Screening for Asymptomatic Coronary Artery Disease in Diabetes

The increased risk for coronary artery disease (CAD) associated with diabetes is well known. Clinical trials evaluating the benefits of tight glycemic control in both type 1 and type 2 diabetes have shown major reductions in microvascular end points. Comparable reductions in death due to macrovascular disease and particularly CAD unfortunately have not been seen (1,2).

Despite major advances in the treatment of acute coronary syndromes, diabetic patients still experience twice the morbidity and mortality related to myocardial infarction compared with their nondiabetic counterparts (3–5). In addition, CAD is often "silent" and not typically accompanied by angina in patients with diabetes (6–8). These factors have raised the interest level in making a diagnosis of CAD before its first clinical expression.

The recent American Diabetes Association/American College of Cardiology Consensus Development Conference (9), which put forth guidelines on screening diabetic individuals for CAD, was convened to arm physicians with the tools to make a preemptive strike against premature death from CAD. A similar set of guidelines published in France (10) was used to test for asymptomatic CAD in the article appearing in this issue of *Diabetes Care* and discussed below. Based on pretest risk and the degree of abnormality on the exercise treadmill test (ETT), appropriate recommendations have been established to perform coronary angiography in selected individuals at the greatest risk for cardiac events. When face to face with an individual patient, however, practitioners are still vexed by the following questions: Should I test for CAD? How do I interpret the results? If coronary angiography is performed and CAD is found, who decides and what data exists to support which treatment is best? This editorial will tangle with some of these issues.

The article by Janand-Delenne et al. (10a) in this issue demonstrates the outcome of screening for asymptomatic CAD in patients with diabetes. From a methodological point of view, it is interesting for two major reasons. The investigators followed a set of published guidelines to identify candidates for screening, and coronary angiography was performed to "verify" the results of noninvasive testing. In 73 type 1 patients, 8 had positive screening tests, but only 3 of these (4.2% overall) demonstrated a lesion(s) >50% on angiography. In 130 type 2 patients, 24 had positive screening tests. In the 20 patients who consented to angiography, 16 demonstrated lesion(s) >50% (12.3% overall). If one assumes that significant lesions would have been found in two of the four patients who refused angiography, 13.8% of the type 2 diabetic subjects could be said to have asymptomatic CAD. This study actually evaluates the prevalence of "asymptomatic CAD" and not "silent myocardial ischemia" (as stated in the article's title), because a fixed (myocardial scar) or reversible (ischemia) defect on thallium 201 imaging led to coronary angiography. Costs of screening according to this algorithm are not mentioned; but in 80 of 130 (62%) type 2 patients, routine ETT could either not be done or was nondiagnostic, and more expensive perfusion thallium imaging was necessary.

The prevalence of asymptomatic CAD found above is not surprising and concurs with a number of recent studies investigating diabetic patients with similar characteristics. The Milan Study on Atherosclerosis and Diabetes (MiSAD) group (11) reported that 112 of 925 (12%) type 2 diabetic patients free of clinical CAD and treated with either oral hypoglycemic drugs or diet demonstrated ST segments suggestive of ischemia on the ETT. Of these 112, 59 patients or 6% overall had a scintigraphic diagnosis of CAD. Koistinen (12) found asymptomatic CAD in 7 of 72 (10%) type 1 and 5 of 64 (8%) type 2 diabetic patients by angiography. Of 40 subjects with positive noninvasive tests, however, only 12, or 30%, displayed CAD on angiography, causing the author to remark that "screening does not seem justified because of ... the inaccuracy of the available test methods." In a similar study using both ETT and angiography, Naka et al. (13) discovered positive exercise tests in 41 of 132 (31%) type 2 diabetic patients, with 14 of 36 (11% of the total population) demonstrating CAD on angiography. As in the study by Koistinen, a positive noninvasive test carried a relatively low positive predictive value for significant CAD on angiography.

A number of factors specific to the diabetic patient can interfere with the sensitivity, specificity, and implications of noninvasive diagnostic tests for CAD. Hypertension in the setting of diabetes results in greater left ventricular mass than either condition alone (14,15) and can produce an abnormal ST segment response to exercise as well as cause false-positive thallium defects. Diabetic cardiomyopathy, even in its mildest form, can cause segmental wall motion abnormalities or thallium defects mimicking ischemia (16). To improve the ability of stress perfusion studies to differentiate ischemic from nonischemic cardiomyopathy, more expensive gated single-photon emission computed tomography sestamibi imaging may be necessary (17). Autonomic neuropathy may blunt the chronotropic response to exercise and dissociate the relation between cardiac and external work (18). In diabetic patients with renal insufficiency, elevated resting levels of adenosine may limit maximal coronary flow reserve induced by persantine and decrease the sensitivity of stress-perfusion thallium or echo imaging (19). In addition, both autonomic neuropathy (20) and endothelial dysfunction (21) may interfere with coronary vasodilatory capacity. "Microvascular" angina—a condition associated with abnormalities on exercise testing in the absence of epicardial CAD—may be more common in the setting of insulin resistance (22,23). It is also not clear whether the exercise test delivers the same prognostic information in diabetic compared with nondiabetic individuals. Although experience can be a fickle teacher, I can remember more diabetic than nondiabetic patients experiencing a coronary event soon after a negative exercise test. It is possible that features such as sympathovagal imbalance (24,25), impaired fibrinolysis, and altered hemostasis that are commonly clustered together in diabetes may trigger coronary plaque disruption and superimposed thrombosis (26) in a more unpredictable manner than in the absence of diabetes.

The justification for screening depends on whether detection of CAD leads to treatment strategies that ultimately reduce cardiac morbidity and mortality. Examples where there is little debate on this matter include the following: *1*) evaluation before renal transplantation (27); *2*) preoperative clearance for major noncardiac or vascular surgery (28–30); and *3*) evaluation before initiation of an exercise program (18). These subgroups will benefit because they face definable periods of excess cardiac risk. Another positive outcome of screening would be the discovery of three-vessel or "high-risk" coronary anatomy, particularly in the presence of left ventricular dysfunction in an asymptomatic patient. Surgical revascularization will prolong life in this otherwise undetected case. It is more likely that CAD of this extent will be found when screening diabetic patients with proteinuria, peripheral vascular disease, autonomic nervous system dysfunction, or unexplained congestive heart failure.

Based on American Diabetes Association/American College of Cardiology guidelines, the majority of diabetic patients to be screened will be type 2 individuals with two or more coronary risk factors. For those people without major end-organ involvement, CAD of a more modest extent will be found and in all likelihood not require bypass surgery. In the study by Janand-Delenne et al. (10a) in this issue of *Diabetes Care*, the extent of CAD was not described, but not one of the 130 screened patients received surgical revascularization, suggesting that single- or double-vessel CAD must have predominated. Of the 19 cases with documented CAD, 7 underwent percutaneous transluminal coronary angioplasty (PTCA) and 12 were treated medically. It is also not stated on what basis PTCA or medical therapy was chosen. The decision to select PTCA over medical therapy was probably based on the lesions' suitability for an interventional approach, because PTCA's advantage in relieving angina was irrelevant in these patients.

But do we know what is the best treatment strategy for these patients? The data evaluating various treatments (medical, surgical, interventional) for CAD derive from randomized clinical trials largely composed of nondiabetic patients (31–33). To assume that the same treatments will yield similar and comparable outcomes in the setting of diabetes may be foolhardy. The Bypass Angioplasty Revascularization Investigation (BARI) (34,35) has illustrated this point emphatically. A National Institutes of Health alert was sounded when it was discovered that PTCA was associated with a lower survival rate compared to bypass surgery for multivessel disease in subjects with diabetes—a finding that might have been "hidden" within the analysis of the total population if patients with diabetes had not been identified as a prespecified group for analysis. The proposed BARI 2 study, a prospective randomized trial comparing medical therapy versus PTCA or coronary bypass surgery in the setting of tight glycemic control, should provide answers to some of the questions posed above regarding optimal treatment for CAD in diabetes.

The discovery of preclinical CAD in the diabetic individual will yield one major unmeasurable benefit, i.e., the patient and physician will know that CAD is present. For the patient, knowledge that CAD is present should promote adherence to treatments proven to reduce cardiac risk, such as lowering blood pressure and cholesterol and participating in regular exercise. The majority of diabetics will be taking aspirin (36,37) and a statin (38) as primary prevention anyway. A physician might consider adding a cardioselective β-blocker to this regimen. β-Blockers provide two to three times the relative benefit in mortality reduction after myocardial infarction when diabetes is present (39). This strategy would concur with the recent suggestion that type 2 diabetic patients should be treated with secondary prevention techniques as primary prevention (40,41).

Knowing that CAD is present, the physician can instruct the patient to heed and report the first sign of angina as well as symptoms such as dyspnea, diaphoresis, or nausea, all of which are typical anginal equivalents in these patients (4). Failure to identify these symptoms as a possible acute cardiac emergency may delay a patient's arrival in the emergency room, where the success of treatment for acute myocardial infarction is time-dependent (42,43). In addition, the physician or caregiver can become educated as to what symptoms, anginal or nonanginal, represent ischemia in an individual patient. This discourse, made relevant by the discovery of CAD, can pay huge dividends in practice.

Two pieces of information are necessary to resolve the issues mentioned above. First, we must establish the prevalence and extent of CAD using such screening algorithms. Second, we must determine which treatment strategies for CAD are most effective in the presence of diabetes.

RICHARD W. NESTO, MD

From the Beth Israel Deaconess Medical Center, Cardiovascular Division, Harvard Medical School, Boston, Massachusetts.

Address correspondence to Richard W. Nesto, MD, Beth Israel Deaconess Medical Center, Cardiovascular Division, Harvard Medical School, 110 Francis St., Boston, MA 02215. E-mail: rnesto@caregroup.harvard.edu.

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