Screening for Coronary Disease in Diabetes: When and How

Yasmine S. Ali, MD, and David J. Maron, MD

Cardiovascular disease is the leading cause of death in patients with diabetes, accounting for as many as 80% of deaths in these patients.[1] The risk of myocardial infarction (MI) in patients with diabetes is similar to that of patients without diabetes who have had a previous MI.[2] Autopsy studies have identified a high prevalence of coronary atherosclerosis in patients with diabetes, even among those without clinical coronary heart disease (CHD). Goraya et al.[3] found advanced coronary lesions in nearly three-fourths of individuals with diabetes who did not have clinically apparent CHD; > 50% of asymptomatic individuals had multivessel disease. The prevalence of coronary calcification is similar in asymptomatic individuals with type 2 diabetes and individuals without diabetes who have symptomatic CHD.[4] Hence, diabetes is considered to be a "CHD equivalent."[5] Furthermore, the prevalence of silent ischemia among asymptomatic individuals with diabetes is high, ranging from 20 to > 50% of patients.[6,7] The question thus arises as to whether asymptomatic patients with diabetes should be screened for CHD and, if so, when and by which modality.

If Diabetes Is a CHD Equivalent, Why Screen?

If we approach all patients with diabetes as if they have already been diagnosed with CHD, what is the rationale for trying to detect the presence of CHD? The reason is that there are important prognostic, management, and therapeutic implications from identifying CHD in patients with diabetes. Patients with diabetes and CHD carry a significantly worse prognosis than those a with diabetes who do not have CHD.[2] In addition to risk stratification, detecting CHD may improve patient motivation to adhere to medical therapy.[8] From a management perspective, patients with high-risk characteristics on testing for ischemia may belong to a subset that would benefit from coronary angiography and revascularization. With regard to medical therapy, the knowledge that a patient with diabetes has CHD may indicate the need to initiate or intensify pharmacological therapy with β-blockers (if ischemia is present), statins, or ACE inhibitors. Current National Cholesterol Education Program guidelines recommend an LDL cholesterol goal of < 100 mg/dl for patients with diabetes without CHD; if CHD is present, the LDL goal is < 70 mg/dl.[9] Not all patients with diabetes are considered candidates for ACE inhibitor therapy; those with CHD should be treated with these agents.[10] Hence, detecting CHD with or without ischemia helps refine the management of asymptomatic patients with diabetes.

IN BRIEF

Coronary atherosclerosis and silent ischemia are highly prevalent in patients with diabetes. Identification of subclinical atherosclerosis and ischemia in asymptomatic patients with diabetes is valuable for risk stratification and for guiding therapy. This article reviews methods of screening and proposes how to implement them in practice.

Screening for Silent Ischemia

Existing guidelines for screening

Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the American Diabetes Association (ADA) recommend graded exercise testing in asymptomatic patients with diabetes who plan to begin a moderate- to high-intensity exercise program and are at increased risk for CHD based on one or more of the following factors: age > 35 years, age > 25 years and type 2 diabetes of > 10 years' duration or type 1 diabetes of > 15 years' duration, any additional risk factors for CHD, and the existence of microvascular disease, such as proliferative retinopathy or nephropathy (including microalbuminuria), autonomic neuropathy, or peripheral vascular disease.[11,12] The greater the number of risk factors, the higher the pretest probability, thus increasing the likelihood that screening will result in useful prognostic information.

The diagnostic accuracy of stress testing is improved when combined with imaging. The ACC Foundation and American Society of Nuclear Cardiology have deemed it appropriate to perform single-photon emission computed tomography (SPECT) myocardial perfusion imaging for asymptomatic individuals with diabetes.[13] It is also considered appropriate to repeat a SPECT study in patients with diabetes at least 2 years after a previously normal SPECT study.

Exercise treadmill testing

In a retrospective study of 1,282 male patients without prior MI who

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underwent exercise stress tests after presenting with chest pain, Lee et al.[14] found the sensitivity of exercise treadmill testing to be 47% in patients with diabetes, with a specificity of 81%. The positive predictive value in individuals with diabetes was 85%; the negative predictive value was 41%. For those who did not have diabetes, the sensitivity of exercise testing was 52%, specificity 80%, positive predictive value 78%, and negative predictive value 55%, demonstrating similar diagnostic and prognostic characteristics in patients with and without diabetes.

In another study of asymptomatic, higher-risk patients with diabetes, Bacci et al.[15] found the positive predictive accuracy of the exercise treadmill test to be 79%. Those with false-negative tests tended to have a longer duration of diabetes and a higher prevalence of peripheral vascular disease.

Nuclear stress imaging

Nuclear stress imaging, the most widely studied stress testing modality in patients with diabetes, has a sensitivity of 88% and specificity of 74% in the population at large, with similar diagnostic characteristics among individuals with diabetes.[16,17] In the Detection of Ischemia in Asymptomatic Diabetics study, Wackers et al.[6] used adenosine SPECT imaging to screen 1,123 asymptomatic patients with type 2 diabetes for myocardial ischemia. The average age was 61 years, with an average duration of diabetes of 8 years. Twenty-two percent of these patients were found to have silent ischemia, and 41% of the abnormal tests would not have been predicted based on the 1998 ADA screening guidelines alone. Notably, the presence of cardiac autonomic dysfunction was strongly associated with silent ischemia in this study.

Rajagopalan et al.[18] examined the relationship of ischemia by SPECT with angiographic findings and total mortality in 1,427 asymptomatic patients with diabetes who did not have known CHD. The average age of subjects was 60 years, and the median duration of diabetes was 10 years. Eighteen percent had high-risk stress SPECT results, defined as a summed stress score ≤ 47 points. Sixty-one percent of patients with high-risk results had angiographically high-risk coronary artery disease (CAD). Subjects with high-risk findings had a high annual mortality rate of 5.9%. Of note, those with low-risk scans also had a relatively high annual mortality rate of 3.6%. The presence of Q waves on electrocardiogram and the diagnosis of peripheral arterial disease were the strongest predictors of abnormal stress test results.

De Lorenzo et al.[19] also evaluated the utility of SPECT imaging in screening asymptomatic subjects with diabetes. One hundred and eighty asymptomatic patients with diabetes underwent 2-day stress SPECT testing and were followed for 36 ± 18 months. Twenty-six percent of patients had perfusion defects, and clinical variables were not associated with the type of defect or subsequent events. "Hard" events were defined as MI or death due to a cardiac cause; "total" events included MI, cardiac death, or revascularization. Two percent of hard events and 5% of total events per year occurred in patients who had a normal SPECT. By comparison, these numbers increased to 9% of hard events and 38% of total events in those with an abnormal SPECT. Thus, the presence of an abnormal SPECT test in these asymptomatic patients seemed to provide added prognostic value over clinical predictors alone.

In a multicenter cohort consisting of 370 asymptomatic patients with diabetes who also had at least two additional cardiac risk factors, Valensi et al.[20] identified silent ischemia in 35% of patients using stress SPECT imaging as well as electrocardiographic stress testing. These patients were followed for 38 ± 23 months, with a significant association found between positive stress results and subsequent cardiac events. The prevalence of silent ischemia was 43% among patients > 60 years of age versus 30% in patients < 60 years of age. Interestingly, the association between the presence of silent ischemia and subsequent cardiac events was statistically significant in the patients > 60 years old but not in those < 60 years old.

Stress echocardiography

Data specifically addressing the predictive value of stress echocardiography in patients with diabetes, particularly those who are asymptomatic, are limited. In a study by Hennessy et al.,[21] 52 patients with diabetes were evaluated by dobutamine stress echocardiography, with a sensitivity for CHD detection of 82% and a specificity of 54%. The positive predictive value of dobutamine stress echocardiography was 84%, and the negative predictive value was 50%.

Elhendy et al.[22] followed 563 patients with diabetes who also had known or suspected CAD and had undergone exercise stress echocardiography over a median follow-up period of 3 years. Event rates were not well predicted by prior angina or stress-induced angina. Patients with multiple wall motion abnormalities had the highest event rates, and echocardiographic abnormalities in a multivessel distribution during exercise provided prognostic information beyond that afforded by clinical and exercise data alone. Conversely, patients with a normal exercise echocardiogram had no events at 2 years. The event rate increased to 7.6% at 5 years, suggesting that, as with nuclear stress testing, the frequency of such stress testing should be in the range of every 2–3 years for the reassessment of risk in patients with diabetes.

Screening for Subclinical Atherosclerosis

Most MIs originate from atherosclerotic plaque that is not obstructive and therefore would not be detected by a test for myocardial ischemia.[23] In addition, patients with diabetes and a normal SPECT have a higher event rate than patients without diabetes who have a normal SPECT.[24] These facts provide the rationale to search noninvasively for

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the presence of subclinical atherosclerosis. The two imaging modalities most commonly evaluated for this purpose are coronary artery calcium (CAC) scanning and measurement of carotid intima-media thickness (cIMT).

CAC

A number of studies have revealed a higher prevalence of CAC in patients with diabetes. Schurgin et al.[25] scanned 139 patients with diabetes for CAC and compared their findings with individuals who did not have diabetes. Seventy-five percent had a CAC score > 0, indicating the presence of subclinical atherosclerosis. Twenty-five percent had CAC scores ≥ 400, compared with 7.2% of randomly selected and 14.4% of matched control subjects without diabetes. The average age of subjects in the group with diabetes was 58 years. Wolfe et al.[26] conducted a retrospective analysis of CAC data for 71 asymptomatic subjects with type 2 diabetes compared with 1,481 asymptomatic patients without diabetes and 71 randomly selected matched patients without diabetes. CAC scores were higher in patients with type 2 diabetes than in those without, independent of traditional cardiac risk factors. The odds ratio for the presence of any coronary calcification (CAC score > 0) was 2.9 in patients with type 2 diabetes. The average age of the patients with diabetes in this study was 55 years. In the Prospective Evaluation Identification of Decompensation by IGT Test study, Elkeles et al.[27] performed CAC screening in 495 subjects with type 2 diabetes, none of whom had a history of CHD. The mean age of these subjects was 62.9 years, with a median duration of diabetes of 8 years. The median CAC score was 119, and duration of diabetes was significantly associated with increased CAC score.

In a study by Raggi et al.,[28] 10,377 asymptomatic patients (903 of whom had type 2 diabetes) were followed for a mean of 5 years after undergoing CAC screening. The primary end point of the study was all-cause mortality. On average, patients with diabetes had a higher CAC score than patients without diabetes, and for every increase in CAC score, there was a greater increase in mortality for subjects with diabetes than for those without. Notably, patients both with and without diabetes who were found to have no coronary calcification had a low risk of death (~1% at 5 years).

cIMT

cIMT is a significant predictor of coronary events.[29–31] In the Insulin Resistance Atherosclerosis Study,[32] diabetes was associated with increased common cIMT. The mean duration of diabetes was 7 years. In the Atherosclerosis Risk in Communities study,[33] a cohort study of 15,792 asymptomatic adults aged 45–64 years, adjusted mean wall thickness was thicker in subjects with diabetes than in those without. Patients with newly detected type 2 diabetes were shown to have increased cIMT in a case-controlled study by Temelkova-Kurktschiev et al.[34] Seventy-one patients with newly diagnosed type 2 diabetes with a mean age of 57 years had significantly increased common cIMT compared with control subjects.

Few prospective studies exist using cIMT measurements to predict cardiac events in patients with diabetes. Yamasaki et al.[35] followed 287 patients with type 2 diabetes for 3 years and determined that baseline cIMT independently predicted nonfatal CHD events.

Recommendations

Identification of subclinical atherosclerosis and ischemia in asymptomatic patients with diabetes is worthwhile for risk stratification and for guiding therapy. Current guidelines fail to identify an unacceptably large proportion of patients, yet evidence is not currently sufficient to define the optimal screening strategy for asymptomatic patients with diabetes in terms of clinical and cost-effectiveness outcomes. In the absence of such evidence, we propose an approach, based on our synthesis of the current evidence, to identify more high-risk individuals in a presymptomatic phase (Figure 1). We acknowledge that further research is needed to define the optimal approach.

We recommend that patients with type 1 or type 2 diabetes who are ≥ 60 years of age or who have had diabetes for ≥ 15 years undergo a stress imaging test for myocardial ischemia. Those with findings consistent with severe ischemia should be referred for cardiac catheterization. In addition, those patients should be started on β-blocker and ACE inhibitor therapy, and statin-based lipid lowering should be intensified to achieve an LDL cholesterol of < 70 mg/dl ("tailored medical therapy"). Those with ischemia that is not severe should not necessarily be referred for cardiac catheterization because the benefit of revascularization in such patients has not been demonstrated. These patients should have tailored medical therapy as described above. Patients without ischemia may be considered for screening for subclinical atherosclerosis. Alternatively, because the likelihood of subclinical atherosclerosis is ~ 60–70% in such patients,[4,28] its presence could be presumed and appropriate medical therapy implemented. Asymptomatic patients with diabetes who are < 60 years of age and who have had diabetes for > 7 years but < 15 years should undergo screening for subclinical atherosclerosis with CAC scoring or carotid ultrasonography. Those with moderate to severe atherosclerosis should be treated with appropriate medical therapy and referred for stress imaging. Those with minimal atherosclerosis should have tailored medical therapy only.

Summary

Subclinical atherosclerosis and silent ischemia in asymptomatic patients with diabetes is common. Screening patients according to traditional risk factors and current guidelines alone will frequently fail to identify CHD, thus losing the opportunity for early diagnosis and intensified management. A more

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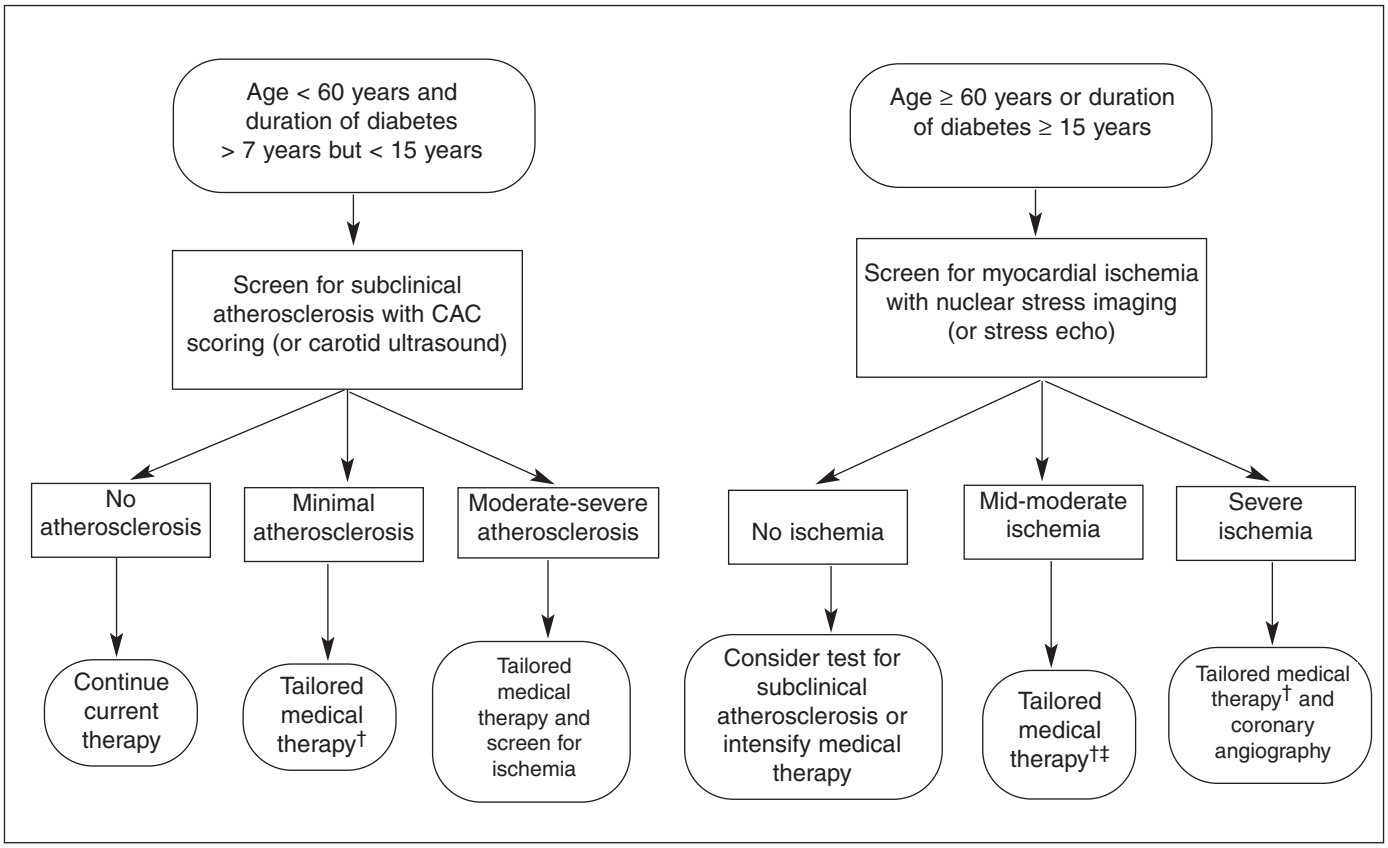

Figure 1. Proposed CHD screening strategy for patients with type 1 or type 2 diabetes and no symptoms. †Initiate β-blocker and ACE inhibitor; intensify statin-based therapy to achieve LDL cholesterol < 70 mg/dl. ‡The benefit of revascularization in a patient with no symptoms and no high-risk features is unestablished.

aggressive approach to identifying asymptomatic coronary disease should therefore be considered in this patient population.

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Yasmine S. Ali, MD, is a fellow in cardiovascular medicine, and David J. Maron, MD, is an associate professor of medicine in the Division of Cardiovascular Medicine at Vanderbilt University Medical Center in Nashville, Tenn.

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