both among those with a normal test and among those with ischemia.

The findings that ischemia as well as rest wall motion abnormalities by stress echocardiography were strong and independent predictors of mortality confirm the predictive value of stress echocardiography in a large unselected population. Previous studies have demonstrated that stress echocardiography with either exercise or pharmacological stress provides information that is incremental to clinical, exercise electrocardiography, and rest echocardiography parameters for predicting mortality and cardiac events in diabetics. However, it is not only the presence of fixed and ischemic wall motion abnormalities but also their extent and severity which are known to be prognostically important. Elhendy et al observed that diabetics with a multivessel distribution of echocardiographic abnormalities had the highest cardiac event rate (33% at 5 years), whereas those with a normal exercise echocardiogram had neither cardiac death nor myocardial infarction during the first 2 years of follow-up, although event rates increased thereafter. Chaowalit et al combined information from the stress echocardiogram with clinical data to stratify patients for mortality and cardiovascular morbidity.

Similarly, in diabetics undergoing myocardial perfusion imaging, abnormal stress perfusion has been shown to be an independent predictor of death and myocardial infarction; multivessel ischemia was the greatest predictor of cardiac
events and a fixed defect in a multivessel distribution was the strongest predictor of cardiac death. Diabetics had a significantly higher cardiac event rate than nondiabetics, despite an increased rate of revascularization in diabetics. However, cardiac survival rates in patients with and without diabetes mellitus were similar when adjusted for clinical risk and stress myocardial perfusion imaging results.11

This study by Cortigiani et al10 includes information about risk factors for CAD, but does not include information about whether patients had cardiac symptoms that may have accounted for the suspicion of ischemia prompting the stress tests. According to current multimodality appropriate use recommendations for detection and risk assessment of ischemic heart disease, symptoms are important in determining the appropriateness of a test that includes imaging.12 For symptomatic patients at intermediate or high risk of CAD or who cannot exercise or have an uninterpretable ECG, stress testing with echocardiography or radionuclide imaging is considered appropriate. However, for asymptomatic patients, stress testing is more controversial.

Appropriate use recommendations classify asymptomatic patients with diabetes mellitus as having high global risk of CAD, and as such, advise that exercise electrocardiography is appropriate when interpretable and the patient can exercise. These recommendations are more cautious about recommending the more costly imaging tests, stating that stress testing with imaging or coronary computed tomographic angiography “may be” rather than “are” appropriate in asymptomatic diabetics.12

However, the 2014 American Diabetes Association13 guidelines do not recommend stress tests for screening of asymptomatic patients with diabetes mellitus and cite as evidence, the Detection of Ischemia in Asymptomatic Diabetics study,14 a randomized controlled trial that demonstrated no reduction in cardiac death or myocardial infarction with routine screening of asymptomatic patients with type 2 diabetes mellitus and normal electrocardiography. However, in the Detection of Ischemia in Asymptomatic Diabetics study, event rates were unexpectedly low, averaging 0.6% per year. Intensification of medical treatment including aspirin, statins, and ACE inhibitors was associated with resolution of ischemia over time.15 Information about use of these medications or about temporal changes in ischemia were not available in Cortigiani et al’s8 study.

Diabetics represent a group in whom cardiac symptoms are notoriously absent. It would have been of interest to know if symptoms in this study were associated with test results or patient outcomes. The stress tests yielded evidence of fixed wall motion abnormalities in 29% of diabetics; we do not know of often these important findings were previously unknown. ECG evidence of silent myocardial infarction has been observed in as many as 1 in 6 patients with newly diagnosed type 2 diabetes mellitus and is associated with increased mortality.16 Additional limitations of the study by Cortigiani et al,8 not surprising in such a large study, are that submaximal and maximal stress tests were not differentiated; the predictive value of negative submaximal tests is known to be diminished.17 Exercise testing, which provides important physiological information including exercise capacity, and heart rate and blood pressure responses, each of which has been shown to have prognostic value,18 was performed in only 15%. Information about the duration of diabetes mellitus is known to be associated with CAD mortality,6,7 but was not available. Information about the cause of death was also not included but would have been interesting. Finally, follow-up was censored at coronary revascularization as the investigators assumed that revascularization changed the predictive value of stress echocardiography; in fact, this may not be true.

Diabetics are known to have an increased lifetime risk of heart failure which is not completely explained by CAD. Diabetes mellitus is associated with concentric left ventricular hypertrophy,19 mild systolic dysfunction, and diastolic dysfunction.20 In addition to assessment of regional wall motion, these parameters could be readily assessed at the time of stress echocardiography and may be prognostically important.

Identification of CAD in patients with and without diabetes mellitus should lead to interventions that improve outcome. Further information is needed not only about the relationship of stress tests with outcome but also when such testing is indicated, in which patients it will be most impactful and, most importantly, how (and if) we can effectively apply such testing to improve patient outcomes. The growing numbers of patients with diabetes mellitus worldwide could benefit greatly.
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