

5-7-2002

Prevention Conference VI: Diabetes and Cardiovascular Disease - Writing Group III: Risk Assessment in Persons With Diabetes

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Publication Info

Published in *Circulation*, Volume 105, Issue 18, 2002, pages e144-e152.

Redberg, R. F., Greenland, P., Fuster, V., Pyörälä, K., Blair, S. N., Folsom, A. R., ... Willson, P. W. F. (2002). Prevention conference VI: Diabetes and cardiovascular disease - Writing group III: Risk assessment in persons with diabetes. *Circulation*, 105(18), e144-e152.

DOI: 10.1161/01.CIR.0000013955.34262.AF

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Prevention Conference VI

Diabetes and Cardiovascular Disease

Writing Group III: Risk Assessment in Persons With Diabetes

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This Writing Group addressed whether the high risk associated with diabetes can be averted by detection of subclinical or early cardiovascular disease (CVD) that would enable earlier focused intervention. This article will discuss current data and recommendations for risk assessment of CVD in persons with diabetes.

Screening Principles

Screening aims at accurately and cost-effectively identifying disease (or risk of disease development) in persons without outward manifestations of the disease. A critical underlying assumption of screening is that test results will lead to a change in clinical management that can decrease morbidity and mortality. Because of the recognized high risk for cardiovascular events in patients with diabetes, the American Heart Association (AHA) currently recommends that they belong in the same high-risk category previously reserved for patients with known CVD.¹ The recently released third report of the National Cholesterol Education Program on detection, evaluation, and treatment of high blood cholesterol in adults is consistent with the AHA guidelines.² The updated recommendations from the Adult Treatment Panel III place patients with diabetes in a category of coronary heart disease (CHD) risk equivalents in which risk equates to that of persons with established CHD. For Adult Treatment Panel III, recommendations for lipid-lowering therapy are the same for CHD risk equivalents and established CHD. If this principle is extended to modification of other risk factors (ie, risk factors in asymptomatic persons with diabetes are treated in the same manner as those for people with established CVD), noninvasive testing for risk stratification among patients with diabetes would do little to change clinical management of risk factors. Specifically, if a patient with diabetes were to undergo screening and results were found to be negative for subclinical CVD, the patient still would be regarded as high

risk on the basis of diabetes alone and should receive aggressive risk factor modification. Conversely, if a screening test were positive for subclinical CVD, this result would also not change recommended management, because the patient is already considered to be at high risk for cardiovascular events. Therefore, again, intensive risk factor identification and intervention would be justified. There are no data showing benefit of treating asymptomatic persons with anti-ischemic medications or revascularization, so risk stratification cannot be recommended on the basis of evidence of benefit of further treatment in this group. However, a current trial (BARI 20) will examine the benefit of early revascularization in persons with diabetes who show evidence of cardiac ischemia, irrespective of symptomatology.

Current Clinical Practice Guidelines for Noninvasive Testing in Persons With Diabetes

Several guidelines in this category will be reviewed.

French Guideline

A French Guideline for Detection of Silent Myocardial Ischemia in persons with diabetes was published in 1995. This guideline recommends screening for silent myocardial ischemia by exercise stress test or thallium stress in persons with diabetes who have peripheral arterial disease (PAD), proteinuria, or major CVD risk factors or who are over 65 years of age. Goals of early detection of CVD are not clearly defined in this guideline, and this limitation is seen in the other available guidelines as well.³

American College of Cardiology/AHA

The American College of Cardiology (ACC)/AHA published guidelines for exercise testing in 1997. Exercise treadmill testing in persons with diabetes was given a data quality rating of IIb (usefulness or efficacy less well established by

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A single reprint of the Executive Summary for this article is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0225. The full conference report of the 6 writing groups, with references, is available online at <http://www.circulationaha.org> in the May 7, 2002, issue of *Circulation*.

(*Circulation*. 2002;105:e144-e152.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000013955.34262.AF

evidence or opinion); the guideline also stated that exercise treadmill testing in general "might be useful in people with heightened pretest risk."⁴

American Diabetes Association/ACC

The most recent guideline was the American Diabetes Association (ADA)/ACC Consensus Statement on Diabetes and Cardiovascular Disease published in 1998.⁵ This guideline recommends noninvasive cardiac testing of asymptomatic persons with diabetes who have PAD or cerebrovascular disease, those with major or minor electrocardiographic (ECG) changes at rest, or those with ≥ 2 CVD risk factors. Various tests were suggested as possible modalities for screening: thallium stress test, stress echocardiogram, or stress ECG. The authors of the guideline stated that in the absence of data, these recommendations were made on the basis of "clinical judgment and subgroup analysis of data from nondiabetic populations."

The goals of early detection are not clearly defined in any of the 3 currently available guidelines. In fact, there are few data on which to base clinical practice recommendations for this type of testing in asymptomatic persons with diabetes.

Conclusion

In the absence of any clinical trial data to suggest a benefit of stress testing for myocardial ischemic disease in asymptomatic persons with diabetes, routine use of these tests cannot be recommended.

Office-Based Risk Factor Assessment

Office-based risk factor assessment has the advantage of being the best-studied method for CVD risk prediction and also of identifying specific risk factors that require intervention (see Table 1 from the Writing Group I report⁶). Thus, it is the reference standard for determining CVD risk. The largest body of data comes from the Framingham Heart Study, a landmark epidemiological study of cardiovascular risk factors that began in the late 1940s. The Framingham risk score, which can be easily calculated by office-based assessment of CVD risk factors, has been validated in other population-based samples over the past 2 decades.⁷ It allows calculation of future risk of cardiac events and allows easy identification of risk factors for modification. The risk based on Framingham score for several different representative persons with diabetes varies by age, sex, and risk factors, but is always $\approx 40\%$ higher in persons with diabetes⁸ (Table 1 from the Writing Group I report). The Framingham score calculator can be downloaded for use on a PalmPilot from www.statcoder.com. It should be recognized that many persons with diabetes have high absolute risk, and therefore, AHA recommendations are to treat them in the same risk category as if they had CVD. Thus, individual absolute risk assessment may not be needed. However, certain groups (eg, young women with diabetes) may be at lower 10-year CVD risk, and the decision to treat may warrant thought and consideration of future risk and benefit over a lifetime.

The United Kingdom Prospective Diabetes Study (UKPDS) also provides data for calculation of risk in persons with diabetes, and the values obtained with this database can be

compared with the Framingham data. The UKPDS risk engine is being developed and will also allow calculation of CVD risk for persons with diabetes.

There are several new markers being evaluated for prediction of cardiovascular risk. Blood markers of inflammation (low albumin and elevated fibrinogen, von Willebrand factor, or white blood cell count) have been shown to be independently, albeit weakly, associated with risk of CVD in persons with type 2 diabetes.⁹ In the Atherosclerosis Risk In Communities (ARIC) study,⁹ the following nontraditional blood risk factors were not independently associated with risk of CVD in persons with diabetes: high-density lipoprotein subfractions, apolipoproteins A1 and B, lipoprotein(a), creatinine, and factor VII. C-reactive protein has been shown to have predictive value in nondiabetic populations¹⁰ but has not been well studied in persons with diabetes.

Conclusion

It is not clear that any of these biochemical assessments add significantly to risk prediction models over traditional risk factor assessment. Therefore, they are not recommended for use in persons with diabetes.

Lifestyle Assessments

Diet

Dietary assessment is crucial for prevention of diabetes and management of persons with diabetes. The most common form of diabetes, type 2, is associated with a metabolic syndrome characterized by central obesity and insulin resistance. The increase in CVD risk associated with diabetes can be ameliorated by controlling the individual risk factors.¹¹ Reducing caloric intake and increasing physical activity to achieve even a modest weight loss can improve insulin resistance and the associated metabolic abnormalities. The risk of microvascular complications of diabetes is greatly reduced by improving glycemic control, although there is less evidence showing a reduction in risk for macrovascular disease.^{12,13} There is recent evidence that dietary cholesterol intake is particularly strongly associated with CHD risk in patients with diabetes.¹⁴

Physical Activity

Physical inactivity or a low level of cardiorespiratory fitness (CRF) is an independent risk factor for CVD.¹⁵ Most of the data on sedentary habits and mortality have been obtained from studies of apparently healthy women and men.¹⁶ Because other CVD risk factors appear to have similar effects in nondiabetic and diabetic populations, it is reasonable to assume that inactivity or low CRF may also be hazardous for patients with type 2 diabetes. Data on inactivity or low CRF as a predictor of mortality in men with type 2 diabetes have recently supported this assumption.¹⁷ Wei et al¹⁷ performed follow-up on a cohort of 1263 men for an average of 11.7 years after a clinical examination that included a maximal exercise test. There were 180 deaths (92 of CVD) during 14 777 person-years of observation. Men reporting no physical activity in the 3 months before the examination were classified as inactive. Inactive men were 1.8 times more likely than active men to die during follow-up (adjusted for

age and examination year). Unfit men were those with low exercise test tolerance, defined by maximal metabolic equivalents (multiples of resting metabolic rate) attained on the test. Unfit men had significantly higher risk for all-cause mortality in high- and low-risk strata of other mortality predictors.

Conclusion

Lifestyle assessment should be undertaken so that appropriate risk reduction measures can be initiated.

Exercise Testing

Assessment of CRF

Exercise testing can be used for several purposes. The traditional ECG-monitored exercise test is used for diagnosis of CVD, and an abnormal test can be predictive of future major coronary events. Exercise testing also can be used to evaluate CRF. CRF has a strong, independent, and inverse association with risk of CVD and all-cause mortality. CRF can be determined by the traditional ECG-monitored exercise test, but it also can be assessed more simply and inexpensively with nonmedically monitored, submaximal exercise tests. Typical approaches to fitness testing involve use of a cycle ergometer or treadmill. Most protocols include at least 2 exercise stages, which often are selected to produce exercise heart rates of $\approx 50\%$ and 70% of age-predicted maximal heart rates.¹⁸ These tests can be administered by nurses, physical therapists, or exercise physiologists in primary care settings and also are available in most communities at health clubs and other exercise facilities. The cost of a submaximal fitness test is modest, often in the range of \$25 to \$50.

Exercise ECG Testing

Exercise testing has been used in numerous studies of persons with diabetes, but the reports are mostly small case series, and it is difficult in many instances to judge study quality. Typical anginal symptoms may not be a reliable way to screen for ischemia in persons with diabetes, because angina does not reliably accompany exercise-induced ischemia.¹⁹ Callahan et al²⁰ showed in a large series of US veterans with diabetes that exercise-induced ST-segment depression was associated with more CVD events on follow-up, and ECG ischemia, with or without associated angina, conferred a worse prognosis for development of CVD. Data from the Coronary Artery Surgery Study registry showed that patients with diabetes with silent myocardial ischemia had worse outcome in terms of CVD events than persons without diabetes with silent myocardial ischemia.²¹

Conclusions

Although symptoms may be less reliable for detection of ischemic heart disease in persons with diabetes, ischemic exercise ECG findings appear to be at least as predictive of prognosis, and possibly indicative of even worse outcome, when diabetes is present as in persons without diabetes. However, there are no outcome data available to show benefit of early identification of asymptomatic CVD in patients with diabetes.

Exercise Echocardiographic Testing

Exercise echocardiographic testing has been shown to provide incremental prognostic information in the general population. Few studies have focused specifically on persons with diabetes. In a study of the long-term prognostic value of a negative, nonischemic stress echocardiogram in patients with and without diabetes, 236 consecutive subjects (89 diabetic patients) who had stress echocardiography and who tested negative for inducible ischemia were followed up for a mean of 25 months.²² Diabetic patients had a significantly higher incidence of cardiac events (19% versus 9.7% , $P=0.03$) and worse event-free survival ($P=0.03$) than patients without diabetes. There were more nonfatal myocardial infarctions in the diabetic group (6.7% versus 1.4% , $P<0.05$) and a trend toward a higher proportion of hard events (myocardial infarction and cardiac death) in diabetic patients (12.4% versus 5.6% , $P=0.11$). The rate of hard events annually was 2.7% in nondiabetic and 6.0% in diabetic patients. Compared with nondiabetic patients, patients with diabetes who have negative stress echocardiograms appear to remain at greater risk for cardiac events, possibly because of a higher prevalence of established coronary disease in patients with diabetes.

Conclusions

On the basis of limited data, it appears that exercise echocardiography offers prognostic information in patients with diabetes, but even with negative studies, patients with diabetes are at higher risk for cardiac events than patients without diabetes. There are no outcome data available that show a benefit of testing in the asymptomatic population, and thus, routine use of this test cannot be recommended.

Nuclear Perfusion Imaging

Nuclear perfusion imaging (single photon emission computed tomography [SPECT]) has been shown to provide incremental prognostic information in the general population. Few studies have specifically focused on persons with diabetes. Kang et al²³ assessed 1271 consecutive persons with diabetes and 5862 persons without diabetes from a coronary angiography population with known or suspected CVD. Most patients were symptomatic and were not reported separately from asymptomatic patients. Over the 2-year follow-up period, patients with diabetes had significantly higher rates of hard events (cardiac death or nonfatal myocardial infarction; 4.3% versus 2.3% per year, $P<0.001$) and higher total event rates (hard events and late revascularization). These investigators concluded that in mostly symptomatic patients, both normal and abnormal SPECT results were predictive of significant clinical outcomes in patients with and without diabetes. In this symptomatic population, abnormal scans were common both in patients with diabetes and in those without diabetes and predicted poor outcomes, whereas normal scans predicted near-normal outcomes in both groups.

In a study of 925 asymptomatic subjects with type 2 diabetes, exercise ECG was performed in all patients, and thallium scan was also used if the exercise ECG was abnormal or equivocal.²⁴ In the 59 patients with diabetes who had an abnormal resting ECG, 25% (15) had an abnormal

thallium scan, whereas in the 866 persons with diabetes who had a normal resting ECG, only 5% (44) had an abnormal thallium scan. Overall, 6% of this population (59 of 925) had an abnormal thallium scan; however, because normal ECGs are much more common than abnormal ECGs, most abnormal scans occurred in patients with normal resting ECGs. This study did not confirm that abnormal exercise tests were associated with significant coronary stenosis or cardiac events.

In a recent study of noninvasive risk stratification, 4755 patients with symptoms of CHD, 929 of whom were diabetic, who were undergoing stress myocardial perfusion imaging were prospectively followed up (2.5 ± 1.5 years) for the subsequent occurrence of cardiac death, myocardial infarction, and revascularization. Patients with diabetes, despite an increased revascularization rate, had 80 cardiac events (8.6%; 39 deaths and 41 myocardial infarctions) compared with 172 cardiac events (4.5%; 69 deaths and 103 myocardial infarctions) in the nondiabetic cohort ($P < 0.0001$). Diabetic women had the worst outcome for any given extent of myocardial ischemia. Thus, as seen for exercise echocardiography, compared with nondiabetic patients, diabetic patients with negative stress perfusion scans are at greater risk for cardiac events than patients without diabetes.^{25,26}

Conclusions

On the basis of relatively limited information, it appears that exercise SPECT imaging results can be useful in assessing prognosis. As in nondiabetic cohorts, pretest probability has been confirmed in persons with diabetes as a predictor of subsequent test results. If any noninvasive study is done in low-probability patients, most studies will be negative. A resting ECG abnormality and the presence of CVD risk factors identify higher pretest probability. There are no outcome data available showing a benefit of testing in an asymptomatic population, and thus, the routine use of this test cannot be recommended.

Measures of Subclinical Vascular Disease

These include a variety of tests to determine the presence of asymptomatic atherosclerosis in various vascular beds. This testing is based on the principle that atherosclerosis is a systemic disease of the arterial tree, with preferential involvement of the aorta and its large branches, coronary arteries, cerebral arteries, and lower-extremity arteries. Pathological studies have documented that the extent of atherosclerosis in all these arterial sites is greater in middle-aged or elderly subjects with diabetes, most of whom have type 2 diabetes, than in nondiabetic subjects of the same age^{27–29}; to some extent, this difference appears to diminish with age.²⁸ Mortality and morbidity caused by CHD and cerebrovascular disease are the most frequent clinical manifestations of atherosclerotic disease in both subjects with and without diabetes; nonetheless, lower-extremity PAD also leads to substantial morbidity and disability, particularly among the elderly. The risk of all these forms of atherosclerotic disease is markedly higher in patients with diabetes than in nondiabetic subjects.

Patients with atherosclerotic disease in one arterial site are likely to have advanced atherosclerosis in other large arteries as well. Pathological studies have revealed correlation between the extent of atherosclerotic involvement in different arterial sites,^{30–32} although these correlations apply imperfectly to individuals. These observations have focused attention on noninvasive methods for the detection of subclinical atherosclerosis in those arterial sites that are easily accessible for a noninvasive evaluation, namely, lower-extremity arteries and carotid arteries. The underlying hope is that subclinical atherosclerosis in these arterial beds could be used as a marker of a generalized atherosclerotic burden and as a predictor of an increased risk of clinical CVD arising from the less-accessible arterial sites, particularly coronary arteries and cerebral arteries. The recent AHA Prevention Conference V³³ addressed the utility of noninvasive tests of atherosclerotic burden for identification of high-risk individuals among asymptomatic subjects in the general population.

Ankle-Brachial Blood Pressure Index

The ankle-brachial blood pressure index (ABI) has proved to be a useful test for detecting subclinical PAD. This test is simple and inexpensive and can be done in a physician's office. If operators are well trained, reliability is good, and the validity for detection of $\geq 50\%$ stenosis in lower-extremity arteries is high.³⁴ The equipment needed consists of an ordinary blood pressure cuff and a Doppler ultrasonic sensor. With a standardized protocol,³⁵ systolic blood pressure is measured in both arms and at the left and right posterior tibial arteries and dorsalis pedis arteries. The ABI is calculated for each leg as a ratio of the higher of the 2 ankle systolic blood pressures (posterior tibial or dorsalis pedis) to the average of the right and left brachial artery systolic pressures. In case the right and left arm pressure difference is ≥ 10 mm Hg, the higher pressure is used. An ABI < 0.90 for either leg has been given as a threshold value indicating the presence of PAD. Lower ABI values indicate more severe stenosing lesions.

Determination of ABI is compromised by noncompressibility of the ankle arteries caused by medial arterial calcification (Mönckeberg's sclerosis), which may occur in elderly nondiabetic subjects but is more common in subjects with diabetes. In such instances, the indirectly measured systolic ankle pressure is > 300 mm Hg or ≥ 75 mm Hg above arm pressure. In this context, it is important to note that medial arterial calcification has been shown to be an independent predictor of the risk of CVD death in patients with type 2 diabetes.^{36–38} The effect of medial arterial calcification on utility of ABI in persons with diabetes merits further study.

Population-based studies have demonstrated the relationship of a low ABI with prevalent clinically manifest CVD arising from other arterial territories³⁹ and the predictive value of a low ABI with regard to future all-cause mortality and CVD mortality and the risk of nonfatal CVD events.^{40–45} In a 10-year follow-up study of the Rancho Bernardo population of men and women with a mean age of 66 years, Criqui et al⁴⁰ found that when subjects with baseline CVD were excluded and adjustment was made for cardiovascular risk factors, the relative risk of dying among subjects with ABI-detected PAD was increased. Among men without

baseline CVD, the 10-year CVD mortality rate was 33.8% among those with subclinical PAD but only 5.6% among those without it. Among women, the corresponding mortality rates were 15.4% and 2.9%. The prevalence of a low ABI is strongly age dependent; low ABI values have been found to become more frequent in subjects older than 50 years.⁴⁶ The findings from the Cardiovascular Health Study appear to indicate that in the absence of clinically manifest CVD, the increase in the risk of CVD death associated with a low ABI would be similar in diabetic and nondiabetic subjects.¹

ABI testing could also be used to screen for PAD in the hope of preventing amputation as a CVD outcome, particularly in high-risk patients such as persons with diabetes. Because the preventive medical treatment is the same for PAD as for CVD, early diagnosis may not change medical management. However, it is important to bear in mind the significant morbidity that occurs from PAD in patients with diabetes, and aggressive risk factor modification may prevent this complication as well. However, evidence of the benefit of ABI screening in this setting has not been demonstrated yet.

Conclusions

There is convincing evidence from population-based studies that the ABI is a useful noninvasive measure for the detection of subclinical PAD and that a low ABI may provide incremental information beyond that provided by cardiovascular risk factor measurements, "especially in people aged 50 years and older or those who appear to be at intermediate or higher risk for CVD on the basis of traditional risk factor assessment, such as cigarette smokers or individuals with diabetes."¹ Population-based studies have demonstrated that the prevalence of PAD, both clinically established and subclinical, is higher among subjects with diabetes than among nondiabetic subjects of the same age and sex. Thus far, studies applying ABI for the detection of subclinical PAD have included too few subjects with diabetes to allow reliable estimations of the contribution of this noninvasive test to the prediction of the future risk of CVD mortality and morbidity among asymptomatic subjects with diabetes.

B-Mode Ultrasound Measurement of Carotid Intima-Media Thickness

B-mode ultrasound can visualize noninvasively the lumen and walls of carotid arteries, aorta, and femoral arteries. Current methods for the measurement of intima-media thickness (IMT) are based on that described by Pignoli et al.⁴⁷ Protocols used in different studies, however, have not been uniform, and therefore, the reliability of the method has been evaluated separately in each study.⁴⁸ The examination is performed bilaterally on the extracranial carotid artery segments: the distal straight 1 cm of the common carotid arteries, the carotid bifurcations, and the proximal 1 cm of the internal carotid arteries. Some studies conducted measurements on both near and far walls of each segment, whereas other studies performed measurements only on far walls, and in yet other studies, measurements were limited to the common carotid artery. Studies also differed in the method of selection of sites for the measurements made on the frozen ultrasound images from videotapes on each carotid artery segment. From

measurements on both sides, mean values can be calculated for each carotid segment and for combined segments. When one interprets results using carotid IMT as a measure of subclinical atherosclerosis, it must be understood that IMT does not directly measure the degree of stenosing atherosclerosis. Pathological studies, however, demonstrate that in the early phases of atherosclerosis, both intimal and medial layers of the arterial wall become involved.

Population-based studies reveal that increased common carotid artery IMT is associated with prevalent CVD^{49–52}; moreover, carotid IMT measurements carry predictive value for future risk of CVD events and stroke.^{53–56} In the ARIC study, the hazard ratio for CVD risk for IMT ≥ 1 mm versus < 1 mm was 5.07 in women (95% CI 3.08 to 8.36); in men, it was 1.85 (95% CI 1.28 to 2.69).⁵⁴ With adjustment for risk factors, these hazard ratios were reduced to 2.62 (95% CI 1.55 to 4.46) and 1.20 (95% CI 0.81 to 1.77) for women and men, respectively. However, the positive association between IMT and CVD risk extended over the IMT distribution. In the Cardiovascular Health Study, a graded positive association between IMT and the age- and sex-adjusted risk of CVD was observed; the relative risk in the highest versus the lowest IMT quintile was 3.87 (95% CI 2.77 to 5.51).⁵⁶ Carotid IMT development is 5 to 10 years more advanced in men than in women, reflecting the well-known sex difference in the development of atherosclerosis.⁵²

Prevention trials of lipid-lowering treatments that used IMT as a surrogate end point have shown that retardation in the progression of IMT is accompanied by a reduction of clinical CVD end points. These findings suggest that IMT may be a useful measure of atherosclerotic burden.^{57–59}

Several studies have demonstrated that in patients with clinically manifest diabetes, carotid artery IMT is significantly greater than in subjects of the same age who do not have diabetes.^{60–64} Findings from the ARIC study suggest that blood glucose may have a positive relationship with IMT that extends to a nondiabetic range of glucose levels.⁶⁰ Haffner et al,⁶⁵ in the Insulin Resistance and Atherosclerosis Study, compared common carotid artery and internal carotid artery IMT in 43 subjects with type 2 diabetes with clinical CVD, 446 subjects with type 2 diabetes without clinical CVD, 47 nondiabetic subjects with clinical CVD, and 975 nondiabetic subjects without clinical CVD. Findings were adjusted for age, sex, and ethnicity. Both diabetes and CVD were associated with greater common carotid IMT. Diabetes was also positively associated with internal carotid IMT, whereas CVD did not show this association. Subjects with diabetes with CVD had the greatest IMT, and nondiabetic subjects without CVD had the lowest IMT. Subjects with diabetes but without CVD had slightly greater IMT than nondiabetic subjects with CVD. This study confirmed that subjects with type 2 diabetes have a markedly increased atherosclerotic burden even without clinical CVD. A recent analysis from the Rotterdam Study of 374 subjects (14% with diabetes) and 1496 controls (7% with diabetes) showed that there was no incremental predictive value of adding IMT to a risk function for CVD.⁶⁶

Data from the ARIC study revealed a moderate association of increased carotid IMT with incident ischemic stroke and

CHD in people with and without diabetes. Compared with lower IMT values, a mean carotid IMT thickness ≥ 1 mm was associated with an approximate doubling of the risk of future cardiovascular events. The relative risks for elevated IMT were similar for those with and without diabetes but were somewhat higher for women than for men. After adjustment for other CVD risk factors, the association was attenuated slightly. Overall, it appeared that measuring IMT would add only modestly to prediction of future CVD events in patients with diabetes.

Conclusions

Prospective population-based studies have shown that IMT provides incremental predictive information on the future risk of CVD in asymptomatic subjects. These observations, however, cannot be directly extrapolated to subjects with diabetes, in whom IMT has been found to be greater than in nondiabetic subjects. There is still a paucity of research addressing the utility of carotid IMT in predicting future CVD risk in subjects with diabetes. Studies specifically designed to address this question that include large enough cohorts of subjects with diabetes are needed.

Electron Beam Tomography Measures of Coronary Calcium

Coronary artery calcium (CAC) is a specific marker of atherosclerosis confirmed by pathology studies.⁶⁷ In clinical coronary disease populations,⁶⁸ and in various reports from apparently asymptomatic people, electron beam tomography (EBT) is capable of detecting CAC associated with arterial stenosis. Although indicative of coronary atherosclerosis of some degree, the presence of EBT-detected calcium is not specific for obstructive coronary stenoses by angiography and therefore cannot imply that silent ischemia is likely.

To date, few studies of EBT have been reported in subjects with diabetes. In one study of mostly asymptomatic persons with type 2 diabetes (mean age 62 years), CAC >0 was associated with other diabetic complications, such as retinopathy, neuropathy, or nephropathy. Coronary risk factors in this study were not predictive of abnormal coronary calcium scores. Compared with age-matched controls, calcium scores were generally higher (worse) in persons with diabetes than in controls (mean of 248 in patients with diabetes versus 149 in controls), but patients in both categories were frequently found to have scores of 0.⁶⁹

EBT has also been used to study the coronary arteries in patients with type 1 diabetes. A group from Pittsburgh⁷⁰ studied 302 adults with type 1 diabetes in a long-term diabetes cohort with a mean age of 38 years. Their main goal was to correlate EBT findings with other evidence of CHD by history, coronary angiography, and resting ECG. CAC scores were compared between the 246 patients without CHD and the 56 with CHD. In this young cohort, 61% of both men and women without clinical CHD had no coronary artery calcium; 44% with clinical CVD had CAC ≥ 400 . The CAC scores correlated well with clinical CHD, especially in men.

In another study from England,⁷¹ 199 persons with diabetes were recruited from a population-based sampling and were compared with 201 persons without diabetes of similar age

(30 to 55 years) and sex (50% women). Almost all subjects were asymptomatic. In persons without diabetes, 54% of men and 21% of women had CAC >0 (age-adjusted odds ratio 4.5 for comparison of men and women). In those with diabetes, 52% of men and 47% of women had CAC (age-adjusted odds ratio 1.2, $P=NS$), and thus, no male/female difference was seen here in diabetes. After adjustment for CVD risk factors, diabetes remained associated with a 3 times higher odds ratio of calcium in women than in men.

Conclusions

EBT detects CAC in many asymptomatic persons with diabetes, both type 1 and 2. However, asymptomatic subjects with diabetes often have CAC scores of 0. CAC scores in some studies appear to correlate with the presence of clinical CVD. Whether CAC scores predict future clinical events in asymptomatic persons with diabetes has not been studied adequately, and such data are needed to help define a role for EBT in asymptomatic patients with diabetes.

Magnetic Resonance Imaging

High-resolution magnetic resonance (MR) is a noninvasive imaging technique with excellent soft-tissue contrast that differentiates plaque components on the basis of biophysical and biochemical parameters (eg, chemical composition and concentration, water content, physical state, molecular motion, and diffusion).⁷²

Further improvement in external coils⁷³ and the use of contrast agents that enhance the different vessel wall components hold great promise and may make MR suitable for clinical use in atherosclerotic plaque diagnosis and in monitoring therapeutic efficacy. Future work in coronary MR plaque imaging will certainly aim at the identification of the different plaque components, with increasing focus on persons with diabetes. This may enable identification of vulnerable plaques before they rupture and may provide a way to target pharmacological intervention to reduce or prevent coronary disease. Further studies are required to explore the potential role of MR imaging in stratifying asymptomatic patients with diabetes according to risk.

Conclusions

The assessment of atherosclerotic plaques by imaging techniques may prove valuable for the identification of vulnerable plaques. In vivo high-resolution multicontrast MR holds promise for noninvasively imaging vulnerable plaques and characterizing the different components in all arteries, including the coronary arteries. MR allows serial evaluation and assessment of the progression and regression of atherosclerosis over time. At the present time, however, information about this technology in patients with diabetes, as well as others, is too limited to recommend use of this modality for clinical purposes.

Older Persons With Diabetes

The prevalence of subclinical CVD is high in older persons (aged >65 years) with diabetes, which makes any testing less useful in stratifying risk. In a study of 1343 persons with diabetes and 1433 patients with impaired glucose tolerance

(mean age 73 years), a composite measure of noninvasive markers of atherosclerosis (carotid wall thickness greater than the 80th percentile, stenosis, low ankle-arm index, ECG or echocardiographic abnormalities, or positive Rose questionnaire) was used. In this study, the prevalence of clinical CVD in persons with diabetes was 40% and the prevalence of subclinical disease was 44%, for a total of nearly 85% of patients with either clinical or subclinical CVD compared with 66% of persons without diabetes. The prevalence was only slightly lower in newly diagnosed older persons with diabetes than in persons with known diabetes. These findings highlight that screening for subclinical disease in older adults with diabetes would probably not be cost-effective given the high prior probability of abnormal test result. It is important that older persons with diabetes be considered at high risk for CHD and that they should receive aggressive preventive management.

Recommendation

Screening for subclinical CVD is not routinely recommended in older persons, but the high rate of atherosclerosis in this age groups warrants aggressive preventive management.

Special Considerations for Type 1 Diabetes

Type 1 diabetes comprises 5% to 10% of all cases of diabetes in the United States. Owing to its earlier age of onset and greater severity of metabolic disturbances, there are some specific issues relating to cardiovascular risk assessment in this group.

Both the absolute and relative risks of CVD are dramatically increased in young adults with type 1 diabetes. For subjects diagnosed in childhood, relative risks for CVD and total mortality are often 10-fold that of the general population.^{74,75} Recent 10-year incidence data suggest an absolute annual mortality risk of 5% and CVD risk of 12% for those with diabetes of ≥ 35 years' duration, a group whose mean age is only 43 years.⁷⁶ Thus, the general concept that CVD risk assessment and risk factor management should be less vigorously applied to young adults does not appear to be valid. Writing Group III thus held that office-based assessment recommendations for adults with type 2 diabetes should also apply to all persons with type 1 diabetes aged ≥ 16 years. This proposal is supported by the recent publication of the predictive power of lipids and blood pressure for CVD events in mortality in type 1 diabetes.

The use of the ABI is complicated by the high rate of medial wall calcification in type 1 diabetes.³⁵ Studies have shown that an ankle brachial difference in systolic blood pressure of ≥ 75 mm Hg has a positive predictive value of 100% for medial wall calcification.³⁵ This measure (ankle brachial difference of 75 mm Hg), however, is also highly predictive of both 10-year total mortality and CVD in type 1 diabetes (relative risks of 6.7 and 3.1, respectively).⁷⁷ It is therefore recommended that when ABI is performed, either an ABI < 0.9 or an ankle brachial difference > 75 mm Hg be considered abnormal and predictive of future events. Although there is increased medial wall calcification in type 1 diabetes, both published studies of EBT in type 1 diabetes show association with CVD risk factors and CVD.^{70,71} Thus,

EBT has the same associations in type 1 diabetes as in the general population, although its incremental predictive power above CVD risk factors is not established in either population.

In contrast to type 2 diabetes, high-density lipoprotein cholesterol levels tend to be normal or high in type 1 diabetes but remain predictive of events.⁷⁸ The younger age at onset of type 1 diabetes often leads to the development of advanced microvascular complications, particularly overt nephropathy, before the onset of CVD. This sequence is in contrast to type 2 diabetes, where the patient may die of CVD before sufficient long-term glycemia and diabetes duration has occurred for these other complications to develop. Overt nephropathy and microalbuminuria are important risk factors for CVD in type 1 diabetes, although it should be recognized that much of the renal-associated CVD risk is linked to blood pressure and lipid disturbances, which thus need to be carefully monitored and treated.⁷⁶

Finally, the relationship between hemoglobin A1c (or glycemic level) and CVD is weak and inconsistent in type 1 diabetes and does not predict events well either cross-sectionally in the United States⁷⁹ or Europe^{79,80} or prospectively in the United States.⁷⁸

Cost-Effectiveness

There are no cost-effectiveness studies of alternative diagnostic and risk assessment strategies for CVD in persons with diabetes, but reasonable estimates may be possible from more general CVD analysis if one extrapolates event rate impact and costs. Given the number of drugs required to manage the multiple CVD risk factors in persons with diabetes, cost-effective assessment and management of CVD in diabetes mellitus will require identification of strategies that are synergistic and address more than one risk factor. Formal, rigorous cost-effective models need to be developed that incorporate the best data available to assess the incremental cost-effectiveness of alternative CVD identification and management strategy (diet, exercise, and smoking cessation; cost of test and intervention; management change; and effectiveness of intervention on outcomes of timing).

Overall Conclusions

Mortality from CVD is greater in persons with diabetes than in those without diabetes. Because of this greatly increased risk, persons with diabetes should receive aggressive risk factor modification as recommended for a secondary prevention patient at high risk for CVD. Lifestyle changes—dietary changes as well as increased physical activity—are cornerstones of any risk management strategy, as is pharmacological therapy, when appropriate. The value of a revascularization strategy in asymptomatic patients has not been established.

Traditional risk factors and a resting ECG can identify patients with a heightened pretest probability of CVD. Office-based risk factor evaluation is mandatory in persons with diabetes, and aggressive risk factor modification should be based on these results. The finding of advanced subclinical atherosclerosis identifies a higher-risk group (true in both persons with and those without diabetes). Exercise ECG or

exercise SPECT appear almost equally predictive of future events in those with and without diabetes. EBT data show that persons with diabetes have detectable atherosclerosis at rates higher than in persons without diabetes, consistent with the clinical epidemiology. There are no long-term follow-up studies yet for EBT results in persons with diabetes. However, because we already know that diabetes places patients in a high-risk group, in general, the results of noninvasive testing, whether negative or positive, would not change medical management, and thus most testing for risk assessment is not useful.

Currently, there are no published data to show that routine noninvasive testing of persons with diabetes leads to better diagnostic or therapeutic outcomes. Additional trials in this area are mandatory to help guide decision making in this high-risk group.

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KEY WORDS: AHA Conference Proceedings ■ diabetes mellitus ■ cardiovascular diseases ■ hypertension ■ lipoproteins ■ myocardial infarction