

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 dia-

betes and CHD carry a significantly worse prognosis than those 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

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

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 aver-

age, 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

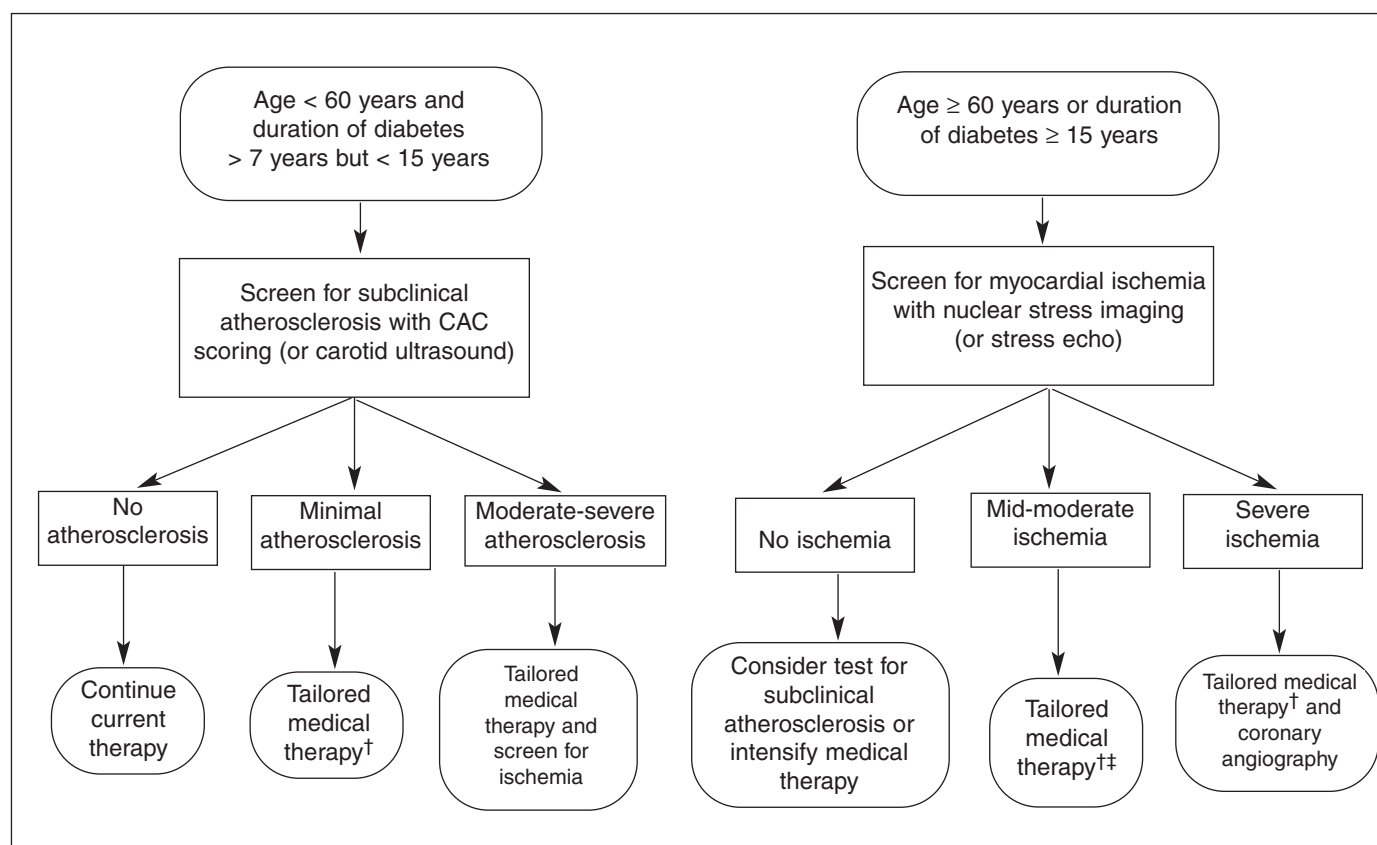


Figure 1. Proposed CHD screening strategy for patients with type 1 or type 2 diabetes and no symptoms.

†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.

REFERENCES

- ¹Bonow RO, Bohannon N, Hazzard W: Risk stratification in coronary artery disease and special populations. *Am J Med* 101:17S–22S, 1996 [discussion *Am J Med* 101:22S–24S, 1996]
- ²Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
- ³Goraya TY, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, Jacobsen SJ, Frye RL, Roger VL: Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *J Am Coll Cardiol* 40:946–953, 2002
- ⁴Khaleeli E, Peters SR, Bobrowsky K, Oudiz RJ, Ko JY, Budoff MJ: Diabetes and the associated incidence of subclinical atherosclerosis and coronary artery disease: implications for management. *Am Heart J* 141:637–644, 2001
- ⁵Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
- ⁶Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE: Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 27:1954–1961, 2004
- ⁷Di Carli MF, Hachamovitch R: Should we screen for occult coronary artery disease among asymptomatic patients with diabetes? *J Am Coll Cardiol* 45:50–53, 2005
- ⁸Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ: Visualizing coronary calcium is associated with improvements in adherence to statin therapy. *Atherosclerosis* 185:394–399, 2006
- ⁹Grundt SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110:227–239, 2004
- ¹⁰Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundt SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA: AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 113:2363–2372, 2006
- ¹¹Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC Jr: ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 106:1883–1892, 2002
- ¹²Zinman B, Ruderman N, Campagne BN, Devlin JT, Schneider SH: Physical activity/exercise and diabetes. *Diabetes Care* 27 (Suppl. 1):S58–S62, 2004
- ¹³Brindis RG, Douglas PS, Hendel RC, Peterson ED, Wolk MJ, Allen JM, Patel MR, Raskin IE, Hendel RC, Bateman TM, Cerqueira MD, Gibbons RJ, Gillam LD, Gillespie JA, Hendel RC, Iskandrian AE, Jerome SD, Krumholz HM, Messer JV, Spertus JA, Stowers SA: ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by

the American Heart Association. *J Am Coll Cardiol* 46:1587–1605, 2005

¹⁴Lee DP, Fearon WF, Froelicher VF: Clinical utility of the exercise ECG in patients with diabetes and chest pain. *Chest* 119:1576–1581, 2001

¹⁵Bacci S, Villella M, Villella A, Langialonga T, Grilli M, Raueo A, Mastroianno S, De Cosmo S, Fanelli R, Trischitta V: Screening for silent myocardial ischaemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol* 147:649–654, 2002

¹⁶Albers AR, Krichavsky MZ, Balady GJ: Stress testing in patients with diabetes mellitus: diagnostic and prognostic value. *Circulation* 113:583–592, 2006

¹⁷Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO Jr, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO: ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 108:1404–1418, 2003

¹⁸Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ: Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol* 45:43–49, 2005

¹⁹De Lorenzo A, Lima RS, Siqueira-Filho AG, Pantoja MR: Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. *Am J Cardiol* 90:827–832, 2002

²⁰Valensi P, Paries J, Brulport-Cerisier V, Torremocha F, Sachs RN, Vanzetto G, Cosson E, Lormeau B, Attali JR, Marechaud R, Estour B, Halimi S: Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. *Diabetes Care* 28:2722–2727, 2005

²¹Hennessy TG, Codd MB, Kane G, McCarthy C, McCann HA, Sugrue DD: Evaluation of patients with diabetes mellitus for coronary artery disease using dobutamine stress echocardiography. *Coron Artery Dis* 8:171–174, 1997

²²Elhendy A, Arruda AM, Mahoney DW, Pellikka PA: Prognostic stratification of diabetic patients by exercise echocardiography. *J Am Coll Cardiol* 37:1551–1557, 2001

²³Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjendahl-Monsen CE, Leavy J, Weiss M, Borricco S, Gorlin R, Fuster V: Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 12:56–62, 1988

²⁴Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R, Borges-Neto S, Berman DS, Waters DD, Heller GV: Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation* 105:32–40, 2002

²⁵Schurgin S, Rich S, Mazzone T: Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care* 24:335–338, 2001

²⁶Wolfe ML, Iqbal N, Gefer W, Mohler ER 3rd, Rader DJ, Reilly MP: Coronary artery calcification at electron beam computed tomography is increased in asymptomatic type 2 diabetics independent of traditional risk factors. *J Cardiovasc Risk* 9:369–376, 2002

²⁷Elkeles RS, Feher MD, Flather MD, Godland IF, Nugara F, Richmond W, Rubens MB, Wang D: The association of coronary calcium score and conventional cardiovascular risk factors in type 2 diabetic subjects asymptomatic for coronary heart disease (the PREDICT Study). *Diabet Med* 21:1129–1134, 2004

²⁸Raggi P, Shaw LJ, Berman DS, Callister TQ: Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol* 43:1663–1669, 2004

²⁹Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 146:483–494, 1997

³⁰Hodis HN, Mack WJ, LaBree L, Selzer RH,

Liu CR, Liu CH, Azen SP: The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 128:262–269, 1998

³¹Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE: Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 96:1432–1437, 1997

³²Wagenknecht LE, D'Agostino R Jr, Savage PJ, O'Leary DH, Saad MF, Haffner SM: Duration of diabetes and carotid wall thickness. The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 28:999–1005, 1997

³³Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG: Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 25:66–73, 1994

³⁴Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, Schaper F, Henkel E, Siegert G, Hanefeld M: Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. *Diabetes Care* 22:333–338, 1999

³⁵Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, Hori M: Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. *Diabetes Care* 23:1310–1315, 2000

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.

Note of disclosure: Dr. Maron is an employee of and stockholder in Cardiovascular Services of America, which provides outpatient cardiac catheterization and computed tomography angiography services.