

Cardiovascular Disease in Diabetes

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This article is based on presentations addressing aspects of cardiovascular disease in diabetic patients at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007, in Chicago, Illinois; at the 55th Annual Advanced Postgraduate Course, 1–3 February 2008, in San Francisco, California (the course is available online at <http://professional.diabetes.org>); and at the Mount Sinai Medical Center Diabetes Grand Rounds, 14 February 2008, in New York, New York.

Evaluation of coronary artery disease

At a symposium on the evaluation of cardiac ischemia and macrovascular disease in patients with diabetes held at the American Diabetes Association (ADA) meeting, Theodore Mazzone (Chicago, IL) discussed approaches to subclinical ischemia in diabetes. There is a well-established relationship between diabetes and adverse outcome, as first demonstrated in the East-West Study of a Northern European population with a 3.5% 7-year cardiovascular disease (CVD) mortality rate among nondiabetic individuals without a history of myocardial infarction. Subjects with a history of myocardial infarction had an 18.8% risk, while those without a history of myocardial infarction but with a history of diabetes had a 20.2% 7-year risk (1), forming the basis of the

argument that type 2 diabetes is a coronary artery disease (CAD) equivalent. Subsequent trials comparing diabetic patients without known CVD to nondiabetic patients with CVD, Mazzone stated, have confirmed that “the risk is pretty close in most populations.” Schramm et al. (abstract 692) presented an interesting view of this phenomenon at the ADA meeting, stratifying the 5-year combined rate of myocardial infarction, stroke, and CVD death by age among 3,274,479 men and women in Denmark followed from 1997 to 2001. There was striking similarity of event rates in both sexes and at all ages among 79,574 nondiabetic individuals with past myocardial infarction compared with those among 71,801 individuals with diabetes alone. In the East-West Study, those with both a history of diabetes and prior myocardial infarction had a striking increase in 7-year risk to 45%, with the Danish study similarly showing markedly increased event rates among diabetic patients with a history of myocardial infarction. Mazzone suggested, however, that one must be cautious in assuming that most individuals with type 2 diabetes “really have CAD,” stating instead that, in a typical individual with diabetes, “we do not know enough.” Furthermore, after a cardiovascular event the biology of the coronary circulation may change such that it is difficult to readily quantitate the “amount of CAD.” (Abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007.)

Mazzone reviewed data from the Framingham Offspring Study, in which the relationship between CVD event rates and abnormalities of the electrocardiogram, echocardiogram, ankle-brachial index, carotid ultrasound, and level of albuminuria were assessed. Eighty-seven percent of diabetic subjects had at least one abnormal test. While these markers of occult

disease were associated with increased risk, the increased event rates among diabetic patients were not fully explained when these measures were taken into account. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study of 522 diabetic individuals with average age 60 years and diabetes duration 8 years, 21% of whom had a history of CAD, sestamibi single-photon emission-computed tomography myocardial perfusion imaging (SPECT) stress testing was abnormal in only 113, of whom 30 had global left ventricular dysfunction and 83 showed a regional perfusion deficit, of moderate or large size in 33 (2).

Is it, then, possible to stratify patients to increase the likelihood of a positive test? Existing predictive equations, such as the Framingham Risk Score and that developed specifically for diabetic patients from the DECODE (Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe) study data, either under- or overestimate risk of fatal CAD by 20–50% when applied to the UK Prospective Diabetes Study (UKPDS) population. Perhaps, Mazzone suggested, LDL and HDL cholesterol, A1C, age, and sex may not be sufficiently precise predictors of CVD event rates. The increased atherosclerosis in diabetes may be related to glycosylated proteins in the vessel wall; to the proinflammatory, procoagulant state of insulin resistance; or to specific elements of diabetic dyslipidemia (such as low HDL cholesterol or the elevated levels of free fatty acids; small, dense LDL; and large, cholesterol ester-rich VLDL particles) (3). Studies of atherectomy specimens from diabetic versus nondiabetic individuals show more macrophages, a larger and more necrotic lipid core, and more superimposed thrombus. In Mazzone's study of potential explanatory factors for coronary artery calcification, however, risk was, again, only predicted by the traditional factors of age, sex, race/ethnicity, systolic blood pressure, and VLDL cholesterol (with most of the patients receiving statins, LDL level was not a significant predictor).

The current ADA recommendations are that cardiac stress testing is warranted for diabetic patients with typical or atypical symptoms and those with an abnormal resting electrocardiogram, with screening not currently recommended for

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Abbreviations: ADA, American Diabetes Association; apo, apolipoprotein; CAD, coronary artery disease; CETP, cholesterol ester transfer protein; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; IMT, intima-media thickness; PET, positron emission tomography; SPECT, single-photon emission-computed tomography myocardial perfusion imaging; UKPDS, UK Prospective Diabetes Study.

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asymptomatic patients (4). Mazzone questioned whether there is evidence that screening will lead to an intervention that will improve outcome. In a trial of nondiabetic patients with CAD, percutaneous coronary intervention plus medical treatment was not different from intensive medical treatment alone in risk of death, myocardial infarction, or other major cardiovascular events (5). "What do we do," Mazzone asked, "when we screen an asymptomatic diabetic patient?" If there is no evidence that percutaneous coronary intervention improves outcome and if there is no strategy clearly differentiating whether a given diabetic patient is at low or high risk, he suggested, "we are left with medical therapy for asymptomatic diabetic patients." The only medical therapy recommendation for which CAD status is considered is the lower LDL cholesterol goal for individuals with established CAD. In most ways, Mazzone suggested, the asymptomatic diabetic patient found to have CAD more resembles one without than one with symptomatic CAD. "Widespread screening," he commented, "will be very expensive and will lead to interventions that will also be very expensive," as well as being associated with substantial risk of restenosis and other procedure-related complications. "We're left with assessing CV risk using the standard risk factors," with the A1C goal <7% the one "for which we have less unequivocal evidence."

Gary Balady (Boston, MA) discussed use of exercise electrocardiography and echocardiography in diabetic patients, noting that stress testing is designed to determine whether there are areas of decreased arterial supply under circumstances of increased demand. A measure of myocardial demand is the product of heart rate and systolic blood pressure, with myocardial wall stress related to ventricular diameter, pressure, and wall thickness and myocardial contractility, the per beat degree of myocardial shortening, also contributing. With graded increments in exercise, heart rate and systolic blood pressure increase to a goal 85% of maximal heart rate, estimated as 220 minus years of age, as lower achieved heart rates may result in falsely negative tests. Ischemic ST depression, either horizontal or downsloping, is measured in millimeters from the PR segment. The sensitivity of the electrocardiogram is lower for inferior or inferolateral ischemia than for ischemia in the distribution of the left coronary artery.

Age, sex, and symptoms are used in assessing the a priori likelihood that a person has significant CAD, but these features are less useful in the diabetic patient, given the greater likelihood of CAD in diabetic women, the occurrence of CAD in diabetic patients at younger ages, and the higher prevalence of asymptomatic CAD in diabetic patients in general. A coronary arteriogram is considered appropriate for distinguishing true- and false-positive and -negative stress testing, but typically it is carried out in individuals who have a positive test and are clinically at high risk, leading to overestimation of sensitivity and underestimation of specificity. In fact, Balady suggested, the sensitivity and specificity of the exercise electrocardiogram are <70% (6). Furthermore, he agreed with Mazzone that one must question the effectiveness of intervention based on a positive test. It may be more important that a negative test be associated with good prognosis. Exercise capacity is a further independent prognostic factor, as is heart rate recovery after exercise, with a pulse decrease by <12 bpm in the first minute associated with increased mortality (7). In a study presented at the ADA meeting, Johansen et al. (abstract 635) found abnormal coronary angiography in 23 of 91 asymptomatic type 2 diabetic patients, showing sensitivity of 0.35 with specificity 0.68 for exercise electrocardiography with ≥ 1 mm ST segment depression and sensitivity of 0.30 with specificity 0.72 for abnormal dobutamine stress echocardiography. Sensitivity was 0.45 with specificity 0.84 when the degree of ST depression was adjusted for the heart rate and was 0.85, with specificity 0.39, for an abnormal heart rate recovery pattern, supporting Balady's view. He suggested that the exercise test can be improved by use of echocardiography, which may show wall motion abnormalities in the inferior portion of the heart and which is useful in patients with left bundle branch block or ST segment depression at rest. The likelihood of events is low for the first few years after a negative study, although after several years risk increases, and there is uncertainty about the interval after which repeat testing should be performed. The diagnostic value of the stress echocardiogram has not, however, been assessed in diabetic patients.

Marcelo Di Carli (Boston, MA) discussed nuclear imaging in diabetic patients, reviewing the high prevalence of CAD in asymptomatic diabetic patients. An autopsy study from the Mayo Clinic

showed that, among individuals with diabetes and without clinical CAD, half had significant disease, which was severe in one-third. Another Mayo Clinic study of asymptomatic diabetic patients showed that half had an abnormal nuclear scan, with scans in 20% showing a high-risk pattern, considerably exceeding the 6% estimate from the DIAD study discussed above. The conventional SPECT study and the newer positron emission tomography (PET) study are aimed to assess myocardial perfusion, with the latter appearing to be more specific, as it also gives information about changes in ventricular function similar to that found with the stress echocardiogram. Assessment of change in the ejection fraction with stress PET gives additional information pertaining to the extent of coronary disease, and PET is more accurate than SPECT imaging in obese patients and in women with large breast size. As with the stress electrocardiogram or echocardiogram, a normal nuclear imaging study implies good prognosis and would justify not performing catheterization, although Di Carli commented that the nuclear data should be seen as additive to the clinical data. As with stress echocardiography, risk increases several years after a normal study. Reversibility of ischemia may guide decision making as to which patient will derive benefit from an intervention, as benefit of revascularization is only demonstrable in individuals with large areas of reversible ischemia (8), although as yet no clinical trial data supports this. Di Carli noted that the symptom of dyspnea is associated with particularly high risk and may justify cardiac imaging and also suggested that coronary calcification assessment may be a useful screening tool to determine the likelihood of a positive stress test.

Paolo Raggi (New Orleans, LA) discussed the use of coronary artery calcium measurement as a marker for the development of clinical CAD among diabetic patients, complementary to "ischemia imaging" approaches (9). Inflammation leads to formation of osteoblast-like cells from vascular smooth muscle cells in the arterial wall, activated by advanced glycation end products, potentially altering vascular function. There are a variety of genetic and environmental factors leading to atherosclerosis and to coronary calcification in particular, with the metabolic syndrome showing stronger association with the coronary calcium score than does hyperglycemia alone.

NEWS FROM THE FOOD AND DRUG ADMINISTRATION

From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.

Issues pertaining to regulation of direct-to-consumer (DTC) advertising, including how it relates to communication with subsets of the general population such as the elderly, children, and racial and ethnic minority communities, remain important to the FDA. The Risk Communication Advisory Committee held a hearing on the topic on 15 May 2008. The serious attention being paid to this topic is exemplified in a warning letter sent to Pfizer on 16 April 2008 regarding DTC advertising for sildenafil (Viagra) reminding the company that some television advertisements have not included warnings about potential adverse effects of sexual activity in individuals with cardiovascular disease and about the potential risks of priapism, non-arteritic anterior ischemic optic neuropathy, and hearing loss associated with use of the agent.

On 27 March 2008, the FDA warned consumers that two products, "Total Body Formula" in Tropical Orange and Peach Nectar flavors and "Total Body Mega Formula" in the Orange/Tangerine flavor, had been sold with hazardous levels of selenium, causing hair loss, muscle cramps, diarrhea, joint pain, deformed fingernails, and fatigue after 5–10 days of use. Many multivitamin supplements contain selenium, with a report last year showing that supplementation of 200 μg daily (twice the recommended daily allowance) is associated with more than a doubling of diabetes risk (Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, Cappuccio FP, Ceriello A, Reid ME: Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med* 147:217-223, 2007). An addendum on 1 May 2008 also noted that toxic levels of chromium were found in these products, suggesting the importance of careful screening of dietary supplements used by patients with diabetes.

Raggi noted that outcome is worse in diabetic than in nondiabetic individuals after intervention, both with bypass and with angioplasty, and at all levels of ischemia, certainly including individuals without evidence of ischemia. However, he also noted that not all diabetic patients are the same and suggested that the concept of diabetes as a CVD risk equivalent is somewhat of an overestimation. Thus, screening is crucial in differentiating higher- from lower-risk diabetic patients. "Calcium," he said, "has been one of the very debated markers," and although "the calcified plaque may be stable, the calcified patient may not be stable," with a high coronary calcium score therefore indicating an individual with a greater degree of atherosclerosis—both occlusive and nonocclusive. In a study of individuals who had cardiac catheterization, coronary calcification scores were more strongly predictive than stenosis of mortality in follow-up. Both the Framingham category and the coronary calcification score are useful in defining risk, and diabetic patients with a low coronary calcium score are at relatively low risk.

When comparing the UKPDS score and Framingham Risk Score with the coronary calcium level, the latter is the more powerful risk marker.

Raggi acknowledged that evidence is lacking that screening for CAD prevents adverse outcome, while pointing out that individuals with mild-to-moderate non-obstructive atherosclerosis will not have evidence of ischemia but are at risk of coronary thrombosis. Furthermore, abnormality of sympathetic tone in the setting of autonomic neuropathy may make a stress test difficult to interpret, perhaps leading to higher false-positive rates in diabetic patients. Ideally, screening should identify individuals who would benefit from intervention; Raggi suggested that at present "there's no clarity in the field," considering the ADA recommendations for screening too restrictive because they require symptoms or evidence of disease in other vascular beds. Although there is no answer as to whether the approach is cost-effective, he suggested that coronary calcium score or, alternatively, carotid intima-media thickness (IMT) measurement might be valid approaches to

noninvasive ascertainment of risk levels in diabetic patients.

CVD prevention

At the Postgraduate Course, Alan Chait (Seattle, WA) reviewed approaches to CVD prevention. Chait noted that there are limited data regarding benefits of glycemic control in reducing CVD. Follow-up of the Diabetes Control and Complications Trial (DCCT) showed that participants who had prior intensive treatment showed a reduction in CVD (26). Furthermore, epidemiologic analysis of the relationship between CVD and glycemia in the DCCT (10), in the UKPDS (11), and in a meta-analysis of a group of studies (12) suggest that as glucose levels increase there is greater likelihood of CVD. Chait reviewed a number of studies, however, suggesting that the relationship between glycemia and CVD not to be as clear, a situation which has been termed the "glucose paradox." (3) In mice with autoimmune type 1 diabetes not expressing the LDL receptor, he said, "hyperlipidemia completely outweighed the effects of glucose." (13) The 16% decrease in myocardial infarction in the UKPDS failed (though barely) to reach statistical significance, and stroke was nonsignificantly increased by 11%. (14) There was a significant 39% decrease in myocardial infarction and a 41% decrease in stroke with metformin monotherapy, although in the same study the combination of metformin with a sulfonylurea led to significantly more deaths than a sulfonylurea alone, as well as to a nonsignificant increase in diabetes-related events (15). A controversial meta-analysis suggested an increased risk of CVD in individuals receiving rosiglitazone (16), although the number of events was small, events were not adjudicated, and incorrect statistical approaches may have been used, with re-analyses of the data not confirming the significance of the association (17,18). CVD reduction may be seen with pioglitazone (19), but both thiazolidinediones increase heart failure, and neither is associated with reduction in cardiovascular mortality (20). Chait asked, "How do we get a solution to this confusion?" It may be, he suggested, that glycemic treatment should not be carried out with a view to reduction in CVD.

The prevalence of CAD is increased in individuals with metabolic syndrome without diabetes but not in those having diabetes without metabolic syndrome (21), and others have shown that the met-

abolic syndrome adds risk to that associated with hyperglycemia (22). Metabolic syndrome, then, may be considered a susceptibility syndrome in which visceral adiposity leads to a constellation of risk factors, not all of which are included in the current definition of the syndrome. Chait considered dyslipidemia the critical component, including elevations in triglycerides and borderline elevations in LDL cholesterol with high apolipoprotein (apo)B and low HDL cholesterol levels. Lipoprotein analysis shows high VLDL, with accumulation of remnants, including abnormal VLDL and IDL particles, as well as small, dense LDL and abnormal HDL particles containing apoA1 without apoAII in the HDL2 fraction. The primary approach of treatment has been to lower LDL cholesterol, although, paradoxically, LDL cholesterol level is not the primary abnormality in diabetic dyslipidemia.

In the Heart Protection Study, simvastatin reduced events by ~25% in all subgroups (23). Subset analysis showed similar benefit in individuals with diabetes with or without CHD, with low or high HDL, and with high or low triglyceride levels. In a meta-analysis, statins were associated with reduced CVD mortality in both type 1 and type 2 diabetes (24). Increased CVD risk in individuals with type 1 diabetes was particularly present in the DCCT among those with components of metabolic syndrome under circumstances of intensive insulin treatment (25) and those with increased urine albumin (26) and might also be anticipated in those with CVD risk factors unrelated to diabetes.

An area of great interest has been the development of combination lipid treatment approaches to complement the benefit of statins. Certainly, there is a direct relationship between LDL cholesterol and event rates (27), leading Chait to suggest that “any form of LDL lowering is associated with benefit.” The VA-HIT (Veterans Affairs High-Density Lipoprotein Intervention Trial) (28) showed that gemfibrozil reduced CVD mortality, nonfatal myocardial infarction, and stroke by 24% both in individuals with and without diabetes, but the large FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study found a nonsignificant 11% decrease in coronary events and a nonsignificant 11% increase in coronary mortality, with increased venous thromboembolic disease and adverse renal effect (29), so the important ques-

tion of whether fibrates have benefit additive to that of statins has not been answered, although coming trials should help address this. The combination of simvastatin with niacin lowered LDL cholesterol and triglyceride and raised HDL cholesterol, with angiographic benefit as well as a significant reduction in clinical events in a small angiographic study (30). Niacin also reduced events in the Coronary Drug Project (31) and is not as likely to worsen glycemia as previously thought, with large clinical trials underway to provide further information about this important agent.

HDL mediates reverse cholesterol transport to the liver, but blockade of cholesterol ester transfer protein (CETP) with torcetrapib, although increasing HDL levels, led to increased mortality, myocardial infarction, angina, and heart failure—perhaps because of a drug-specific off-target effect in increasing blood pressure or perhaps by generating dysfunctional HDL (32). Chait commented, “HDL is incredibly complicated,” noting the myriad of proteins present in HDL and its many functions beyond that of reverse cholesterol transport, including anti-inflammatory and antioxidant effects as part of the innate immune system, such that approaches to reduce CETP activity may be inherently flawed (33).

The association of blood pressure with adverse outcome has particularly been shown in individuals with diabetes (34), and there is particularly good evidence of benefit of aggressive blood pressure-lowering treatment for diabetic individuals, with the Hypertension Optimal Treatment study showing a 66% CVD risk reduction (35), and much reduction in stroke, heart failure, and microvascular end points, though with “no real [CAD] benefit,” in the blood pressure treatment substudy of the UKPDS (36). The benefit of aspirin in diabetic patients was shown in the Bezafibrate Infarction Prevention study (37) and in the Antiplatelet Trialists’ Collaboration (38). “Finally,” Chait asked, “where does adiposity fit in?” He noted, “If you block adiposity, you could probably block all of the downstream events.” (39,40) Given these considerations, Chait suggested that, particularly in light of the Steno-2 trial (41), one should offer all individuals with diabetes the benefit of intensive treatment with statins, angiotensin-directed antihypertensive agents, and aspirin, as well as

endeavor to maintain adequate glycemic control.

ApoB

At the Postgraduate Course, Allan Sniderman (Montreal, Canada) asked whether we are “measuring the right things” in assessing dyslipidemia, suggesting that apoB is a better index of the concentration of atherogenic lipids in plasma and, therefore, a better target than LDL cholesterol or non-HDL cholesterol (42,43). The atherosclerotic lesion, he said, is not simply a pool of cholesterol in the arterial wall but a complex biologic response to the trapping of an apoB particle with both protective fibroproliferative and harmful immunoinflammatory responses. The key initiating event is the entry and trapping of an apoB lipoprotein particle, typically though not always LDL, with subsequent oxidation of its cholesterol, apoB, and phospholipid coat, leading to the accumulation of lipids, particularly cholesterol, in macrophages, with immune-mediated inflammation gradually eroding the protective fibrous cap, leading to acute thrombosis.

LDL cholesterol refers to the cholesterol mass within LDL and IDL particles and non-HDL cholesterol to the cholesterol mass within all apoB-containing particles. The number of LDL particles is ~9 times greater than that of VLDL particles, and LDL particles are substantially smaller, such that LDL is the dominant atherogenic particle. ApoB can be measured on nonfasting samples because it is driven by LDL particle number. LDL remodeling involves cholesterol ester-triglyceride exchange and hydrolysis via CETP, with cholesterol ester moving from LDL to VLDL and triglyceride from VLDL to LDL, the triglyceride-enriched LDL then hydrolyzed to smaller, denser particles, each still containing one apoB molecule.

Sniderman showed a compilation of 18 studies that have prospectively evaluated apoB vs. LDL, all showing the former to be more strongly associated with CVD. Analyses of the Framingham population shows the association of LDL cholesterol with CVD to be insignificant when LDL particle number is a covariate (44). “It is the LDL particle itself which creates the atherogenic lesion in the arterial wall,” Sniderman said, suggesting that neither small nor large particles are preferable; rather, it is the number of particles that is relevant, with apoB the simplest measure of particle number. ApoB measurement is

relatively inexpensive, accurate, and standardized and does not require fasting. Furthermore, standard laboratory measurements do not distinguish patients with normal apoB and high triglyceride levels from those with elevations in both, although only the latter have increased CVD risk. Use of apoB will allow better diagnosis of type III hyperlipidemia, familial combined hyperlipidemia, and familial hypercholesterolemia.

ApoB may be particularly useful in individuals with diabetes for whom the Friedwald equation is incorrect in accurately calculating LDL cholesterol, with the 95% CIs of an LDL of 100 ranging from 69 to 134 mg/dl. Although LDL is not characteristically high in type 2 diabetes, apoB is elevated in the majority of type 2 diabetic individuals, “so this is a major problem in your patients.” A substantial number of diabetic patients have apparently normal lipid profiles, and apoB may explain differences between diabetic populations in macrovascular risk. Women developing diabetes have an increase in apoB, perhaps explaining their particularly greater risk of CVD.

In intervention studies that have compared change in apoB with change in LDL cholesterol or non-HDL cholesterol, Sniderman said, “the evidence supports” apoB as a better target. He showed an analysis of 11 studies comprising 17,731 individuals undergoing statin treatment, in whom LDL cholesterol decreased by 42%, non-HDL cholesterol 40%, and apoB 30%. Because statins reduce cholesterol to a greater extent than triglycerides, the relatively higher triglyceride level after statin treatment tends to lead to smaller particles, potentially further increasing the “treatment gap” in the three measures. ApoB, he said, correlates more strongly with markers of inflammation and of glycemia. The LDL cholesterol treatment targets of 70 and 100 mg/dl and the non-HDL cholesterol treatment targets of 100 and 130 mg/dl represent the 10th and 25th population percentiles. Extrapolating from this, he recommended that individuals at high and intermediate risk should have apoB treatment targets of 80 and 90 mg/dl, an approach that might better reduce atherogenic particle number and “make your clinical path much simpler.”

Diabetes and stroke

At the Mount Sinai conference, Jesse Weinberger (New York, NY) discussed the interrelationships between diabetes

and stroke. He pointed out that stroke is the leading cause of long-term morbidity and the third leading cause of death in the US and, because of its higher frequency in Asia, the second leading cause of death worldwide. Hemorrhagic stroke, mainly from hypertension, comprises ~15%, with ischemic stroke making up the remaining 85% potentially caused by atherosclerosis alone, by emboli as seen with atrial fibrillation and heart failure, and by a variety of other conditions. Risk factors for stroke include blood pressure, cigarette use, alcohol excess, and diabetes. Insulin resistance is associated with stroke. A variety of measures, including proinsulin, fasting insulin, postload insulin, and the proinsulin-insulin and insulin-to-glucose ratio are stroke risk factors (45–49), and obesity is associated with stroke outcome. In the NOMAS (Northern Manhattan Stroke) study of 3,298 stroke-free individuals, 44% had metabolic syndrome, which was associated with a 1.5-fold increase in stroke risk (50).

Diabetes is associated with intracranial arterial abnormalities and with small artery nonatherosclerotic disease, due to lipohyalinosis associated with fibrin deposition around the narrowed artery, similar in some ways to the pathology of diabetic glomerular disease, contributing to lacunar stroke and ultimately causing multi-infarct dementia. In an aside about whether carotid IMT has been validated as an intermediate measure to be used as a proxy for outcome, Weinberger noted that IMT can be seen as a marker of the presence of foam cells, representing a stage in the evolution of atherosclerosis before appearance of plaque, explaining some of the confusing data about whether it is useful in predicting outcome.

A number of treatment approaches have been validated for stroke prevention in diabetic patients. Antiplatelet treatment has been of great importance. Aspirin shows similar benefit in the overall population in doses from 50–600 mg daily, although there is some evidence of resistance to aspirin and other antiplatelet agents among diabetic patients (51,52). There is evidence that other antiplatelet agents may have greater benefit, with both ticlopidine (53) and the combination of aspirin with dipyridamol (54) showing 20% greater reduction in stroke than seen with aspirin. Such benefit has not been reported in several large studies using clopidogrel (55,56), although studies currently in progress may change this impression. Other treatment approaches

shown to reduce stroke in diabetic patients include statins (57) and blood pressure-lowering treatment, particularly with angiotensin-directed agents (58,59). The Steno-2 study showed benefit of multifactorial intervention (41). In its most recent report, 5 of 80 microalbuminuric diabetic patients with the intensive intervention, but 30 of 80 control subjects, had strokes during >13 year follow-up (60).

Weinberger termed the evidence equivocal that glycemic control reduces stroke, with the UKPDS suggesting not (14) and the DCCT suggesting that there may be such a relationship (26). Metaanalysis of three epidemiologic studies in individuals with type 2 diabetes showed a pooled relative risk for stroke of 17% for each 1% increase in A1C (12). Interestingly, subset analysis of the PROactive study showed pioglitazone to be associated with a 47% reduction in stroke in trial participants with history of a stroke before study entry (61), and there is intriguing evidence that sulfonylureas might have benefit in reducing infarct volume, with the possibility that they have neuroprotective effect (62).

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