Ischemia Imaging and Plaque Imaging in Diabetes

Complementary tools to improve cardiovascular risk management

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Cardiovascular disease is the most frequent cause of death and disability in diabetes, and the morbidity and mortality for coronary artery disease (CAD) in this population is two to four times higher than in nondiabetic subjects. Traditional risk factors do not fully explain the level of cardiovascular risk, and coronary disease events are often silent in diabetic patients. Thus, research has recently focused on improving the risk assessment of an individual patient with new tools in an effort to better identify subjects at highest risk and in need of aggressive management. Cardiovascular imaging has proven very helpful in this regard. Traditional methods to assess CAD are based on detection of obstructive luminal disease responsible for myocardial ischemia. However, acute coronary syndromes often occur in the absence of luminal stenoses. Hence, the utilization of imaging methodologies to visualize atherosclerosis in its presymptomatic stages has received mounting attention in recent years. In this article, we review the current literature on the utility of traditional imaging modalities for obstructive CAD (nuclear and echocardiographic stress testing) as well as atherosclerosis plaque imaging with carotid intima-media thickness and coronary artery calcium for risk stratification of diabetic patients.

Diabetes Care 28:2787–2794, 2005

Almost 140 million people in the world are affected by diabetes, and this number is estimated to reach 300 million by the year 2025 (1). In developed countries, a sedentary lifestyle, obesity, and the increasing population age are the probable main culprits for the observed escalation in the prevalence of this disease (2,3). In 1995, the prevalence of diabetes in U.S. adults aged >20 years was estimated to be 4%. Today, 6.3% of the population is estimated to suffer from diabetes (~90% type 2 diabetes), though as many as 5.2 million are not aware of suffering from this condition (4,5). Diabetes has long been recognized as an independent risk factor for coronary artery disease (CAD), and the morbidity and mortality due to CAD are two to four times greater than in nondiabetic subjects (6,7). Interestingly, it has been reported (8) that in the past several decades there may not have been a reduction in CAD mortality in diabetic patients as large as that seen in the general population, although these epidemiological data are still awaiting prospective confirmation. The societal outcome of this severe disease is a cost for diabetes and its complications estimated at ~$132 billion per year, ~28% of the U.S. Medicare budget (9). In view of such societal cost, an attempt to conduct early detection and treatment of atherosclerosis in diabetes appears desirable, although it is not yet supported by strong evidence. In this article, we review the current (1999–2005) English literature on the application of myocardial ischemia testing as well as atherosclerosis imaging in diabetic patients. Our goal was to write a practical review for the clinician faced with the everyday dilemma of risk stratification of an individual patient in the office or clinic setting. Given the very large published evidence, we decided to evaluate only peer-reviewed manuscripts with a minimum of 50 enrolled patients that provided information on the occurrence of soft and/or hard coronary events related to the use of the imaging modalities under analysis. We limited our review to four imaging modalities: nuclear and echocardiograhic stress testing for ischemia imaging and coronary artery calcium (CAC) and carotid intima-media thickness (CIMT) for atherosclerosis imaging. Our goal was to verify whether existing data support the use of these techniques in isolation or as complementary tools for improved risk prediction.

MYOCARDIAL ISCHEMIA IMAGING

Nuclear stress testing

CAD is often silent in diabetic patients, and it is typically in advanced stages of development by the time it manifests (10). Hence, several investigators have utilized various forms of stress testing to detect silent obstructive CAD. Abnormal electrocardiographic stress tests have been reported in 12–31% of asymptomatic diabetic individuals (11–17). Among the different noninvasive imaging tests used to diagnose obstructive CAD, stress nuclear myocardial perfusion imaging (MPI) has established itself as one of the most reliable and informative tools. Obstructive CAD is demonstrated by detecting a reduced uptake (perfusion abnormality) of a radiotracer after stress in one or more areas of the myocardium perfused by a coronary artery with a critical (>50%) luminal stenosis. Perfusion defects can be elicited via treadmill exercise stress testing or after the injection of drugs with vasodilator (for example adenosine) or inotropic (for example dobutamine) effects. The most frequently employed radiopharmaceutical agents are thallium-201– or technetium-99m–based tracers (Tc-99m sestamibi or Tc-99m tetrofosmin), each with different pharmacodynamic and pharmacokinetic

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Received for publication 20 March 2005 and accepted in revised form 10 August 2005.

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CCS, coronary calcium score; CIMT, carotid intima-media thickness; CT, computed tomography; DSE, dobutamine stress echocardiography; MPI, myocardial perfusion imaging; SE, stress echocardiography.

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

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characteristics. Thallium-201 has a long half-life (~73 h), a lower peak emission rate than technetium-99m, and recirculates in and out of viable cells utilizing the same membrane channels as potassium (18–20). Due to its rapid redistribution, imaging must proceed quickly after the injection of the tracer at peak exercise to detect stress-induced perfusion defects. Delayed imaging (usually 4 h from stress imaging) is then performed to verify whether a difference in perfusion (tracer uptake) can be detected between the stress and rest phase in any region of the left ventricular myocardium. Tc-99m has a higher peak emission rate and a shorter half-life (~6.5 h) than thallium-201. It recirculates minimally in and out of viable cells and remains essentially trapped in the location of initial uptake, giving an instantaneous impression of the perfusion status at the time of injection. Due to its lack of redistribution, Tc-99m–based tracers must be injected at peak exercise and reinjected at rest to compare stress and rest images (18–20). The greater peak emission rate but shorter half-life of Tc-99m tracers allow the use of larger doses than thallium-201, with overall better image quality and performance of accurate gated segmental wall motion and left ventricular function. On the other hand, thallium-201 may be preferable to Tc-99m tracers for the performance of vasodilator stress (21) and myocardial viability (22) studies.

MPI has been employed in several series to test the prevalence of silent ischemia or to analyze the prognostic impact of perfusion abnormalities in diabetes. In the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study (23), 1,124 type 2 diabetic patients were enrolled at 14 sites in the U.S. and Canada. Half of the patients were randomized to an adenosine Tc-99m sestamibi MPI and half were not. In the imaging cohort, 22% of the individuals showed abnormal MPI results, and 1 in every 18 subjects (5.5%) showed a moderate to severe perfusion defect indicative of poor prognosis. Since the entry criteria required an established diagnosis of type 2 diabetes, a normal electrocardiogram, and no known CAD, the authors concluded that obstructive CAD would remain undetected in as many as 41% of type 2 diabetic patients if the current American Diabetes Association recommendations (24) for CAD screening were strictly followed. Although this study helped establish the presence of silent ischemia in diabetes, it did not provide any information on the outcome of patients with abnormal scans, and a long-term follow-up has therefore been planned.

De Lorenzo et al. (25) submitted 180 asymptomatic adult-onset diabetic patients to exercise MPI with Tc-99m sestamibi to detect asymptomatic obstructive CAD. In this study, a short-term follow-up (36 ± 18 months) was conducted to correlate the imaging findings with patients' outcome. A positive test result was reported in 26% of all subjects. During follow-up, 34 patients suffered cardiac events: 7 cardiac deaths, 6 nonfatal myocardial infarctions, 10 coronary artery bypass surgeries, and 11 percutaneous coronary angioplasties. Male sex and perfusion abnormalities were independent predictors of cardiac events. Inducible myocardial ischemia on MPI added incremental prognostic value to clinical variables and exercise stress test variables for the prediction of hard ($\chi^2 = 5.4$, $P < 0.001$) as well as total ($\chi^2 = 7.4$, $P = 0.0001$) events.

Kang et al. (26) also investigated the incremental prognostic value of MPI over clinical data for prediction of events in 1,271 diabetic and 5,862 nondiabetic patients. During an average follow-up period of 24 months, diabetic patients suffered almost twice the number of events (myocardial infarction, death, and coronary revascularizations) compared with the nondiabetic subjects. Findings on MPI added significant prognostic information ($P < 0.001$) to clinical and historical data in both subsets of patients.

In a single-center study, Berman et al. (27) reported on the incremental prognostic value of adenosine stress MPI in 1,222 consecutively tested diabetic and 4,111 nondiabetic patients. For the nondiabetic patients, a normal, mildly abnormal, and moderately to severely abnormal MPI study was associated with cardiac death rates ranging from 0.8 to 6.1% per year of follow-up. The event rates were similar among nondiabetic men and women. However, diabetic women with perfusion defects demonstrated significantly higher death rates than diabetic men ($P < 0.0001$). Furthermore, in the setting of a normal MPI the death rate increased from ~0.6% for nondiabetic subjects to 1.8% for noninsulin-requiring to 2.5% for insulin-requiring diabetic patients, respectively. These observations were echoed by the report by Giri et al. (28). In this large multicenter study, 4,755 patients (20% had diabetes) were followed for an average of 2.5 years after a baseline MPI (28). The primary end points were the occurrence of cardiac death and nonfatal myocardial infarction or the performance of revascularization procedures. An abnormal MPI test was a significant predictor of cardiac death and myocardial infarction in both diabetic and nondiabetic subjects, though diabetic patients suffered more events in each category. A stepwise increase in cardiac death rate was observed with increasing numbers of ischemic segments of the left ventricle in both diabetic ($\chi^2 = 15.1$, $P = 0.002$) and nondiabetic ($\chi^2 = 38.8$, $P < 0.0001$) subjects. However, the stepwise increase was greater in diabetic patients where ischemia even in a single-vessel territory increased the risk of death significantly. As noted above, two more results from this large muticenter study are worth remarking on. Although a normal MPI was associated with a high event-free survival in the short range, diabetic patients with a normal perfusion stress test had a fourfold higher morbidity and mortality during follow-up than nondiabetic subjects with normal MPI tests. Furthermore, the "protective effect" of a normal MPI study in diabetic patients appeared to expire after ~2 years from testing, when events started occurring very rapidly.

A retrospective analysis (29) of 1,427 diabetic patients referred for MPI to a single center was recently published. An abnormal MPI study was reported in 58% and a high-risk scan in 18% of the subjects. The best predictors of an abnormal MPI were the presence of Q waves on the resting electrocardiogram and the diagnosis of peripheral arterial disease. Not unexpectedly, the annual mortality rate was high (5.9%) in patients showing high-risk findings on MPI. However, the mortality rate was also very high in patients with low-risk scans (3.6% per year) (28). In this series, 46% of the patients from the community were asymptomatic and had been referred for CAD screening. Although this study was limited by substantial referral bias, it illustrates two important points in the care of diabetic patients: the need physicians feel to screen for CAD in asymptomatic diabetic subjects and the high event rate even in the presence of "seemingly reassuring" test results.

Hence, the actual cardiovascular risk of diabetic patients is greater than what can be assessed by simply seeking myocardial ischemic responses to stress to predict the presence of obstructive coro-

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nary disease. These observations lend support to the concept of refining risk stratification in diabetes using plaque imaging techniques. Indeed, these techniques identify the presence of arterial plaque burden not causing obstructive disease and may prove useful in improving risk prediction in diabetes.

ECHOCARDIOGRAPHIC STRESS TESTING — Stress echocardiography (SE) was introduced as an alternative to nuclear perfusion imaging and has demonstrated very high diagnostic accuracy. With SE, myocardial ischemia is demonstrated when segmental wall motion abnormalities of the left ventricle, such as new or worsening hypokinesia, new akinesia, or dyskinesia, are induced by either exercise or pharmacological stress testing. Due to poor acoustic windows, patient habitus, excessive respiratory motion artifacts, and limited technical experience of the operator, ~5–10% of all SE tests are nondiagnostic. In comparison, the nondiagnostic rate with stress nuclear testing varies between 1 and 2%. However, SE offers the advantage of easy portability, lower cost, and no radiation exposure compared with nuclear stress testing, and it has therefore gained substantial popularity.

The diagnostic accuracy for obstructive CAD of SE in diabetic patients has been reported to be similar to that noted in nondiabetic subjects. Penfornis et al. (30) performed dobutamine stress echocardiography (DSE) in 56 asymptomatic diabetic subjects who were also submitted to electrocardiographic and MPI stress testing. They reported a positive predictive value of 60, 69, and 75% for electrocardiographic stress testing, DSE, and MPI, respectively, for the detection of obstructive CAD. The authors concluded that DSE and MPI are equivalent, though in this particular study both showed a moderate accuracy.

SE and DSE were utilized in a multicenter study (31) involving 937 predominantly type 2 diabetic patients with known or suspected CAD. The follow-up was as long as 9 years from the time of SE testing, and the primary end point was all-cause mortality. A very high mortality was recorded both for patients with resting as well as for stress-induced wall motion abnormalities (123 of 275 subjects, 45% mortality and 115 of 232 subjects, 50% mortality). In multivariable models, the strongest predictor of mortality was a referral for pharmacological stress testing (emphasizing the importance of limited exercise tolerance as an indicator of risk), followed by the visualization of ischemic changes on echocardiographic imaging, presence of heart failure, and age. Similarly, in a smaller study of 259 diabetic patients followed for an average of 24 ± 22 months, the presence of ischemic myocardial changes on SE was an independent predictor of cardiac death and nonfatal myocardial infarction (32). However, in the study by Marwick et al. (31), the yearly event rate for patients with a normal SE varied between 2 and 3%. Hence, as shown using nuclear techniques (27,28), the event rate for diabetic patients with nonischemic myocardial stress tests was much higher than that of nondiabetic patients with negative tests. These findings suggest once again that tests for atherosclerosis may aid refining risk stratification in diabetic patients beyond myocardial ischemia imaging.

CAC IMAGING — CAC is intimately related to atherosclerosis, and the area of coronary artery calcification measured on cardiac computed tomography (CT) has been shown to closely correlate with the extent of atherosclerotic plaque (33). Hence, coronary calcium is considered an accurate marker of atherosclerosis. The first CT developed for this purpose was the electron-beam CT scanner, followed more recently by multidetector spiral CTs. The extent of calcification is measured by means of a calcium score calculated by the computer software on the basis of plaque size and density or as volume of calcified plaque (34). Though often misrepresented, the main purpose of calcium screening is not to identify patients with obstructive CAD but to detect vessel wall atherosclerosis. Identifying nonobstructive plaque, in fact, may be as important as assessing stenosis severity since many acute coronary events occur on the basis of nonobstructive disease (35,36).

CAC in type 2 diabetes

Mielke, Shields, and Broemeling (37) studied a cohort of 3,389 patients suffering from type 2 diabetes and showed that diabetic patients tend to harbor larger amounts of CAC than nondiabetic patients of similar age and with a similar risk-factor profile. Moreover, the amount of CAC was similar to that of patients with established CAD but without diabetes. Similarly, Khaleeli et al. (38) showed that asymptomatic diabetic patients present the same prevalence of CAC as nondiabetic individuals symptomatic for CAD (89 vs. 73%, P = NS). Furthermore, both studies showed that diabetic women harbor as much CAC as diabetic men, confirming the clinical evidence that diabetes negates the well-known advantage of women over men in prevalence and extent of atherosclerosis (37,38). Schurgin, Rich, and Mazzone (39) screened a cohort of 139 asymptomatic diabetic patients and matched control subjects. They concluded that extensive CAC (calcium score >400) is more prevalent (25.9%) in diabetic patients than nondiabetic control subjects both without (7.2%) and with (14%) traditional risk factors. These findings are of interest since a calcium score >400 is associated with a high risk of myocardial perfusion impairment (40) and a high risk of any cardiovascular event in the short term (41,42). Furthermore, the calcium imaging data are supportive of the well-known clinical data showing that an asymptomatic diabetic patient presents the same cardiovascular risk as a patient with established CAD but without diabetes (43).

Recently Raggi et al. (44) published a report of 10,377 asymptomatic individuals (903 type 2 diabetic patients) followed for an average of 5 years after having been referred by a primary care physician for CAC screening. The primary end point of the study was all-cause mortality. In that study, the risk of all-cause mortality was higher in diabetic patients than nondiabetic subjects for any degree of calcification, and the risk increased as the calcium score increased. In diabetic patients, there was a 44% (95% CI 20–80) increased risk of death for every increase in coronary calcium score (CCS) grouping from 11–100 to 101–400, 401 to 1,000, and >1,000 (P = 0.0001). Finally, a risk-adjusted model showed that there was a significant interaction of CCS with diabetes ($P < 0.00001$), indicating that for every increase in CCS, there was a greater increase in mortality for diabetic individuals than nondiabetic subjects. Interestingly, the absence of CAC predicted a low short-term risk of death (~1% at 5 years) for diabetic patients as well as nondiabetic subjects. Hence, both the presence and absence of CAC were important modifiers of risk in diabetes. Discordant with these results were the findings reported by Qu et al. (45). In that study, the investigators followed 269 type 2 diabetic patients for an average of 6.3 years. They noted an increased prevalence of CAC in diabetic

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patients compared with control subjects and observed an increased risk of cardiovascular events in the patients with CAC compared with those without CAC. However, they were unable to prove that CAC adds incremental prognostic value to diabetes for the prediction of future events. This apparent discrepancy may have been due to the smaller cohort used in the study by Qu et al. (45) and the utilization of high-risk subjects (mostly men, on average 10 years older than the patients included in the study by Raggi et al. [44]) .

Sequential CAC imaging has been proposed as a method to monitor effectiveness of medical therapy in the general population (46), and CAC progression appears to be linked to the occurrence of adverse outcomes (47). In a retrospective analysis, the progression of CAC and the occurrence of myocardial infarction were compared in 157 type 2 diabetic patients and 1,153 nondiabetic control subjects during a follow-up of 1–3 years (48). Both event-free diabetic subjects and diabetic patients who suffered a myocardial infarction demonstrated a significantly greater progression of CAC than did nondiabetic patients. Though statin therapy slowed the progression of CAC in all groups, such treatment was significantly less effective in diabetic subjects.

CAC in type 1 diabetes

In the CACTI (Coronary Artery Calcification in Type 1 Diabetes) study (49), 656 diabetic patients showed a higher prevalence and extent of CAC than 764 age- and sex-matched control subjects. Though there tended to be more CAC in men than women, after adjustment for waist-to-hip ratio, waist circumference, or visceral fat, the sex difference in CAC was not significant in diabetic subjects. The authors concluded that insulin resistance, associated with an android deposition of fat, might be one of the mechanisms responsible for the increased prevalence of CAC in women with type 1 diabetes. Of interest, Colhoun et al. (50) reported that the increased prevalence of CAC in women affected by type 1 diabetes is not associated with traditional risk factors for atherosclerosis or the size and concentration of various lipoproteins, while it is associated with the extent of systemic inflammation.

Extensive vascular calcifications were detectable even in young (17–28 years of age) adults with type 1 diabetes (51) and have been associated with factors such as genetic polymorphism for hepatic lipoxygenase (LIPC-480 T) (52) or more conventional ones like smoking, elevated serum lipoprotein(a) (51), or suboptimal glycemic control (52,53).

No prospective outcome data exist in type 1 diabetic patients related to the presence of CAC, and only cross-sectional observational data are available. Olson et al. (54) investigated 302 type 1 diabetic patients (146 men and 156 women) with a history of myocardial infarction, angina, or evidence of ischemia on stress testing or surface electrocardiograms. Patients were participants in the Pittsburgh Epidemiology of Diabetes Complications study, a 10-year prospective follow-up study of risk factors for complications of type 1 diabetes diagnosed before the age of 17 years. Electron-beam CT imaging showed that the prevalence of CAC clearly increased with age (from 11% before age 30 years to 88% in individuals aged 50–55 years or older). Among subjects without clinical manifestations of CAD, 5% had a CAC score ≥400 (indicative of a large atherosclerosis burden), as opposed to 25% of the subjects with angina or ischemic electrocardiogram changes and 80% of the patients with myocardial infarction or luminal stenosis on coronary angiography. CAC showed a sensitivity of 84 and 71% for clinical CAD in men and women, respectively, and 100% sensitivity for myocardial infarction or obstructive CAD. In multivariable regression analyses, CAC was independently correlated with myocardial infarction or obstructive CAD in both sexes and was the strongest independent correlate for men. The authors suggested that CAC in type 1 diabetes may be a marker of risk, independently of other risk factors. Obviously, prospective investigations will be necessary to support and expand these observations.

CIMT MEASUREMENT IN DIABETES

— The thickness of the wall of the carotid arteries measured ultrasonographically was shown almost 2 decades ago to bear a good correlation with the presence and extent of atherosclerosis of the aorta (55–57). Subsequently, several randomized and epidemiological studies demonstrated the value of the CIMT as a marker of increased risk for cardiovascular events. Increased CIMT, even in the absence of obstructive luminal disease of the carotid arteries, has been associated with risk of myocardial infarction and stroke in the elderly (>65 years) (58) as well as younger age-groups (59–61). Furthermore, an increase of merely 0.03 mm per year in CIMT has been associated with a twofold increase in relative risk of myocardial infarction and cardiac death during follow-up (60). CIMT bears a modest relationship with obstructive CAD in nondiabetic (62,63) as well as diabetic (64) subjects, indicating that this surrogate is a marker of atherosclerosis burden rather than an index of the severity of CAD.

Increased CIMT in diabetes has been associated with risk factors for atherosclerosis such as high serum triglyceride levels and low total-to-HDL cholesterol ratio (65,66), age and BMI (67), lipoprotein(a) (68), microalbuminuria (69,70), and endothelial dysfunction and low-grade inflammation (71,72). Insulin resistance alone, even in the absence of clinical diabetes, has been associated with an increased CIMT (73).

Diabetes is an independent predictor of CIMT progression (74,75), and CIMT appears to progress faster in diabetes than in other conditions (59,76,77). Such accelerated progression appears at least in part related to glycemic control expressed both as fasting serum glucose levels (78) as well as HbA_{1c} levels (79). Furthermore, baseline age and carotid wall thickness (79), as well as systolic hypertension and development of nephropathy (80), have been identified as predictors of CIMT progression.

Sequential CIMT measurements have been utilized to assess efficacy of medical therapy in several studies (81–85) in the general population but only in a limited number of studies in diabetic patients. Nathan et al. (86) conducted first a short- then a long-term follow-up study of 1,229 type 1 diabetic patients randomized to either standard hypoglycemic therapy or intensive therapy and age- and sex-matched individuals. Progression of CIMT was not different at the end of the 1st year of follow-up between control subjects and all diabetic patients, but CIMT progressed significantly more in diabetic than control subjects by the end of 6.5 years of follow-up. Furthermore, at the end of the long-term follow-up, CIMT was shown to have progressed significantly more in diabetic patients who received standard therapy than in those randomized to intensive therapy. A small study of 34 patients affected by type 1 diabetes demonstrated that successful transplantation of pancreatic islet cells was associated with a slower CIMT progression and fewer cardiovascular events at 3 years (87). In a recent study (88),

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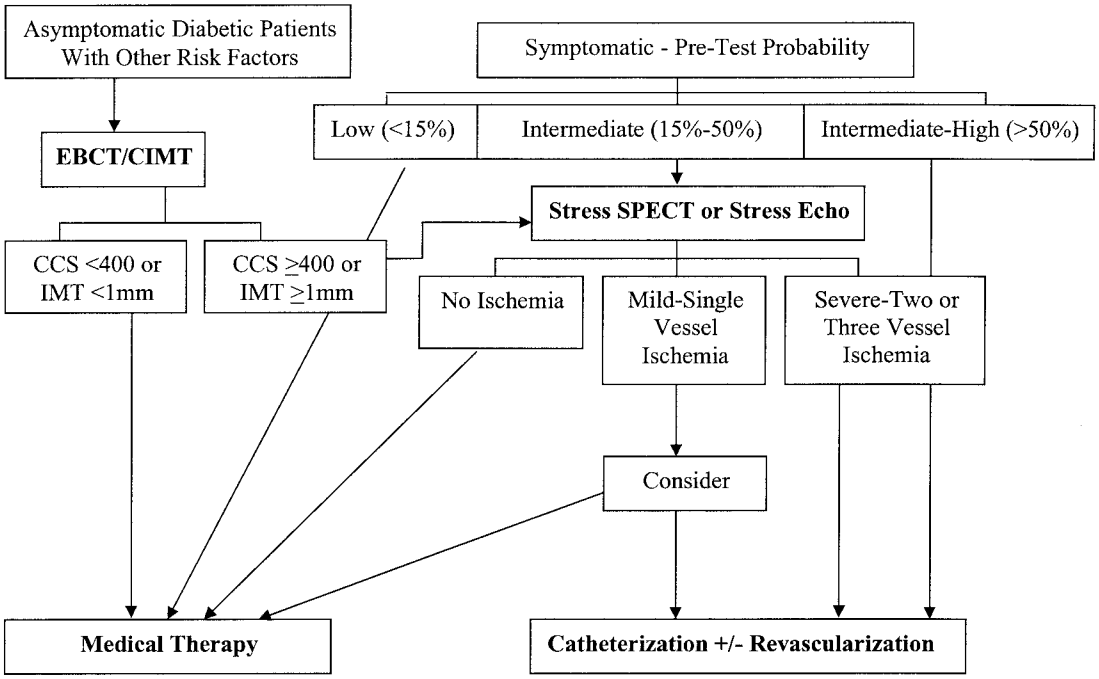

Figure 1—*EBCT, electron-beam CT; Echo, echocardiography; SPECT, single-photon emission CT.*

sequential carotid artery IMT measurements were utilized to assess the effect of statin therapy compared with placebo in 250 type 1 diabetic patients. At the end of 2 years of follow-up, there was no difference in the progression of CIMT, though the number of cardiovascular events was significantly smaller ($P = 0.006$) in patients treated with statins. The effectiveness of statins on reduction of cardiovascular events in diabetes was clearly consonant with the results of the Heart Protection Study (89) and the Collaborative Atorvastatin Diabetes Study (90). However, to demonstrate an effect on CIMT progression, a longer follow-up time may have been required. Finally, in two small randomized trials of type 2 diabetic patients, antiplatelet therapy based either on aspirin, ticlopidine (91), or cilostazol (92) was shown to slow progression of CIMT after a follow-up of 3 years (91) and 1 year (92), respectively.

The evidence presented, though clearly indicative of a greater atherosclerosis burden and attendant risk in diabetic patients with increased CIMT, identifies important limitations of the current knowledge in this field. First, while CIMT is an independent predictor of cardiovascular events in the general population, such evidence is of modest strength in diabetes. An isolated example in diabetes is represented by the study performed by Yamasaki et al. (79) on 287 type 2 diabetic Japanese patients, where baseline CIMT was identified as an independent predictor of incident nonfatal CAD (angina and myocardial infarction) during a follow-up period of 3 years. Second, although IMT progression can be slowed both in diabetic and nondiabetic patients with various interventions, little is known of the prognostic significance of CIMT progression in either patient group. Finally, no study has yet demonstrated the incremental prognostic value of CIMT over other conventional risk factors in either diabetic or nondiabetic individuals.

LIMITATIONS — This analysis does not constitute a systematic review of the current medical literature (utilizing meta-analytic methods) and does not offer an assessment of the cost-effectiveness of integrating various imaging modalities for the detection and care of CAD in diabetic patients. Furthermore, the current evidence on use of nontraditional imaging modalities to improve risk prediction is limited and often based on preselected populations. It represents, however, an attempt at summarizing a vast amount of information related to a subject that has received a large amount of interest in the most recent literature.

Figure 1 is an algorithm with a proposed approach to the diagnosis of CAD in diabetes in an attempt to integrate ischemia and atherosclerosis imaging. The thresholds utilized to define risk were chosen based on personal opinion and the data published in the current medical literature. Whether all asymptomatic diabetic patients should be tested remains debatable and unlikely to be financially affordable for society. To make asymptomatic screening more affordable, at least one of the following conditions should probably be present: one additional cardiovascular risk factor, an abnormal resting electrocardiogram, microalbuminuria, or autonomic neuropathy.

CONCLUSIONS — Cardiovascular disease remains the main health concern in diabetes. Conventional imaging tools based on ischemia imaging perform well at detecting obstructive coronary luminal disease. Nonetheless, the high event rate seen in subjects with normal functional and perfusion studies, as well as the frequent occurrence of silent events in diabetic patients, provide support for disease detection in its preclinical stages. Atherosclerosis imaging modalities, such as CT for CAC and ultrasonography for CIMT, offer an opportunity to improve our ability to acquire prognostically important information. Indeed, the integration of myocardial ischemia imaging tools and tools to image atherosclerosis (93) may improve outcome in high-risk patients through the early implementation of aggressive medical and interventional therapies. Furthermore, sequential quan-

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tification of progression of atherosclerosis may allow monitoring of treatment efficacy and hopefully facilitate adherence to recommended treatment regimens. Continued research will be needed to confirm that the integration of several imaging modalities improves clinical outcome in a cost-effective manner.

References

1. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
2. Goraya 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
3. American Diabetes Association, National Heart, Lung, and Blood Institute, Juvenile Diabetes Foundation International, National Institute of Diabetes and Digestive and Kidney Diseases, American Heart Association: Diabetes mellitus: a major risk factor for cardiovascular disease (Editorial). *Circulation* 100:1132–1133, 1999
4. National Institute of Diabetes and Digestive and Kidney Diseases: *Diabetes Statistics*. Bethesda, MD, National Diabetes Information Clearinghouse, 1999, p. 99–326 (NIH publ. no)
5. Nesto RW, Peter L: Diabetes mellitus and the cardiovascular system. In *Heart Disease: A Textbook of Cardiovascular Medicine*. Braunwald E, Zipes DP, Libby P, Eds. Philadelphia, Saunders, 2001, p. 2133–2150
6. Jacoby RM, Nesto RW: Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis. *J Am Coll Cardiol* 20:736–744, 1992
7. Kannel WB, McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 2:120–126, 1979
8. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. *JAMA* 281:1291–1297, 1999
9. American Diabetes Association: Diabetes statistics [article online], 2004. Available from http://www.diabetes.org/diabetes-statistics.jsp. Accessed 3 October 2004
10. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
11. Alexander CM, Landsman PB, Teutsch SM: Diabetes mellitus, impaired fasting glucose, atherosclerotic risk factors, and prevalence of coronary heart disease. *Am J Cardiol* 86:897–902, 2000
12. Milan Study on Atherosclerosis and Diabetes (MiSAD) Group: Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic risk factors in noninsulin-dependent diabetes mellitus. *Am J Cardiol* 79:134–139, 1997
13. Koistinen MJ, Huikuri HV, Pirttiaho H, Linnaluoto MK, Takkunen JT: Evaluation of exercise electrocardiography and thallium tomographic imaging in detecting asymptomatic coronary artery disease in diabetic patients. *Br Heart J* 63:7–11, 1990
14. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V: Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care* 22: 1396–1400, 1999
15. May O, Arildsen H, Damsgaard EM, Mickley H: Prevalence and prediction of silent ischaemia in diabetes mellitus: a population-based study. *Cardiovasc Res* 34:241–247, 1997
16. Naka M, Hiramatsu K, Aizawa T, Momose A, Yoshizawa K, Shigematsu S, Ishihara F, Niwa A, Yamada T: Silent myocardial ischemia in patients with non-insulin-dependent diabetes mellitus as judged by treadmill exercise testing and coronary angiography. *Am Heart J* 123:46–53, 1992
17. Koistinen MJ: Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. *BMJ* 301:92–95, 1990
18. Cullom SJ: Principles of cardiac SPECT imaging. In *Cardiac SPECT Imaging*. 2nd ed. DePuey EG, Garcia EV, Berman DA, Eds. Philadelphia, Lippincott, Williams and Wilkins, 2001, p. 25–48
19. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, Van Train KF, Berman DS: Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 36:2138–2147, 1995
20. Sharir T, Berman DS, Lewin HC, Friedman JD, Cohen I, Miranda R, Agafitei RD, Germano G: Incremental prognostic value of rest-redistribution (201) Tl single-photon emission computed tomography. *Circulation* 100:1964–1970, 1999
21. Shanoudy H, Raggi P, Beller GA Soliman A, Ammermann EG, Kestner R, Watson DD: Comparison of ^{99m}Tc-Tetrofosmin and ^{201}Thallium SPECT imaging for detection of myocardial perfusion defects in patients with coronary artery disease. *J Am Coll Cardiol* 31:331–337, 1998
22. Mehta D, Iskandrian AE: Myocardial viability: nuclear assessment. *Echocardiography* 22:155–164, 2005
23. Wackers 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
24. Kang X, Berman DS, Lewin H, Miranda R, Erel J, Friedman JD, Amanullah AM: Comparative ability of myocardial perfusion single-photon emission computed tomography to detect coronary artery disease in patients with and without diabetes mellitus. *Am Heart J* 137:949–957, 1999
25. De 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
26. Kang X, Berman DS, Lewin HC, Cohen I, Friedman JD, Germano G, Hachamovitch R, Shaw LJ: Incremental prognostic value of myocardial perfusion single photon emission computed tomography in patients with diabetes mellitus. *Am Heart J* 138:1025–1032, 1999
27. Berman DS, Kang X, Hayes SW, Friedman JD, Cohen I, Abidov A, Shaw LJ, Amanullah AM, Germano G, Hachamovitch R: Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men: impact of diabetes mellitus on incremental prognostic value and effect on patient management. *J Am Coll Cardiol* 41:1125–1133, 2003
28. Giri 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
29. Rajagopalan 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
30. Penfornis A, Zimmermann C, Boumal D, Sabbah A, Meneveau N, Gaultier-Bourgeois S, Bassand JP, Bernard Y: Use of dobutamine stress echocardiography in detecting silent myocardial ischaemia in asymptomatic diabetic patients: a comparison with thallium scintigraphy and exercise testing. *Diabet Med* 18:900–905, 2001
31. Marwick TH, Case C, Sawada S, Vasey C, Short L, Lauer M: Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. *Diabetes Care* 25: 1042–1048, 2002
32. Bigi R, Desideri A, Cortigiani L, Bax JJ, Celegon L, Fiorentini C: Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. *Diabetes Care* 24:1596–1601, 2001

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33. Rumberger JA, Sheedy PF 2nd, Breen JF, Fitzpatrick LA, Schwartz RS: Electron beam computed tomography and coronary artery disease: scanning for coronary artery calcification. *Mayo Clin Proc* 71:369–377, 1996
34. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R: Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 15:827–832, 1990
35. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W, Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT: From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation* 108:1772–1778, 2003
36. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM: Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 20:1262–1275, 2000
37. Mielke CH, Shields JP, Broemeling LD: Coronary artery calcium, coronary artery disease, and diabetes. *Diabetes Res Clin Pract* 53:55–61, 2001
38. Khaleeli 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
39. Schurgin S, Rich S, Mazzone T: Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care* 24:335–338, 2001
40. He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, Mahmarian JJ: Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 101:244–251, 2000
41. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, Zelinger A, Mahmarian JJ: Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 101: 850–855, 2000
42. Rumberger JA, Brundage BH, Rader DJ, Kondos G: Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clin Proc* 74:243–252, 1999
43. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
44. Raggi 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
45. Qu W, Le TT, Azen SP, Xiang M, Wong ND, Doherty TM, Detrano RC: Value of coronary artery calcium scanning by computed tomography for predicting coronary heart disease in diabetic subjects. *Diabetes Care* 26:905–910, 2003
46. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ: Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. *N Engl J Med* 339:1972–1978, 1998
47. Raggi P, Callister TQ, Shaw LJ: Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. *Arterioscler Thromb Vasc Biol* 24:1272–1277, 2004
48. Raggi P, Cooil B, Ratti C, Callister TQ, Budoff M: Progression of coronary calcification and occurrence of myocardial infarction in patients with and without diabetes mellitus. *Hypertension* 46:238–243, 2005
49. Dabelea D, Kinney G, Snell-Bergeon JK, Hokanson JE, Eckel RH, Ehrlich J, Garg S, Hamman RF, Rewers M: Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. *Diabetes* 52:2833–2839, 2003
50. Colhoun HM, Schalkwijk C, Rubens MB, Stehouwer CD: C-reactive protein in type 1 diabetes and its relationship to coronary artery calcification. *Diabetes Care* 25: 1813–1817, 2002
51. Starkman HS, Cable G, Hala V, Hecht H, Donnelly CM: Delineation of prevalence and risk factors for early coronary artery disease by electron beam computed tomography in young adults with type 1 diabetes. *Diabetes Care* 26:433–436, 2003
52. Hokanson JE, Cheng S, Snell-Bergeon JK, Fijal BA, Grow MA, Hung C, Erlich HA, Ehrlich J, Eckel RH, Rewers M: A common promoter polymorphism in the hepatic lipase gene (LIPC-480C>T) is associated with an increase in coronary calcification in type 1 diabetes. *Diabetes* 51:1208–1213, 2002
53. Snell-Bergeon JK, Hokanson JE, Jensen L, MacKenzie T, Kinney G, Dabelea D, Eckel RH, Ehrlich J, Garg S, Rewers M: Progression of coronary artery calcification in type 1 diabetes: the importance of glycemic control. *Diabetes Care* 26:2923–2928, 2003
54. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ: Coronary calcium in adults with type 1 diabetes: a stronger correlate of clinical coronary artery disease in men than in women. *Diabetes* 49: 1571–1578, 2000
55. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 74: 1399–1406, 1986
56. Wong M, Edelstein J, Wollman J, Bond MG: Ultrasonic-pathological comparison of the human arterial wall: verification of intima-media thickness. *Arterioscler Thromb* 13: 482–486, 1993
57. Persson J, Formgren J, Israelsson B, Berglund G: Ultrasound-determined intima-media thickness and atherosclerosis: direct and indirect validation. *Arterioscler Thromb* 14:261–264, 1994
58. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 340: 14–22, 1999
59. Chambless 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
60. Hodis 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
61. Bots 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
62. Wofford JL, Kahl FR, Howard GR, McKinney WM, Toole JF, Crouse JR 3rd: Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. *Arterioscler Thromb* 11:1786–1794, 1991
63. Holaj R, Spacil J, Petrasek J, Malik J, Haas T, Aschermann M: Intima-media thickness of the common carotid artery is the significant predictor of angiographically proven coronary artery disease. *Can J Cardiol* 19:670–676, 2003
64. Mitsuhashi N, Onuma T, Kubo S, Takayanagi N, Honda M, Kawamori R: Coronary artery disease and carotid artery intima-media thickness in Japanese type 2 diabetic patients. *Diabetes Care* 25:1308–

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1312, 2002
65. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M: Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA_{1c} level. *Diabetes Care* 23:1830–1834, 2000
66. Teno S, Uto Y, Nagashima H, Endoh Y, Iwamoto Y, Omori Y, Takizawa T: Association of postprandial hypertriglyceridemia and carotid intima-media thickness in patients with type 2 diabetes. *Diabetes Care* 23:1401–1406, 2000
67. Guvener N, Tutuncu NB, Oto A, Erbas T: Major determinants of the carotid intima-media thickness in type 2 diabetic patients: age and body mass index. *Endocr J* 47:525–533, 2000
68. Yamamoto M, Egusa G, Yamakido M: Carotid atherosclerosis and serum lipoprotein(a) concentrations in patients with NIDDM. *Diabetes Care* 20:829–831, 1997
69. Agewall S, Wikstrand J, Ljungman S, Fagerberg B: Urinary albumin excretion is associated with the intima-media thickness of the carotid artery in hypertensive males with non-insulin-dependent diabetes mellitus. *J Hypertens* 13:463–469, 1995
70. Mykkanen L, Zaccaro DJ, O'Leary DH, Howard G, Robbins DC, Haffner SM: Microalbuminuria and carotid artery intima-media thickness in nondiabetic and NIDDM subjects: the Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 28: 1710–1716, 1997
71. Leinonen ES, Hiukka A, Hurt-Camejo E, Wiklund O, Sarna SS, Mattson Hulten L, Westerbacka J, Salonen RM, Salonen JT, Taskinen MR: Low-grade inflammation, endothelial activation and carotid intima-media thickness in type 2 diabetes. *J Intern Med* 256:119–127, 2004
72. Hayaishi-Okano R, Yamasaki Y, Katakami N, Ohtoshi K, Gorogawa S, Kuroda A, Matsuhisa M, Kosugi K, Nishikawa N, Kajimoto Y, Hori M: Elevated C-reactive protein associates with early-stage carotid atherosclerosis in young subjects with type 1 diabetes. *Diabetes Care* 25:1432–1438, 2002
73. Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R, Falezza G, Muggeo M: Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients: relationship with insulin resistance. *Diabetes Care* 20:627–631, 1997
74. Folsom 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
75. Espeland MA, Evans GW, Wagenknecht LE, O'Leary DH, Zaccaro DJ, Crouse JR, Howard G, Haffner SM: Site-specific progression of carotid artery intimal-medial thickness. *Atherosclerosis* 171:137–143, 2003
76. Wagenknecht LE, D'Agostino RB Jr, Haffner SM, Savage PJ, Rewers M: Impaired glucose tolerance, type 2 diabetes, and carotid wall thickness: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 21:1812–1818, 1998
77. Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O'Leary DH, Haffner SM: Diabetes and progression of carotid atherosclerosis: the Insulin Resistance Atherosclerosis Study. *Arterioscler Thromb Vasc Biol* 23:1035–1041, 2003
78. Wagenknecht 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
79. Yamasaki 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
80. Frost D, Friedl A, Beischer W: Determinants of early carotid atherosclerosis progression in young patients with type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 110:92–94, 2002
81. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF: Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 357:577–581, 2001
82. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 110:3512–3517, 2004
83. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN: ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 106:2055–2060, 2002
84. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G: Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation* 103:1721–1726, 2001
85. Furberg CD, Adams HP Jr, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA, et al.: Effect of lovastatin on early carotid atherosclerosis and cardiovascular events: Asymptomatic Carotid Artery Progression Study (ACAPS) research group. *Circulation* 90:1679–1687, 1994
86. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S: Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 348: 2294–2303, 2003
87. Fiorina P, Folli F, Bertuzzi F, Maffi P, Finzi G, Venturini M, Socci C, Davalli A, Orsenigo E, Monti L, Falqui L, Uccella S, La Rosa S, Usellini L, Properzi G, Di Carlo V, Del Maschio A, Capella C, Secchi A: Long-term beneficial effect of islet transplantation on diabetic macro-/microangiopathy in type 1 diabetic kidney-transplanted patients. *Diabetes Care* 26: 1129–1136, 2003
88. Beishuizen ED, van de Ree MA, Jukema JW, Tamsma JT, van der Vijver JC, Meinders AE, Putter H, Huisman MV: Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care* 27:2887–2892, 2004
89. Collins R, Armitage J, Parish S, Sleigh P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361: 2005–2016, 2003
90. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364:685–696, 2004
91. Kodama M, Yamasaki Y, Sakamoto K, Yoshioka R, Matsuhisa M, Kajimoto Y, Kosugi K, Ueda N, Hori M: Antiplatelet drugs attenuate progression of carotid intima-media thickness in subjects with type 2 diabetes. *Thromb Res* 97:239–245, 2000
92. Ahn CW, Lee HC, Park SW, Song YD, Huh KB, Oh SJ, Kim YS, Choi YK, Kim JM, Lee TH: Decrease in carotid intima media thickness after 1 year of cilostazol treatment in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 52:45–53, 2001
93. Raggi P, Berman DS: Computed tomography coronary calcium screening and myocardial perfusion imaging. *J Nucl Cardiol* 12:96–103, 2005

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