Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People With Diabetes

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AMERICAN DIABETES ASSOCIATION

Cardiovascular disease, which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease, is the leading cause of mortality in people with diabetes. Most of these deaths are due to complications of coronary artery disease (CAD). Individuals with diabetes have at least a twofold to fourfold increased risk for having cardiovascular events compared with age-matched subjects without diabetes. After myocardial infarction (MI), people with diabetes have a twofold to threefold greater morbidity and mortality. Although diabetic patients have a higher prevalence of traditional CHD risk factors (i.e., hypertension, dyslipidemia, obesity) compared with people without diabetes, these risk factors account for less than half the excess mortality associated with diabetes. Thus, the diagnosis of diabetes is a major independent risk factor for the development of CHD and for adverse outcomes following a myocardial event.

Many therapies have been shown to be beneficial in reducing the incidence of cardiovascular events in people with diabetes. These therapies include treatment of hypertension and elevated lipids and the use of aspirin, β-blockers, and ACE inhibitors. However, for any of these therapies to be maximally effective, early identification of patients with CAD is important. Recognition of a previously undiagnosed MI or knowledge of the presence of CAD will have an impact on the type and aggressiveness of therapy. In the patient with diabetes who has no clear evidence of CAD, clinicians must decide when to initiate testing for CHD, and equally important, what testing algorithm(s) is optimal. To provide guidance to physicians faced with these issues, the American Diabetes Association (ADA) and the American College of Cardiology convened a Consensus Development Conference, 10–11 February 1998, Diagnosis of Coronary Heart Disease in People with Diabetes. A seven-member panel heard presentations from 16 experts, complemented by audience participation, on the epidemiology and pathophysiology of CHD in diabetic patients, predicting CHD, and testing for CHD. An extended and interactive discussion among presenters and the audience brought further insight to the topics.

The panel then developed a consensus position on the following questions:

1. What constitutes CHD in people with diabetes?
2. What are the benefits of diagnosis?
3. Which patients with diabetes are at increased risk for coronary events and should undergo cardiac testing? What factors should be considered in making this evaluation? With what frequency should testing be done?
4. What are the most appropriate tests to detect the presence of CHD?
5. What is the appropriate follow-up to a positive test result?
6. What are the limitations and provisos of these recommendations?

QUESTION 1: What constitutes CHD in people with diabetes?

There is clear evidence that the complications of CHD, which include angina, congestive heart failure, MI, and sudden death, are a major complication of both type 1 and type 2 diabetes. In type 1 patients, who often lack the traditional cardiovascular risk factors, duration of diabetes is the most important predictor of premature CAD. Because type 1 disease often begins early in life, CAD can present as early as the 3rd and 4th decade of life. In contrast, type 2 patients frequently have many of the traditional CAD risk factors and usually present with CAD in the 5th or 6th decade of life or later, often after a relatively short period from diagnosis of diabetes, or even at diagnosis. Not infrequently, diabetes is first identified when the patient with CHD presents with angina, MI, or heart failure.

The premature occurrence of CAD in diabetic patients, the more extensive disease at the time of diagnosis, and the higher morbidity and mortality following MI raise the question of whether the atherosclerotic process is different in diabetes. Careful pathological studies indicate that the atherosclerotic plaque in the coronary artery of the diabetic patient appears morphologically similar to plaque in nondiabetic subjects. However, there is both pathological and angiographic evidence that the coronary arteries are involved more diffusely and that disease may extend more distally in diabetes. In patients with diabetes, CAD may be associated with generalized endothelial dysfunction and abnormalities of small vessels as well. Most importantly, diabetic patients more frequently have multiple coronary vessels involved by the time coronary disease is diagnosed or at the time of an MI.

Diabetic patients are at increased risk for developing congestive heart failure. This tendency is more striking in women. To

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Abbreviations: ADA, American Diabetes Association; BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; DIGAMI, Diabetes Mellitus Insulin-Glucose Infusion Acute Myocardial Infarction; ECG, electrocardiogram; ETT, exercise treadmill test; MI, myocardial infarction; PAI, plasminogen activator inhibitor; PTCA, percutaneous transluminal coronary angioplasty.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

some extent, the greater likelihood of congestive heart failure reflects a more diffuse coronary atherosclerotic process, particularly as it occurs in the post-infarction setting. However, diabetes-associated impaired ventricular function is not limited to the post-MI setting. Impaired diastolic function has been demonstrated in diabetic patients in the absence of significant atherosclerotic CAD. Debate persists as to whether a specific "diabetic cardiomyopathy" may, per se, lead to significant systolic dysfunction and ventricular dilation.

Acute coronary syndromes such as acute MI, unstable angina, and perhaps sudden death, commonly involve lumenal thrombus formation. Over time, increased thrombotic activity may accelerate the atherosclerotic process. The coagulation abnormalities associated with diabetes (e.g., increased platelet aggregation and increased levels of fibrinogen and plasminogen activator inhibitor [PAI-1]) may accelerate development of coronary thrombosis. Increased platelet aggregation may, in part, be related to the hyperglycemia of diabetes or insulin resistance. Elevated levels of PAI-1 may be related to the hypertriglyceridemia and hyperinsulinemia frequently seen in diabetes.

The autonomic innervation of the heart can also be affected in people with diabetes, leading to a characteristic elevation in resting heart rate and decreased beat-to-beat variation. As autonomic dysfunction progresses, the heart rate response to posture or Valsalva and the circadian changes in blood pressure are both diminished. Symptomatic autonomic neuropathy identifies individuals at increased risk for sudden death. Whether cardiac autonomic neuropathy contributes to silent ischemia is unclear, but the pain response to ischemia is often blunted in people with diabetes, complicating detection of CAD. As a result, diabetic patients may be asymptomatic or present in an atypical manner with, for example, symptoms of easy fatigability, exertional dyspnea, or indigestion.

QUESTION 2: What are the benefits of diagnosis?

The potential benefits of diagnosing asymptomatic CAD in patients with diabetes include *1*) the implementation of preventive programs aimed at the reducing risk of future coronary morbidity and mortality, *2*) the initiation of treatment with anti-ischemic medications, and *3*) the early identification of the patient for whom revascularization is appropriate.

Evidence from subgroup analysis of secondary prevention trials enrolling diabetic patients with known CAD indicates that aggressive treatment can effectively reduce cardiovascular morbidity and mortality. Although these results support risk factor intervention in patients with diabetes and known CAD, similar data are not available for a population of patients with asymptomatic coronary disease. Nevertheless, the increased morbidity and mortality from CHD in patients with diabetes provides a rationale for diagnostic evaluation in asymptomatic diabetic patients and aggressive "secondary" intervention when CAD is identified.

The design of prevention programs

The most compelling rationale at the present time for prompt diagnosis of coronary disease in patients with diabetes are the striking benefits observed in recent lipid-lowering trials. In the Scandinavian Simvastatin Survival Study (4S), cholesterol-lowering was associated with a 42% reduction in cardiovascular mortality and a 30% reduction in total mortality in an overall group of 2,200 men and women with coronary disease, compared with an equal number of patients receiving placebo (1). About 5% of the subjects had diabetes, and simvastatin treatment in that group was associated with a 55% reduction in major coronary events. In another secondary prevention study, the Cholesterol and Recurrent Events Trial (CARE) (2), where ~14% of the participants had diabetes, a 25% reduction in CHD events with pravastatin therapy was seen in both the diabetic and nondiabetic subjects.

Thus, early diagnosis of asymptomatic CAD disease should encourage aggressive lipid-lowering therapy. The National Cholesterol Education Program (NCEP) guidelines (3) and the recently published ADA recommendations for treating dyslipidemia (4) differentiate goals of therapy according to the absence or presence of coronary disease. This distinction suggests that diagnosis of presymptomatic CAD should influence therapeutic decisions.

Control of hypertension in patients with diabetes is clearly important to reduce the onset or progression of diabetic nephropathy. The new Joint National Committee report recommends that patients with diabetes be treated to a systolic and diastolic blood pressure of <130/85 (5). Although no stratification of treatment is made by the presence or absence of CHD in diabetic patients, demonstration of the presence of coronary disease or abnormal left ventricular function might have an impact on the choice of the antihypertensive agent prescribed.

There are no well-controlled studies demonstrating that improved glucose control will reduce cardiovascular disease in patients with diabetes. However, in the Diabetes Control and Complications Trial (DCCT) (6), the intensive treatment group had a trend toward fewer cardiovascular events, although the number of actual events in this relatively young group of individuals was very low, and the effect of treatment did not reach statistical significance. In the Diabetes Mellitus Insulin-Glucose Infusion Acute Myocardial Infarction (DIGAMI) Study (7), hospital use of insulin-glucose infusion, followed by 3 months of intensive insulin therapy in patients with acute MI, was associated with a 29% reduction in cardiovascular mortality after 1 year. Thus, there are suggestive data that improved glycemic control may reduce coronary events, and if this hypothesis is confirmed by the U.K. Prospective Diabetes Study, which is nearing completion, aggressive glycemic control will be another approach to the prevention of cardiac events.

The efficacy of aspirin therapy in reducing CHD has been studied extensively. The diabetic subjects included in the meta-analysis of 145 prospective studies of aspirin use conducted by the Anti-Platelet Trialists (8) had reductions in MI, stroke, transient ischemic episodes, or development of signs and symptoms of coronary disease similar to nondiabetic subjects. In the Early Treatment Diabetic Retinopathy Study (9), diabetic patients without preexisting coronary disease who received aspirin had a 15% reduction in the incidence of first MI over a 7-year period. In that study, diabetic patients with preexisting CHD also benefited. In a subgroup analysis of the Physicians Health Study (10), diabetic physicians receiving aspirin for primary prevention had a reduced relative risk of MI. These data have led the ADA to recommend the consideration of aspirin therapy for primary prevention in high-risk men and women and the use of aspirin therapy as a secondary prevention strategy in men and women with evidence of large vessel disease (11). Thus the diagnosis of coronary disease would underscore the need for aspirin.

The use of ACE inhibitors is already recommended as first-line treatment of hypertension in diabetes and in diabetic patients with proteinuria (12). However, the demonstration of coronary disease, and identification of left ventricular dysfunction, would also be a strong indication for ACE inhibitor treatment in the normotensive, nonproteinuric patient.

Initiation of anti-ischemic therapy

Knowledge of the presence of asymptomatic CAD could be used to initiate early treatment to prevent ischemia. β-Blocker therapy is important in patients with diabetes who have had an MI, thus making the diagnosis of a previously unrecognized MI critical. In the recent Bezafibrate Infarction Prevention Study (13), patients treated with β-blockers had an ~50% reduction in mortality, compared with those patients not receiving that treatment. β-Blocker therapy was also effective in the DIGAMI Study. Also, use of cardioselective β-blockers might be particularly beneficial in diabetic patients with reduced heart rate variability.

Referral for revascularization

Testing for asymptomatic coronary disease may help identify patients with severe coronary obstruction in whom revascularization should be considered, although the benefit of percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) in people with asymptomatic CHD and diabetes is not clear. The recent Bypass Angioplasty Revascularization Investigation (BARI) trial (14) indicated excellent 5-year survival in symptomatic diabetic patients with advanced multivessel coronary disease treated with CABG. In selected patients who received an interval mammary artery graft, cardiac mortality was 2.9% at 5 years. On the other hand, the BARI trial raised serious concern for the use of PTCA in multivessel disease, since diabetic patients randomized to PTCA had a greatly increased 5-year mortality (35% overall and 20% cardiac) compared with patients randomized to CABG with or without an interval mammary artery graft (19% overall and 6% cardiac). Although nonrandomized patients in the BARI registry and other patients in observational studies with multivessel disease have shown a higher survival rate when treated with PTCA, there remains concern for the use of multivessel PTCA to improve the prognosis in asymptomatic patients with diabetes. The high restenosis rate associated with PTCA in diabetic patients (40–60%) also limits the use of routine balloon angioplasty for asymptomatic patients with single-vessel disease. Even though placement of intracoronary stents reduced the incidence of restenosis seen with balloon angioplasty in the general population, early studies raised concern about a high restenosis rate (60%) in patients with diabetes implanted with intracoronary stents, but included many patients with vein graft disease after CABG. In contrast, a recent study (15) suggests that the restenosis rate may be reduced to as low as 20% in diabetic patients with optimal anatomy. Nonetheless, there is limited data on the use of coronary stents for the primary treatment of single-vessel disease in diabetes, and it should be limited to highly selected patients.

Table 1—*Indications for cardiac testing in diabetic patients*

Testing for CAD is warranted in patients with the following:
1. Typical or atypical cardiac symptoms
2. Resting electrocardiograph suggestive of ischemia or infarction
3. Peripheral or carotid occlusive arterial disease
4. Sedentary lifestyle, age ≥35 years, and plans to begin a vigorous exercise program
5. Two or more of the risk factors listed below (a–e) in addition to diabetes
   a) Total cholesterol ≥240 mg/dl, LDL cholesterol ≥160 mg/dl, or HDL cholesterol <35 mg/dl
   b) Blood pressure >140/90 mmHg
   c) Smoking
   d) Family history of premature CAD
   e) Positive micro/macroalbuminuria test

QUESTION 3: Which patients with diabetes are at increased risk of coronary events and should undergo cardiac testing? What factors should be considered in making this evaluation? With what frequency should testing be done?

People with diabetes may present for evaluation with an established CHD history or for having a prior cardiac event, in which case they warrant testing for risk stratification. However, the challenge faced by the physician caring for a patient with diabetes is to accurately identify patients without a prior history of an event and patients not manifesting symptoms strongly suggesting CAD, in whom additional testing is indicated. Table 1 summarizes indications for CAD testing, and these are discussed individually below.

Cardiac symptoms

Typical symptoms of cardiac disease are common in people with diabetes, in spite of the frequent occurrence of "silent" ischemia and atypical symptoms. Indeed, it has been reported that ~16% of people with type 2 diabetes over age 65 will have angina. Atypical symptoms with exertion are also common and may include dyspnea, fatigue, and gastrointestinal symptoms. These features can easily be recognized with a careful medical history and often justify cardiac testing, unless there is an obvious other cause for the symptoms.

Resting electrocardiogram (ECG) is suggestive of ischemia or infarction

The occurrence of silent ischemia means that some patients will present with evidence of previously unrecognized events on a resting ECG (e.g., evidence of infarction). These patients always require further evaluation. For this reason, the value of a resting ECG in people with diabetes may be greater than in people without diabetes.

Peripheral or carotid occlusive arterial disease

A medical history of claudication or transient ischemic attacks suggests occlusive arterial disease. A diminished or absent posterior tibial pulse found by palpation, or a femoral bruit on auscultation, have a relatively high sensitivity for identifying lower-extremity occlusive arterial disease (16). The association of peripheral atherosclerosis with CAD justifies cardiac testing since it has been reported that most diabetic patients with lower-extremity occlusive arterial disease die from cardiovascular disease. These clinical findings can be confirmed by measuring the ankle/brachial blood pressure. Carotid bruits are indicative of possible cerebrovascular disease. The use of carotid ultrasound testing is warranted if there is concern about the reliability of the finding or clinical significance of carotid bruit.

Vigorous exercise

Exercise is an important therapeutic modality in people with type 2 diabetes. Many people with diabetes have sedentary lifestyles. Initiation of a graded walking exercise program can be accomplished without additional cardiac testing. However, in the small subset of patients ≥35 years old who have previously been sedentary and now indicate a desire to begin a more vigorous exercise program, a cardiac exercise test may be of value in identifying those at high risk of an acute event during exercise, and may provide guidance in tailoring the exercise program for the individual.

Traditional and diabetes-specific risk factors

The total burden of risk factors is additive, and multiple risk factors in the same patient substantially increase the possibility of identifying significant CAD that requires intervention. For example, data from the Multiple Risk Factor Intervention Trial demonstrate an increased cardiovascular death rate, from ~30–90 per 10,000 person-years, with the addition of two other risk factors to the presence of diabetes. The American College of Cardiology Guidelines for Exercise Testing considered the presence of multiple risk factors to be a possible indication for exercise testing. The high prevalence of CHD in people with diabetes and the demonstration of the additive influence of other risk factors strengthens the recommendation for cardiac testing in people with diabetes. The acknowledged tendency for patients with diabetes to accumulate multiple risk factors for coronary disease has been much discussed. The "dysmetabolic syndrome" or "insulin resistance syndrome" further underscore the need for risk factor assessment of each patient with diabetes.

This recommendation does not address the potential impact of other risk factors (e.g., lipoprotein(a) [Lp(a)] and elevated homeocysteine) where adequate data are not available. One high mortality rate risk factor unique to diabetes does require some discussion. That is, clinical evidence of cardiac autonomic neuropathy has been strongly associated with a poor prognosis in several studies. This abnormality may contribute to the difficulty in identifying symptomatic cardiac disease in some patients. These patients tend to have diabetes of long duration, often with multiple-organ complications. There are insufficient data to address whether autonomic neuropathy is an independent risk factor for CHD. As a result, it is not included among the risk factors that warrant cardiac testing (Table 1). However, when there is definite evidence of cardiac autonomic neuropathy in the patient over age 35 who has had diabetes for >25 years, cardiac testing should be considered.

Currently, within the diabetic population there are limited data addressing the relationship of blood glucose control and major cardiac events. The limited evidence available did not allow the panel to make a specific recommendation regarding the inclusion of a glycemic level as a definite risk factor. Thus, although good glycemic control should be a goal for all people with diabetes, the level of glycemic control that increases cardiac risk in patients with diabetes remains unknown.

Microalbuminuria and nephropathy

The presence of increased urinary albumin predicts patients at risk of progressing to overt nephropathy. Also, a recent meta-analysis confirmed that in patients with type 2 diabetes, an increase in microalbuminuria predicts a high mortality rate from cardiovascular disease (17). Patients with type 1 diabetes and overt nephropathy develop extensive atherosclerosis. In all patients with type 2 diabetes and in type 1 patients ≥35 years old, presence of persistent microalbuminuria or overt nephropathy indicate the need for cardiac testing.

Reevaluation

The status of a patient is not static. Patients should be reevaluated at least annually for the development or progression of risk factors that would prompt cardiac testing, and the appropriate evaluation should be obtained.

QUESTION 4: What are the most appropriate tests to detect the presence of CHD?

In general, the test chosen will depend on the purpose of the test. For example, is the test being performed to detect the presence of CAD or to predict the long-term likelihood of adverse fatal or morbid cardiovascular events? The reasons for choosing one test or another to detect coronary disease in patients with diabetes is similar to other nondiabetic populations with suspected coronary disease, except that, as a group, diabetic patients are less likely to be able to satisfactorily perform a standard treadmill test. An initial clinical assessment may lead to the conclusion that a patient may be better assessed by pharmacological stress imaging, rather than by a simple exercise test, and the choice between echocardiography or perfusion imaging (with thallium or MIBI) may depend on local expertise. Figures 1 and 2 suggest algorithms for the evaluation of symptomatic and asymptomatic diabetic patients.

If the test is being used for screening a patient at low risk for cardiovascular events (e.g., clearing an asymptomatic patient with few risk factors and a normal resting ECG for an exercise program), then the standard treadmill exercise test would usually be chosen (Fig. 2). On the other hand, if the diabetic patient has typical angina or Q waves on a resting ECG, a perfusion imaging study should be chosen to assess ventricular function and to provide quantitative information on the extent of the perfusion abnormality (Figs. 1 and 2) and in the case of MIBI to assess ventricular function. There are sufficient data to support the recommendation that nuclear imaging with perfusion tracers provides incremental prognostic information compared to a standard electrocardiographic stress test in patients with known CAD. At this time, similar prognostic data for stress echo testing is not available. Although several additional testing modalities are discussed below, it should be apparent from Figs. 1 and 2 that exercise stress testing, stress echocardiography, and nuclear perfusion imaging provide the cornerstones for the diagnostic testing that will be discussed.

Ambulatory monitoring of ST segment changes

In general, the utility of ambulatory monitoring of electrocardiographic ST segment changes to detect coronary disease in asymptomatic populations has been disappointing and not cost-effective. In addition, in the recent Asymptomatic Cardiac Ischemia Pilot (ACIP) study, ambulatory monitoring showed less measurable ischemia in diabetic patients despite more extensive CAD (18). The use of such testing is therefore not recommended as a screening tool in asymptomatic diabetic patients.

Coronary artery calcification

Coronary artery calcification detected by electron beam–computed tomography (EBCT) increases with age and is usually

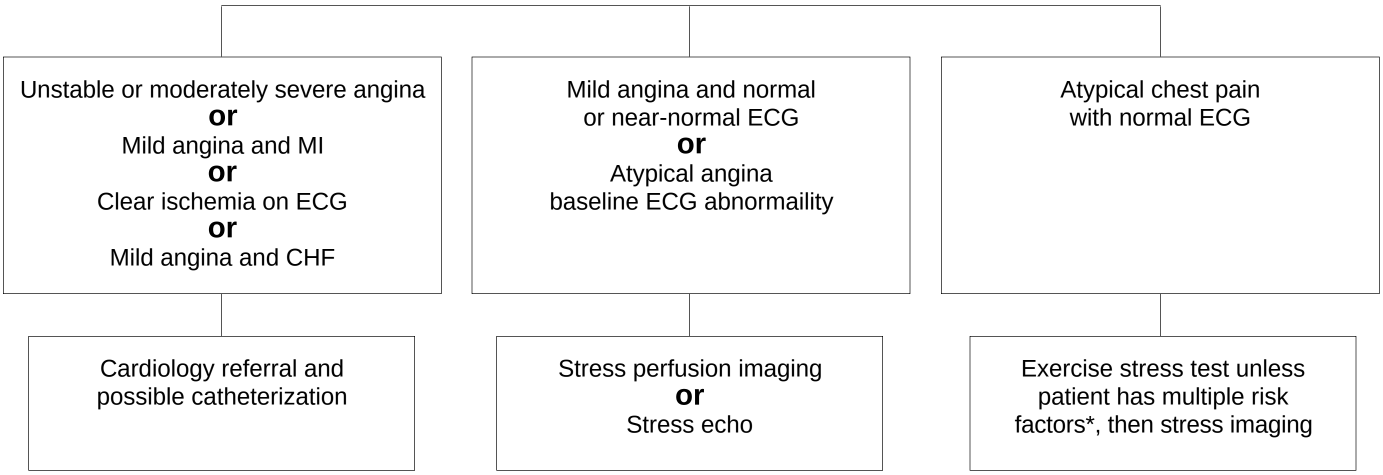

Figure 1—*Cardiac testing of the symptomatic diabetic patient. In patients with diabetes and symptoms that are either clearly related to ischemia or atypical in nature but suspected to be of cardiac origin, testing can be undertaken using the algorithm above. *A multiple risk factor patient is defined as an individual with two or more risk factors (see Table 1).*

associated with coronary artery atherosclerosis. Relationships have been established between coronary artery calcium, pathological plaque area, and the severity of coronary artery stenoses, but significant coronary stenoses can exist in the absence of detectable calcification. While some studies have suggested a relationship between adverse cardiovascular events and coronary calcium scores, others have not. At best, the association between coronary artery calcification and subsequent cardiovascular events is weak even though patients with diabetes seem to have calcification. As a screening test in an asymptomatic population, detecting coronary artery calcification does not appear to have a useful role (R. Detrano, personal communication).

Exercise electrocardiography

In patients who can exercise on a treadmill and can be expected to have exercise-interpretable ECGs (i.e., resting ECG without LBBB, digitalis effect, WPW, or >1-mm ST segment depression), a simple exercise test will detect the great majority of patients with left main or significant multivessel CAD. These patients may also exhibit poor exercise capacity, marked ST segment changes, or a hypotensive response to exercise. On the other hand, a completely normal test is a marker for a good prognosis (19), despite its relatively low sensitivity overall for detecting single-vessel disease. It must be remembered that pharmacological therapy (e.g., β-adrenergic receptor blockade) can delay the time to onset of ischemia and attenuate the heart rate response to exercise, so that if detection of disease is the purpose of the test, consideration should be given to performing it in the absence of cardiac medications likely to influence the results. An inadequate test (in which the patient fails to achieve ~85% of the maximal predicted heart rate response to stress) reduces the predictive value of the test; in such situations, additional testing should be considered. In patients with a low pretest probability of CAD, there is a significant problem with false-positive tests that will then require follow-up imaging.

Stress perfusion imaging

Stress perfusion imaging with thallium or technicium-labeled MIBI detects heterogeneous flow distribution due to decreased coronary flow reserve during exercise or pharmacological vasodilatation. This technique has a high success rate (<1% of images are not interpretable), and with MIBI it also provides a measurement of ejection fraction. A key clinical feature of perfusion imaging is that it allows quantification of perfusion abnormalities, and this provides an important ability to prognostically stratify patients.

In patients with single-vessel coronary disease, stress perfusion imaging may be superior to stress echocardiography, while the techniques are similar for detecting multivessel disease. Likewise, in the setting of prior infarction, perfusion imagery is superior to stress echo in detecting ischemia. An increased number of abnormal perfusion segments and quantification of large defects or areas of reversibility are predictors of adverse cardiovascular outcome, as are reduced ventricular function, increased lung uptake, and transient left ventricular dilation. Conversely, normal perfusion images even when associated with angiographically detectable CAD confer a good prognosis. Interestingly, even in patients with normal coronary angiograms, concurrent abnormalities of perfusion imaging scans may suggest endothelial dysfunction and increased likelihood of future cardiac events, compared with patients who have normal perfusion scans. Numerous studies have shown that perfusion imaging adds incremental information, which allows prediction of long-term outcome in both diabetic and nondiabetic subjects. However, for comparable perfusion deficits, patients with diabetes have higher event rates. In summary, perfusion imaging is useful in patients with diabetes since the technique provides quantifiable data and identifies low- and high-risk patients for future adverse cardiovascular events.

Stress echocardiography

Stress echocardiography depends on the detection of regional wall motion abnormalities induced by myocardial ischemia and the clear imaging of the endocardium. Approximately 5–10% of patients have poor acoustic windows precluding echocardiographic study. Treadmill exercise is generally preferred to pharmacological stress (e.g., with Dobutamine). An experienced echocardiographer is required to obtain high-quality, post-stress images within 60 s of termination of exercise and in order to avoid

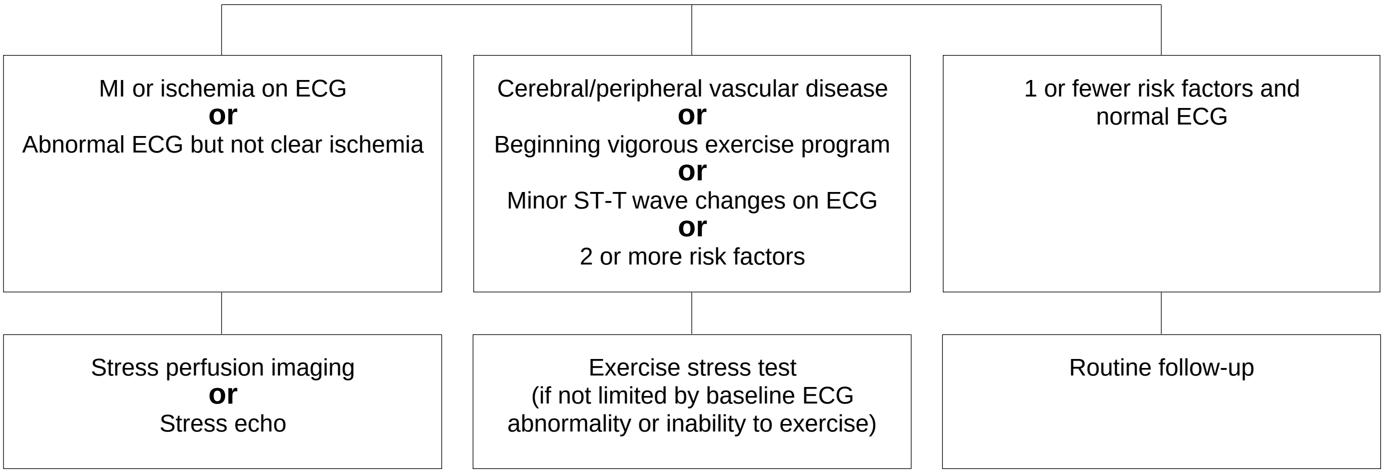

Figure 2—*Cardiac testing of the asymptomatic diabetic patient. Asymptomatic patients with diabetes and one or fewer risk factors (see Table 1) and a normal ECG do not require cardiac testing. Patients with two or more risk factors or those beginning a vigorous exercise program should have an exercise stress test. In patients with clear or suggestive evidence of ischemia or infarction on ECG, stress perfusion imaging or stress echo should be used. If expertise with both modalities is available, perfusion imaging would be preferred.*

an incorrect interpretation of artifacts. Stress echocardiography is comparable to perfusion imaging for detecting multivessel CAD. However, currently there are insufficient outcome data in diabetic patients following stress echocardiography to define its role as a prognostic tool.

QUESTION 5: What is the appropriate follow-up to a positive test result?

Interpretation of treadmill results is based on exercise capacity, electrocardiographic findings, hemodynamic responses to exercise, and development of symptoms. Such testing has been used effectively to place patients into low-, intermediate-, and high-risk groups in the overall population. However, patients with diabetes and significant CHD may not experience chest pain with exercise, and this may affect the risk grouping. In addition, the heart rate response to exercise may be attenuated by autonomic neuropathy, and the inability to reach the target heart rate renders a negative test indeterminate. Pharmacological stress imaging should be used in the case of an indeterminate test. If the patient does complete the stress test by reaching 85% of the maximum predicted heart rate, the outcome of exercise stress testing together with the assigned pretest likelihood can be used to guide further diagnostic and treatment strategies. Figure 3 suggests the appropriate follow-up after a screening exercise test in asymptomatic diabetic patients.

A negative test at a high workload (e.g., completing 9 min exercise or stage 3 of a Bruce treadmill protocol or another exercise equivalent to 10 METS) should provide a high degree of reassurance for the patient and physician that there is a minimal chance of advanced disease that might have a major impact on prognosis. As the test does not wholly exclude the presence of CAD and a patient's status may change over time, close follow-up is warranted in patients with high pretest risk.

Asymptomatic diabetic patients with a "mildly" positive stress test, e.g., modest (1–1.5 mm) ST depression at a moderate-to-high exercise level (Bruce stage 3 or greater), are generally in a relatively low-risk group. Follow-up perfusion imaging should be considered in moderate- to high-risk individuals in whom further stratification may be warranted. In low-risk patients, perfusion imaging or stress-echocardiography should be utilized to exclude false-positive electrocardiographic responses, particularly since most of these patients are being tested in anticipation of beginning a vigorous exercise program. Asymptomatic patients with mildly positive tests do not usually warrant directly proceeding to cardiac catheterization. If perfusion imaging in these patients suggests limited or no disease, these patients should have regularly scheduled clinical evaluations, including an ECG. In the absence of new symptoms, many physicians favor repeating stress imaging within 2 years in diabetic patients with multiple risk factors and minor abnormalities on initial stress imaging, because of the potential risk of CHD progression.

In asymptomatic diabetic patients who have "moderately" positive electrocardiographic stress tests, further noninvasive stratification with perfusion imaging is also warranted. Normal or near-normal perfusion studies indicate a very good prognosis. Even in diabetic patients with established CAD, the annual cardiac event (MI or death) rate is ~2% when perfusion studies are normal or near-normal. Moderate or large perfusion defects indicate a significant risk of cardiac events over the next 1–2 years and identify patients in whom delineation of the coronary anatomy is desirable to determine the need and the technical suitability of the arteries for revascularization. Abnormal lung uptake of tracer and transient left ventricular dilatation during exercise may also indicate high-risk diabetic patients in whom there should be a low threshold to perform cardiac catheterization. The exception to the above-mentioned strategy is a moderately positive stress test in a diabetic patient with a high pretest likelihood of CAD, for whom catheterization may be more cost-effective.

In asymptomatic diabetic patients with a "markedly" positive stress test, there should be a high level of concern. This would be indicated by features including hypotension during exercise; a positive test with a heart rate <120, or exercise capacity <6 min (stage 1 or 2 of a Bruce protocol or 5 METS of other protocols); ST depression involving 5 or more leads; or >2-mm maximum ST depression. Although relatively

Pre-Test Risk	ETT Results			
	Normal	Mildly Positive	Moderately Positive	Markedly Positive
HIGH 4-5 risk factors**	√√	√√√	√√√√	√√√√
MODERATE 2-3 risk factors	√	√√√	√√√	√√√√
LOW 0-1 risk factors	√	√√√	√√√	√√√√

√	Routine Follow-up
√√	Close Follow-up
√√√	Imaging
√√√√	Cardiology Referral/Possible Catheterization

Figure 3—*Appropriate follow-up after screening exercise treadmill test (ETT). When initial exercise stress testing is done in asymptomatic diabetic patients, the type of follow-up depends on the pretest risk and the degree of abnormality on the stress test. Normal follow-up indicates annual reevaluation of symptoms and signs of CHD and ECG. A repeat ETT should be considered in 3–5 years if clinical status is unchanged. Close follow-up means shorter intervals between evaluation and follow-up ETT, i.e., 1–2 years. Pretest risk is assigned based on the presence of other vascular disease and risk factors (Table 1).*

uncommon in asymptomatic patients, a strongly positive exercise test generally warrants direct evaluation with coronary angiography.

The risks of complications (renal insufficiency, vascular injury) of cardiac catheterization are low when appropriate precautions are taken, including hydration and a minimum use of X ray contrast material. Although there is debate as to the incremental prognostic value of coronary angiography over nuclear perfusion imaging, it should be emphasized that angiography is critical to determine not only the severity of disease but, perhaps more importantly, the suitability of the vessels for either coronary interventional procedures or surgical bypass. The identification of significant left main coronary disease, multivessel, or proximal left artery disease (LAD) is of particular significance.

Recommendations for revascularization should be individualized, and determined by the severity, extent, and configuration of the stenoses and the size and distribution of the affected vessel(s). In the case of angioplasty or intracoronary stent placement, the size of the vessel and the complexity of the lesion determine the procedural risk and the restenosis risk. In the case of surgery, the quality of the distal vessels determines the technical feasibility and long-term graft patency.

If a decision is made to manage the patient medically, reevaluation of myocardial perfusion and left ventricular function should be undertaken after 1–2 years. Left ventricular dysfunction often develops in patients with coronary disease and diabetes and has a major negative impact on prognosis. Patients with ejection fractions <45% should be considered at increased risk for adverse cardiac events, and this should prompt reconsideration of the need for revascularization and indicate the need for treatment with ACE inhibitors.

QUESTION 6: What are the limitations and provisos of these recommendations?

A few general points warrant consideration in terms of diagnostic testing before considering the recommendations made in this statement. Medical tests can provide information about a patient's diagnosis and prognosis. Because few tests provide perfect information, the effect of any test result is to modify the pretest probability of disease into a revised probability. Decisions about when to perform diagnostic studies are driven first by the benefits and the risks of treating a disease that might be identified by that test. Assuming that a beneficial treatment is available, decisions about who should be tested reflect the information the test might provide (often measured by its sensitivity and its specificity) and the risks of the test. In the world of limited resources in which we now practice, the economic costs of testing must also be considered.

When testing patients in whom the pretest probability of disease is relatively low (a situation often called "screening"), careful thought must be given to the impact of a false-positive test. Such false-positive results often induce risks and costs of far greater magnitude than the economic or complication burdens of the initial test itself. These effects in patients who do not have the disease, for which we screen, must be balanced against the benefits which disease identification can provide to those patients who actually have the disease. In an ideal world, such decisions would be based on reasonably reliable clinical evidence that addresses those risks, benefits, and costs in the target population.

For patients with diabetes who do not have clinically manifest CHD, the identification of patients with occult disease might provide benefit in several ways. Patients identified with very severe disease might benefit from some form of myocardial revascularization. A larger cohort of patients with less disease will likely benefit from pharmacological and lifestyle interventions, which could retard the development of more severe disease and its complications, such as death, MI, disabling angina, and congestive heart failure. Because the benefit of preventative therapy may be greater for patients with more risk factors, who also have a greater likelihood of developing severe disease sooner, patients with more risk factors (and perhaps those with more severe disease) should receive more intensive preventive therapy. Finally, for some patients (and their physicians), the prognostic information that testing might provide may motivate more aggressive intervention, better compliance, or perhaps better personal planning about employment and family life. Thus, diagnostic and therapeutic programs should be individualized, based on the patient's specific characteristics.

Unfortunately, extensive data about the benefits of revascularization, anti-ischemic treatment, and prevention strategies in diabetic patients with occult coronary disease are not available. Thus, most of the recommendations in this consensus statement are based on clinical judgment, subgroup analysis of data from large studies in predominantly nondiabetic populations, and the recognition that diabetic patients are clearly at greater risk. In these large studies, few data include diabetic patients free of the clinical symptoms of CAD.

In making the recommendations found in this statement, the consensus panel assumed that asymptomatic diabetic patients, identified to have CAD by noninvasive testing, were at substantial risk. Data from the Framingham Study suggests that even asymptomatic diabetic patients with multiple risk factors have an ~3% per year incidence of cardiac events. Furthermore, we assume that physicians will carefully weigh the benefits and risks of revascularization and select those patients with disease who are most critical and most amenable to revascularization. It must be kept in mind, however, that CAD in some patients with diabetes may be less optimal for revascularization. In addition, the benefit of relatively more sustained and complete revascularization with CABG should be considered for multivessel disease despite higher short-term term risks of revascularization with surgery compared to PTCA.

Thus, it seems likely that many patients identified at high risk through the screening and evaluation protocol proposed here may have multivessel disease, which would require surgery. Our recommendations about noninvasive testing in asymptomatic diabetic patients include the use of standard ECG stress testing, which has a relatively low sensitivity for detecting single-vessel disease, particularly when it does not involve the proximal left anterior descending artery. The rationale for use of the exercise stress test includes the assumptions that asymptomatic patients with limited single-vessel disease are at a low risk of death and would have little benefit from revascularization. If the consequences of single-vessel disease in patients with diabetes are worse than in nondiabetic patients, then the true risk of death in diabetic patients could be greater. If more effective nonsurgical revascularization becomes available, then diagnostic studies would be appropriate at lower probabilities of disease and a more sensitive testing strategy would be recommended.

Given the vast economic burden of diabetes (approaching $100 billion annually, the majority reflecting vascular disease), the paucity of data and the lack of objective trials in diabetic patients are disappointing. The cost-effectiveness ratios of CABG for myocardial revascularization in symptomatic nondiabetic patients with left main disease, or with multivessel disease and depressed ventricular function, fall well within the boundaries of customary therapies (20). We suspect that the cost-effectiveness ratio will be even more favorable in such patients with diabetes, despite the somewhat higher complications of revascularization and duration of hospitalization. However, perhaps most important is the issue of the utility of revascularization procedure in asymptomatic diabetic patients with severe CAD and normal ventricular function, but a detailed analysis of its efficiency in preventing MI and death has not yet been performed.

Any studies in these populations should consider not only coronary anatomy and ventricular function, but also the degree of underlying renal disease, the duration of diabetes, the degree of glycemic control, and the patient's lipid status. It may be impossible to enroll sufficient patients to generate adequate data in each of these separate subgroups, but a carefully performed multivariate survival analysis should provide reasonable insight into the issue. Such data may already exist in large retrospective registries (such as the Duke cardiovascular database), and a deliberate examination of those data sets could be the first step in further refining strategies to optimally managed CHD in patients with diabetes.

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APPENDIX

Consensus panel

Eugene J. Barrett, MD, PhD, Chair; Henry N. Ginsberg, MD; Stephen G. Pauker, MD, MACP, FACC; John D. Rutherford, MD, FACC; Sidney C. Smith, Jr., MD; Lawrence H. Young, MD, FACC; Bruce R. Zimmerman, MD.

Presenters at the conference

Paresh Dandona, MD, FRCP, PhD, FACP, FACC; John Dent, MD; Robert C. Detrano, MD, PhD; Katherine M. Detre, MD, DrPH; Victor F. Froelicher, MD; Thomas D. Giles, MD; Ami E. Iskandrian, MD; Barbara E.K. Klein, MD, MPH; Andrzej Krolewski, MD, PhD; Anatoly Langer, MD; Richard W. Nesto, MD; Michael P. Stern, MD; Aaron I. Vinik, MD, PhD; Renu Virmani, MD; Frans J. Th. Wackers, MD; Peter W.F. Wilson, MD.

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