Cardiovascular Disease and Diabetes

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This is the fourth in a series of articles covering the 2002 American Diabetes Association Annual Meeting, San Francisco, CA, 14–18 June 2002.

Mortality and morbidity in diabetes

Peter Savage (Ellicott City, MD) discussed secular trends in cardiovascular disease (CVD) among patients with diabetes. Two-thirds to three-quarters of patients with diabetes will eventually die of CVD. Diabetes is becoming more important as a cause of CVD in the population because of its increasing prevalence, due to the high incidence in minority populations and the increasing obesity of the population. The "key question," Savage stated, is whether persons with diabetes are different from those without diabetes in not enjoying the same decline in CVD that has been seen in the overall population over the past 50 years, presumably reflecting a variety of advances in the treatment of risk factors. In a study of time trends in mortality in U.S. adults between surveys in 1971–1975 and in 1982–1984, diabetic men had a decline of 13% in age-adjusted CVD mortality, while that for nondiabetic men was 36%, and diabetic women had an increase of 23%, while women without diabetes had a decline in CVD mortality of 27% (1). Although microvascular disease is relatively specific for diabetes, macrovascular disease appears as an acceleration of the illness seen in persons without diabetes. High LDL is a risk factor in those with and without diabetes, but persons with diabetes tend to have low HDL, high triglyceride, and abnormal LDL particle size. They have the hypertension of the insulin resistance syndrome, which becomes exacerbated with renal disease (and diabetic patients with renal disease have extraordinarily high rates of CVD). Diabetes is associated with coagulation abnormalities and inflammation, as well as hyperglycemia, glycation, and secondary effects on CVD risk factors. Insulin resistance and hyperinsulinemia are additional factors in persons with diabetes.

Savage pointed out that persons with diabetes and CVD have poorer overall prognosis, with poorer short-term survival, increased risk of recurrent disease, poorer response to surgery, and increased risk of congestive heart failure (CHF). There are particular problems in minority populations, whose CVD rates appear to be increasing, with diabetes a more important risk factor in these groups. Data are, however, somewhat limited and longitudinal follow-up is particularly difficult to obtain, particularly in view of changing diagnosis and treatment of diabetes and risk factors and given the new classification criteria. In the Framingham Heart Study, assessment of the relative CVD risk of those with diabetes compared with those without in 1956, 1966, 1972, and 1979 suggests little relative change at approximately twice the level seen in nondiabetic individuals. Other studies have shown, however, that death rates from CVD in the U.S. from 1985 to 1999 have declined in nondiabetic men and women in most ethnic groups, though to varying degrees, while there may be an increase in CVD in American Indian populations, perhaps in association with their high prevalence of diabetes.

The effects of treatment of patients with diabetes with statins are similar to those for nondiabetic groups. Blood pressure lowering also appears to convey similar relative benefit to patients with and without diabetes. Thus, CVD risk factor treatment is at least as effective as it is in persons without diabetes, although the greater absolute risk of diabetic subjects gives them greater absolute benefit from the interventions. One difficulty may be that patients with diabetes require such a great deal of preventive treatment; subsequently, their rates of compliance with recommended treatment may be lower than desirable.

The Cardiovascular Health Study showed that rates of glucose, blood pressure, and lipid control, and of aspirin administration for older persons with diabetes, are less likely to be at goal than for those without diabetes (recognizing that goals are stricter for persons with diabetes) (2). Savage concluded that there is only limited evidence that patients with diabetes are benefiting less from the decline in CVD, and that there are some unique aspects of CVD in persons with diabetes that require particular attention. He stated that the "benefit of controlling hyperglycemia on CVD risk remains to be proven," although he believed it was an appropriate goal. He pointed out the importance of aggressive control of known risk factors, the need for heightened provider awareness and effort, and the need for improved health care system support.

Steven Haffner (San Antonio, TX) discussed the primary prevention of CVD in patients with type 2 diabetes. (For a summary of this presentation, see http://diabeteshighlights.org/summary/summary.asp?sid=1&stid=15&ld=2002-06-17.) Levels of prevention can be classified as primary prevention of diabetes itself, secondary prevention of complications in diabetic subjects free of disease, and tertiary prevention of further complications in those persons with diabetes who already have evidence of CVD. Haffner pointed out that there is high out-of-hospital mortality before first myocardial infarction in men with diabetes (3) and increased CVD prior to the onset of type 2 diabetes (4), suggesting that the truly appropriate approach should be diabetes prevention rather than frequent screening and treatment of those persons who have evidence of CVD. Prevention studies include the Da Qing Study (showing 31–46% risk reduction), the Finnish Prevention Study (showing 58% risk re-

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Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass graft; CHF, congestive heart failure; CML, carboxymethyllysine; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DECODE, Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMA, internal mammary artery; LVH, left ventricular hypertrophy; MG, methylglyoxal; NF, nuclear factor; SU sulfonylurea; UKPDS, U.K. Prospective Diabetes Study.

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duction), the Diabetes Prevention Program, and STOP-NIDDM (showing 25% reduction); thus, a variety of approaches may be useful. In addition, there is evidence that pravastatin, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blocker (ARB) treatment may reduce rates of development of diabetes by 25–30%. Two major clinical trials are in progress, the Diabetes REduction Approaches with ramipril and rosiglitazone Medications (DREAM) Study and the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Study, to further address approaches to prevention of diabetes and CVD complications.

Among persons with diabetes, risk factors in the Multiple Risk Factor Intervention Trial (MRFIT) show similar effect, but at higher rates than in persons with diabetes (5). In the U.K. Prospective Diabetes Study (UKPDS), glycemic and blood pressure treatment decreased in microvascular and macrovascular disease. Also, metformin may have led to greater benefit than sulfonylurea (SU) and insulin, but this is unclear as those patients treated with metformin plus SU did less well than those treated with SU alone. Epidemiologic analysis of the UKPDS shows correlations of both hypertension and hyperglycemia with microvascular and macrovascular disease, with the latter group of complications, which are more common, being less affected by glycemia than by hypertension. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) and other studies show that postglucose load hyperglycemia may be particularly disadvantageous, so that the HbA_{1c} alone may be insufficient for fully appreciating the adverse effect of glycemia. Haffner also reviewed data showing that hyperinsulinemia in nondiabetic persons is associated with adverse CVD risk.

Epidemiologic analysis suggests optimal systolic blood pressure levels to be <120 mmHg. Blood pressure treatment is effective, with interesting new data that ARBs may be better than β-blockers in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) study (6). Multivariate analysis of baseline characteristics of patients in the UKPDS shows dyslipidemia to be the major predictor of CVD risk (7). Haffner reviewed the Heart Protection Study, which showed benefit of statins in persons with diabetes, with both LDL cholesterol levels >100 mg/dl and lower LDL cholesterol levels (8). Fibrates have shown benefit in patients with diabetes in the Helsinki Heart Study, the Diabetes Atherosclerosis Intervention Study (DIAS), and the Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT), with coming trials addressing potential benefits of combination treatment with fibrates plus statins. Nicotinic acid, particularly in moderate doses, may offer another approach for lipid treatment for persons with diabetes. The Adult Treatment Panel (ATP) III guidelines suggest that the primary target of therapy to be LDL cholesterol, and considers diabetes to be a CVD risk equivalent, so that the goal for persons with diabetes is LDL <100. After the LDL goal is met, if triglyceride levels exceed 200 mg/dl, lowering the non-HDL cholesterol below 130 mg/dl becomes a secondary target (9). These guidelines also suggest that persons with the metabolic syndrome are at high risk, resulting in a population of ~21 million persons in the U.S. requiring risk factor treatment. This figure is in addition to the 13 million persons with diabetes in the U.S., 90% of whom also have features of insulin resistance. There are interesting studies of the effects of thiazolidinediones on surrogate markers for CVD, and ongoing studies of outcome with these agents will be important.

As goals, Haffner suggested having an HbA_{1c} <7%, or, perhaps, referring to the AACE recommendations, 6.5%; having blood pressure <130/80 mmHg, with ACE inhibitors and ARBs the preferred agents; and having LDL cholesterol <100, HDL cholesterol >45, and non-HDL cholesterol <130 mg/dl. Special interventions to be considered may include attention to postprandial glycemia and use of antioxidants.

Robert Frye (Rochester, MN) discussed secondary prevention of CVD in patients with diabetes, addressing outcomes of coronary revascularization in type 2 diabetes and features of secondary prevention. The Bypass Angioplasty Revascularization Investigation (BARI) compared angioplasty with coronary artery bypass graft (CABG) in patients with multivessel coronary disease who had angina and were eligible for either approach at a time prior to the availability of stents (10). The CABG approach used internal mammary artery (IMA) grafting in 82% of persons treated, with a mean of 3.1 arteries bypassed. For those without diabetes, at 10 years, CABG and PTCA led to virtually identical 78.2 and 76.8% survival in 734 and 742 patients. For those with diabetes, however, the 10-year mortality levels were 57.1 and 44.1%, respectively, in 180 and 173 patients, with all of the excess mortality being due to cardiac disease. Those who did not have an IMA graft, interestingly, did not have the same degree of benefit as those for whom this procedure was performed. Both patients receiving oral agents and those receiving insulin had similar gradient of CABG being better than angioplasty, although the insulin-treated group showed worse outcome. The BARI 2D study has been designed to reduce cardiac mortality in patients with type 2 diabetes through the comparison of aggressive medical therapy with and without immediate revascularization, as there is no proof that the latter improves mortality, and the comparison of insulin sensitizer and secretagogue treatment to reach a goal of an HbA_{1c} <7%.

Helen Vlassara (New York, NY) gave the Edwin Bierman Lecture on genes versus environment in the complications of diabetes. The steep rise in incidence of diabetes with aging (11) and its increase in frequency in the population suggest the importance of assessing the underlying genetic predisposition to diabetes and its complications. Hyperglycemia, via glycation and increase in activity of the protein kinase C pathway, appears to cause oxidative stress. Both proteins and phospholipids are modified by glycation with reducing sugars, and subsequent oxidation may contribute to diabetic complications. A large number of glycated chemical structures exist, with 4-hydroxyhexenal, a precursor to one of the major metabolites of lipid hydroperoxide degradation, and related forms appearing to be important in the reactions. The advanced glycation end products (AGEs) are now seen as rapidly developing inflammatory molecules affecting a variety of target organs. The AGE receptors, AGE-R1, R2, and R3, receptor for AGE (RAGE), and the scavenger receptor, exist in monocyte/macrophages, T-cells, endothelial cells, renal mesangial and tubular cells, fibroblasts, smooth muscle cells, and neuronal and glial cells. AGEs have important interactions with lysozyme, lactoferin, defensins, and galectins, resulting in endocytosis, degradation, and

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signaling increasing levels of reactive oxygen species, inflammation, and vascular permeability, and causing a procoagulant state. It is noteworthy that there are AGE receptor polymorphisms, perhaps explaining variations in susceptibility to complications. AGE-R1 overexpression suppresses nulcear factor (NF)-κB in endothelial cells, so that there may be beneficial and as well as adverse effects of AGEs.

Vlassara noted that AGEs are not only derived from high blood glucose, but also have exogenous sources, absorbed from diet (12) and from cigarette smoke, which leads to glycation of lipids and proteins. Tissue carbonyl-compounds, such as derivatives of carboxymethyllysine (CML) and methylglyoxal (MG), correlate with their dietary loads. In particular, LDL isolated from patients with diabetes after high AGE meals are associated with adverse cellular effects in vitro. Low dietary AGE intake may be shown to decrease type 1 diabetes development in animal models, with a decrease in T-cell numbers and changes in lymphokine levels, suggesting an immune-modifying effect. In type 2 diabetes models, these diets reduce body weight and serum insulin levels and increase HDL cholesterol and adiponectin, with improvement in pancreatic islet morphology. In models of atherosclerosis, the low-AGE diet protect against atherosclerosis despite hyperglycemia and dyslipidemia. These diets also protect against diabetic nephropathy and appear to promote wound healing.

Persons with diabetes placed on diets of low-AGE content show influences on CML, MG, and AGE-LDL modification, with lower levels of C-reactive protein (CRP), tumor necrosis factor (TNF)-α, and vascular cell adhesion molecule (VCAM)-1, suggesting that this approach may lead to clinical benefit. Vlassara suggested that diabetes alone might be less important than dietary AGE effects on complications, and that changing the environment in which persons with diabetes live may convey particular benefit. In a study from her laboratory, Cai et al. (706-P) administered diets differing fivefold in AGE content for 6 weeks to 10 persons with diabetes whose fasting glucose averaged 115 mg/dl with normal lipid levels (abstract numbers refer to ADA Scientific Sessions, *Diabetes*, Vol. 51, Suppl. 2). While patients followed the high AGE-diet, LDL had 2.1-fold higher CML levels and showed a 1.5-fold greater NF-κB stimulatory activity on human endothelial cells than LDL isolated from patients following the low-AGE diet. These data suggest the potential of dietary AGE to exacerbate vascular toxicity of diabetic LDL. Peppa et al. (69-OR) from this group studied the effect of dietary AGEs on wound healing in diabetic *db/db* $^{(+/+)}$ mice, showing full healing of a full-thickness 1-cm wound in 63% of mice on a low-AGE diet, but in only 38% on a diet with AGE levels five times higher. Glucose levels, food intake, and body weight were similar, but serum AGE levels were 52% higher and skin from mice on the high-AGE diet had two to three times greater levels of CML derivatives.

Cardiomyopathy

Wilson Tang (Cleveland, OH) addressed connections between diabetes and CHF and discussed the effects of insulin resistance in patients with heart failure. More than two-thirds of patients with diabetes will develop CVD. Patients with diabetes have similar CVD risk to those without diabetes with history of myocardial infarction. In 1972, autopsy studies showed left ventricular hypertrophy (LVH) and other histopathologic characteristics, suggestive of a specific entity of diabetic cardiomyopathy (13). Heart failure is a clinical syndrome, whereas the term "cardiomyopathy" refers to a structural abnormality. Insulin resistance has recently been recognized as an important characteristic of patients with CHF, with all the features of insulin resistance worsening CVD and contributing to CHF. Diabetes may not only produce vascular damage, but it may also impair glucose entry into cells, thereby causing myocardial injury. Cardiomyopathy may present with systolic or diastolic dysfunction, as well as with neurohumoral manifestations.

Tang suggested that it is necessary to identify cardiac dysfunction even without heart failure and that screening to identify LVH and LV dysfunction as potential targets for therapy should be practiced. In patients with diabetes, the Framingham Study showed increased risk of developing CHF (two- to threefold in men and three- to fivefold in women). Recent Kaiser Permanente registry analysis shows that diabetes is associated with increased prevalence and annual incidence of CHF (14). Female sex, age, ischemic heart disease, oral agent and insulin use, serum creatinine, and duration of diabetes are all predictors. Patients with lower HbA_{1c} and those whose HbA_{1c} fell during follow-up had higher incidence of CHF, though a biological explanation of this is uncertain.

Patients with diabetes and ischemic cardiomyopathy fare worse than those without diabetes, as shown from a recent analysis (15). There is no evidence that patients with diabetes have larger infarctions, a greater extent of coronary narrowing, or a greater degree of abnormal remodeling. The finding that glycemic control in the postmyocardial infarction period improves outcome suggests a potential adverse effect of glycemia (16). Patients with diabetes may also have blunting of the compensatory hyperkinesis of noninfarcted tissue and may have adverse effects of autonomic neuropathy.

An important question is why some patients have improvement in cardiac remodeling, while others fail to show such an improvement. In a comparison of carvedilol-treated patients who did and did not show benefit of treatment, there is evidence that those who respond have a greater prevalence of the insulin resistance syndrome. Early identification of CHF in persons with diabetes may be particularly important in leading to early initiation of treatment. Tang noted that metformin may be well tolerated as an insulin sensitizer among persons with CHF, although there is potential for toxicity with hepatic and renal dysfunction.

Richard B. Devreux (New York, NY) reviewed data from the Strong Heart Study of a Native American population with extremely high diabetes prevalence. Echocardiographic measurement of wall thicknesses and chamber diameter allows good estimation of LV mass. The risk of a variety of adverse end points is increased 2- to 10-fold in persons with LVH, with increased mortality. Diabetes, adjusted for a variety of other potential risk factors, is associated with increased frequency of LVH by a number of measures, independent of age, blood pressure, antihypertensive treatment, and obesity. Persons with diabetes and LVH have 1.5- to 2-fold increases in rates of morbid events, suggesting a role of echocardiography in determining which patients should be placed on multiple medication regimens.

Dividing the Strong Heart Study into patients with and without diabetes and with and without hypertension, the frequency of LVH is ~10% with neither,

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20% with diabetes alone, 25% with hypertension alone, and nearly 40% among individuals with both risk factors. Similar data have been shown in other population groups. Persons with diabetes show decreased ventricular systolic function, again with additive effects of diabetes and hypertension. Ventricular contractility, again, is decreased in diabetes, in persons with hypertension, and, to a greater extent, in those with both abnormalities.

The LIFE trial with losartan showed decreased myocardial contractility among persons with diabetes and moderately severe hypertension, which was associated with increased mortality rates. Higher HbA_{1c} levels were not associated with worse contractility, but measures of renal dysfunction showed strong correlation with worsening of these parameters. Abnormalities of diastolic ventricular relaxation are seen to a similar extent in persons with either diabetes or hypertension, with additive effects of the two factors. Abnormal LV relaxation was significantly more prevalent in persons with higher HbA_{1c}, suggesting an effect of prevailing levels of glycemia.

Carotid wall thickness is influenced by both hypertension and atherosclerosis. Diabetes leads to greater and more diffuse carotid disease. Sixty percent of persons with diabetes have evidence of carotid atherosclerosis with presence of plaque. Arterial stiffness also increases with both diabetes and hypertension, the latter because of greater distending pressure of the arteries, which are stretched to their maximal size, whereas in diabetes the arteries, while not stretched, are almost as stiff.

Devreux ended with a discussion of the association between hyperinsulinemia and abnormal cardiac function. Fasting insulin shows significant association with a variety of measures of LVH as well as with increased cardiac output (17). Many of these associations are not significant on multivariate analysis, however, suggesting effects of age, BMI, and blood pressure, rather than primary effects of hyperinsulinemia. After adjustment for these factors, fasting insulin levels are related to greater LV size and cardiac output in men and to LV wall thickness in women.

This analysis suggests that an echocardiogram should be done in patients with type 1 and type 2 diabetes if signs or symptoms of CVD are present, or if one is considering intensive blood pressure treatment. Devreux noted that the echocardiographic abnormalities are highly prevalent and are seen within several years after the diagnosis of type 2 diabetes. "It would be in many clinical settings a luxury to routinely do echocardiograms on all diabetics," he stated, but "in the Strong 30% had LVH and about 20% had evidence of subnormal myocardial function [. . .]. [T]hese are not rare abnormalities[. . .]. We are about to initiate a trial [of] the hypothesis that even more aggressive lowering of blood pressure and LDL will have beneficial effects in type 2 diabetes using echocardiographic and carotid artery measures of preclinical disease as our bioassay."

Postprandial hyperglycemia

Jaime Davidson (Dallas, TX) debated John Buse (Chapel Hill, NC), taking the position that postprandial glucose should be measured and monitored. Both tried to define goals and approaches to the treatment of this parameter. Davidson stated, "We need to have data, and we need to have judgment," pointing out that the ADA currently does not set goals for postprandial glucose levels, defined as the glucose level 2 h after the start of the meal. He referred to the ADA "postprandial glucose consensus" position statement, which points out that in normal individuals, glucose levels are maximal around 1 h after the beginning of a meal and rarely exceed 140 mg/dl, but that there is no definite evidence as to whether this should be a goal of therapy. According to the statement, these levels should be monitored with gestational diabetes, with suspected postprandial hyper- or hypoglycemia, and in patients receiving agents specifically directed at glucose during this period. Postprandial hyperglycemia is one of the earliest abnormalities in diabetes, so that monitoring this is necessary for full assessment of early diabetes. Davidson also noted that the postprandial glucose plays a major role in the determination of HbA_{1c} levels, and that some studies suggest stronger correlation of HbA_{1c} with post- than with preprandial glucose (18).

Has managing postprandial glucose been shown to improve HbA_{1c} levels? In a comparison of 135 persons treated with glyburide for whom addition of insulin lispro was compared with treatment directed at the fasting glucose, either metformin or NPH insulin, the postprandial treatment approach with insulin lispro had the greatest effect in lowering HbA_{1c}, although NPH insulin lowered fasting glucose most effectively (19). Similarly, in another study of persons with diabetes failing to respond to SU treatment, addition of insulin lispro lowered 2-h postprandial glucose from 335 to 254 mg/dl, with HbA_{1c} decreasing from 9.0 to 7.1%. In a study of 66 women with gestational diabetes who required insulin therapy, preprandial monitoring with a glucose goal of 60–105 mg/dl (<90 fasting) vs. 1-h postprandial monitoring with a goal of <140 mg/dl resulted in improved HbA_{1c} and outcome, with a marked reduction in neonatal hypoglycemia and Caesarean section in the latter group (20).

The DECODE Study showed that high 2-h glucose is associated with CVD mortality independent of fasting glucose (21). Similar findings were reported from Pacific and Indian Ocean populations, with isolated 2-h hyperglycemia associated with doubled mortality (22). Furthermore, analyses of various indicators of adverse CVD risk show that imparied glucose tolerance (IGT) but not impaired fasting glucose (IFG) is a CVD risk factor (23). In the Diabetes Intervention Study, among 1,139 persons with diabetes followed for 11 years, myocardial infarction and mortality increased more with postprandial than with fasting hyperglycemia (24). In the Honolulu Heart Study, the 1-h postchallenge glucose was associated with increased CVD (25). Finally, the Risk Factors in IGT for Atherosclerosis and Diabetes (RIAD) Study showed that 2-h postchallenge glucose was associated with increased carotid intima-media thickness, with fasting glucose not contributing in multivariate analysis (26).

"A glucose is a glucose," Davidson pointed out, implying that if postchallenge hyperglycemia is associated with increased risk, it should be treated. He stated that "a reasonable goal" is for the 2-h glucose to be <140 mg/dl, based on the levels in persons without diabetes, and asked, "If postprandial is bad in IGT, why is it not bad in patients with diabetes?" We desire to attain good glycemic control, he stated, and "unless we target all the glucoses that we need to target, we are not going to get there." Rather than criticizing this as being unsafe, he implied that studies such as the Diabetes Control and Complications Trial (DCCT) and Kumamoto, in which patients were tested at

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these times, may have had additional benefits such as reduced frequency of hypoglycemia. Subsequent to these studies, the development of rapidly acting insulin analogs and secretagogues targeting postprandial glycemia has further allowed us to improve HbA_{1c}. "If you don't believe in tight control," Davidson commented, "then your patients are not going to believe in tight control." He asked whether "pressure from payers and other interested parties prevents us from doing what we need to do," and asked those treating patients with diabetes not to "give in" to these pressures.

Buse responded to Davidson's "eloquent and impassioned argument," stating that he had previously been a "therapeutic zealot," but was influenced by criticisms that before we "make leaps of faith that sometimes can be quite expensive," we must follow the results of clinical trials. "Clearly, measuring postchallenge glucose in screening for impaired glucose tolerance and for diabetes is extremely important," he stated, but "those are not truly postprandial glucose data," which "could be quite different." We "need to separate in our minds the well-defined benefits of agents which specifically manage postprandial glucose [from] the need for monitoring." He further criticized the "intensive marketing effort on the part of [. . .] numerous pharmaceutical companies to further justify the need for their agents which specifically deal with postprandial glucose as well as device manufacturers which make their profit by the strip."

He stated that he agreed that the DCCT, Kumamoto, and UKPDS studies were, indeed, important, but argued that one cannot find any data in these studies that support the use of postprandial glucose testing. Although lowering of HbA_{1c} is important, and "it is possible that treatment aimed at lowering postprandial glucose would lower HbA_{1c} and therefore lower the risk of complications," such an approach has not been demonstrated to be effective. Reviewing the gestational diabetes study, he pointed out that when comparing a preprandial glucose target up to 105 mg/dl versus a postprandial glucose target up to 140, "the real driver of the difference in outcomes was that the preprandial target was just inadequate" as this group had a mean HbA_{1c} of 7.5%. Further, when we aim for an HbA <7%, "it is clear that preprandial monitoring is necessary to discover unrecognized and unsuspected hypoglycemia as a first step to avoiding severe hypoglycemia." The fact that a 2-h blood glucose after oral glucose administration is associated with greater cardiovascular risk than the fasting glucose, he stated, need not mean that we need to monitor postprandial glucose, but, rather, indicates that one should use more sensitive markers for the insulin resistance syndrome. The 2-h glucose also is an indicator of abnormal insulin secretory dynamics, Buse noted, and in the Hoorn study report presented at the meeting, the 2-h glucose effect was not significant after correction for lipid and blood pressure, further suggesting that this is not "a primary treatment target." (See Dekker et al. [258-OR].)

As far as glycemic therapy, Buse stated, there is no good evidence that agents targeting postprandial glucose are more effective than those targeting preprandial glucose, and in any event, monitoring postprandial glucose need not be routinely performed in patients receiving such treatment. Finally, asking what is the appropriate target of postprandial glucose, he stated, "it's very hard to come up with a guideline that will work for everyone." Retinopathy increases at 2-h postchallenge glucose levels "that are really quite high," he commented. He referred to a study of glycemic patterns in nondiabetic persons given standard meals with 12.5, 25, and 50% of total daily calories. Peak plasma glucose varied as a function of meal size, reaching 159 mg/dl after the medium and 178 mg/dl after the large meal (although an audience questioner noted that these were peak and not 2-h postprandial glucose levels) (27). He agreed that one could use postprandial glucose measurement for certain patients, but suggested that this would only be relevant for those who had reached preprandial targets without achieving HbA_{1c} targets or for those who had evidence of postprandial hypoglycemia. His target for postprandial glucose was 180 mg/dl for such circumstances, and he stated that "we need additional clinical trials to routinely advocate for the use of postprandial glucose monitoring in the management of type 2 diabetes." Furthermore, he stated, "Almost certainly having people perform extra glucose monitoring will prevent them from doing other things," considering the importance of not only glycemic treatment but also of lipid treatment, blood pressure treatment, etc. He mentioned that it has been considerably more of a challenge to achieve the postprandial goal of the ACCORD study of a 2-h glucose level <140 mg/dl than the other glycemic goals of HbA_{1c} <6% and fasting glucose <105 mg/dl. A questioner noted that alternate site testing may lead to lower postprandial glucose levels than simultaneously measured fingertip or venous blood glucose, and Buse agreed that this would make optimizing postprandial glucose even more difficult.

At a symposium on the association of postprandial glycemia and risk of CVD, Jaakob Tuomilheto (Helsinki, Finland), one of the investigators of the DECODE study, discussed postchallenge glucose and the risk of CVD, presenting new analysis of this data. Normal glucose tolerance is associated with rapid first-phase insulin response, and the early defect in this step leads persons with IGT and, particularly, persons with type 2 diabetes to display postmeal hyperglycemia. The prevalence of asymptomatic diabetes is greater among men before age 60 years, and older persons frequently have postchallenge hyperglycemia. At lower levels of hyperglycemia, men with IGT tend to have higher fasting glucose levels, whereas women have higher postchallenge levels. Compared with persons previously known to have diabetes, there is a linear increase in mortality with increasing 2-h glucose, to a greater extent than that with fasting hyperglycemia. Comparing fasting glucose and 2-h glucose of normal, IGT, and type 2 diabetes, among men there is an increase in mortality with both increasing fasting and 2-h glucose levels, while among women the highest mortality is seen among those with both fasting and postload hyperglycemia. A similar pattern of increasing CVD mortality is seen with increasing 2-h glucose among men and among women, while fasting hyperglycemia is associated with lesser increase in mortality risk. Comparing mortality among persons with fasting glucose ≤6 vs. >6 mmol/l (108 mg/dl), adjustment for the 2-h glucose eliminates the mortality association of fasting hyperglycemia among men, but not among women, for whom, Tuomilheto stated, the fasting glucose remains a risk marker. The greatest absolute number of deaths is seen among persons with elevated 2-h glucose and normal fasting glucose levels because of the larger size of this subset, implying that

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if treatment is shown of benefit, then these individuals may comprise the most important group for intervention.

The systolic blood pressure is ~15 mmHg higher in persons with postchallenge hyperglycemia than in those with normal postdchallenge glucose. Those persons in the DECODE dataset with diabetes and the lowest fasting glucose levels had the highest serum cholesterol, suggesting that the different components of the metabolic syndrome, dyslipidemia, and hyperglycemia may behave differently. Cigarette use is associated with increased CVD and total mortality, most notably among women with diabetes. Those women with diabetes who had hypercholesterolemia, hypertension, and obesity had the highest CVD mortality. Why, Tuomilheto asked, is postchallenge hyperglycemia producing such a great deal of increase in mortality? He suggested that even lower glucose levels than those currently used for defining diabetes are associated with increased mortality, and he also noted that hyperglycemia may produce a greater relative increase in mortality among women than among men.

The findings of the Workgroup on Outcomes of Hyperglycemia (also see http://diabeteshighlights.org/summary/june17.asp?sid=1) were described by Marian Rewers (Denver, CO). He noted that "postprandial" is not the same as "postoral glucose challenge," and represents "a simplification where we are measuring glucose 2 hours after a glucose load." The results of continuous glucose monitoring may be very interesting in that they more clearly show actual glucose levels encountered in persons at varying levels of risk. Further, he noted that plasma venous glucose levels are higher than the whole-blood levels measured in many settings. Thirty-one groups from around the world contributed to his data on all-cause and CVD mortality; these groups included the DECODE group, 11 U.S. studies, and studies of Pacific Island natives and Japanese persons. Participants were aged 45–84 years, and persons with diabetes taking insulin or oral medications were excluded; among 50,567 persons, there were 8,700 deaths. Based on the 2-h glucose, 18% of persons had IGT and 10% had diabetes; based on fasting glucose criteria, 12% had IFG and 6% diabetes. Europeans and Caucasian Americans were somewhat overrepresented in the study. All-cause mortality showed increase at both the lowest and highest deciles of fasting and 2-h glucose levels. For CVD mortality, rates were highest among those in the highest glucose groups. In review of the DECODE population, non-Hispanic whites in the U.S., and non-Caucasian populations, there was an increase in CVD mortality among persons diabetes defined with either fasting or 2-h glucose. The relative importance of hyperglycemia as a predictor of mortality was greater at younger than older ages. There is an effect of the 2-h glucose for any given fasting glucose level, while increasing fasting glucose did not affect mortality within a given 2-h glucose group.

Adjusting for cigarette use, blood pressure, BMI, lipids, age, sex ,and ethnicity, with data available for 27,000 persons (of whom 3,700 died), with the fasting and 2-h glucose each divided into 6 categories, the 2nd to 6th deciles were compared with the 1st, 7th, 8th, 9th, and 10th deciles. Fasting glucose groups were ≤84, 85–100,101–104, 105–109, 110–125, and >126, respectively; the 2-h glucose was divided at cut points of 85, 101, 104, 110, 140, and 200 mg/dl. Persons with diabetes and those with fasting glucose ≤84 had the highest mortality. Even after adjusting for all of the CVD risk factors and for the 2-h glucose, those in the highest fasting glucose group remained at the highest risk. IFG adjusted for the 2-h glucose added little to the prediction of CVD mortality among Europeans, whereas diabetes, based on glucose >125 mg/dl, was a strong predictor. Looking at the 2-h glucose, those with the lowest 2-h glucose had low CVD risk. Those with 2-h glucose 140–169 had similar increase in mortality risk to that seen with 2-h glucose 170–199, and those with 2-h glucose <140 did not have increased risk, whereas CVD and total mortality were increased to an even greater extent in persons with diabetes based on 2-h glucose ≥200. The excess mortality risk related to diabetes was similar for patients diagnosed based on both fasting and 2-h glucose, while that for IGT was approximately one-third greater than that for IFG, and IGT predicted death independently of the fasting glucose, while IFG did not predict death independently of the 2-h glucose.

Rewers stated that he believed we need to be cautious in applying these data to treatment decisions, as we do not know whether hyperglycemia leads to CVD or whether glucose is simply a marker of at-risk groups, for which "manipulating the glucose per se" may not be the answer. Whether glucose tolerance testing should be used, and, if so, whether it should be used to find persons at high risk of CVD, or at high risk of diabetes, or with previously undetected diabetes, are further important policy questions.

Several presentations at the meeting added further information to these fascinating areas of uncertainty. Borenstein et al (891-P) reviewed 12 prospective and 2 cross-sectional studies of the association of postchallenge glucose with cardiovascular outcomes and all-cause mortality in type 2 diabetes, reporting that 12 studies documented a positive association and, of 7 studies comparing fasting and postchallenge glucose, 5 found the latter to have greater predictive power. Hunt et al (929-P) compared persons aged 45–64 years at enrollment in the San Antonio Heart Study who were followed at a mean of 7.7 years to determine whether diabetes had developed. A total of 1,038 had normal glucose tolerance and did not develop diabetes, and over an additional 7.7 years of follow-up, 152 deaths occurred, 70 of which were from CVD. Compared with those with normal glucose tolerance who did not develop diabetes, all-cause mortality was 1.5-, 1.02-, and 1.86-fold greater and CVD mortality was 2.13-, 1.16-, and 2.81-fold greater among 94 who had IGT and developed diabetes, 187 with IGT who did not develop diabetes, and 76 with normal glucose tolerance who developed diabetes, respectively. These data led the authors to suggest that it is diabetes per se that conveys increased risk.

Haffner et al. (919-P) compared glucose tolerance testing with the use of a predictive model incorporating BMI, blood pressure, fasting glucose and lipids, and medical history (28) using the Insulin Resistance Atherosclerosis Study database. Persons with IGT who met the Diabetes Prevention Project criteria for increased risk had a 37% 5-year incidence of diabetes as compared with 8% among those with normal glucose tolerance, but no increase in carotid intima-media thickness. Those in the highest vs. lower tertiles of the predictive model had a similar 32 vs. 8% diabetes risk but also showed carotid wall thickness of 856 vs 781 μm. Thus, the approach with multiple CVD

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risk factors is similarly effective in assessing diabetes risk, as shown in the initial study developed from the San Antonio Heart Study dataset, and was more effective (as might be expected) in identifying subclinical CVD.

In terms of treatment addressing the postprandial glucose among persons with diabetes, Abbasi et al (2449-PO) analyzed patients treated with diet alone, glipizide, metformin, or rosiglitazone. Fasting glucose showed strong correlation with the integrated glucose over 4 h following breakfast(r from 0.83 to 0.97) and a somewhat less strong correlation with average glucose during the 4 h following lunch (r from 0.69 to 0.90). Similarly, Agrawal et al. (372-P), who compared 71 persons receiving placebo with 64 receiving rosiglitazone 8 mg daily, showed a 47% decrease in the 4-h glucose area after a standard mixed meal, as well as a 25% decrease in fasting glucose. Thus, many treatments decrease both fasting and postprandial glucose. These observations may be treatment-dependent, however, as shown by a study by Baron et al. (376-P) of 58 and 83 type 2 diabetic persons receiving diet alone or metformin, respectively, with addition of nateglinide versus placebo. Blood glucose 2 h after breakfast decreased 44 and 49 mg/dl, while fasting glucose decreased 15 mg/dl in each group, suggesting that the 1.1 and 0.8% decreases in HbA_{1c} with this agent was caused mainly by the decrease in postmeal glycemia. Interestingly, however, Carroll et al. (379-P) reported similar 32-mg/dl postprandial glucose-lowering effects of prebreakfast nateglinide and glipizide compared with placebo in 20 persons with type 2 diabetes. Reviewing another approach, Hanefeld (404-P) reported analysis of three studies of orlistat versus placebo in 372 versus 383 persons with type 2 diabetes, showing decrease in postprandial glucose of 29 vs. 2 mg/dl at 24 weeks.

References

1. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. *JAMA* 281:1291–1297, 1999
2. Smith NL, Savage PJ, Heckbert SR, Barzilay JI, Bittner VA, Kuller LH, Psaty BM: Glucose, blood pressure, and lipid control in older people with and without diabetes mellitus: the Cardiovascular Health Study. *J Am Geriatr Soc* 50:416–423, 2002
3. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilehto J: Impact of diabetes on mortality after the first myocardial infarction: the FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 21:69–75, 1998
4. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
5. 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
6. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359:1004–1010, 2002
7. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in noninsulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23) *BMJ* 316:823–828, 1998
8. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360: 7–22, 2002
9. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
10. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 335:217–225, 1996
11. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyerm H-M, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998
12. Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H: Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci U S A* 94: 6474–6479, 1997
13. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 30:595–602, 1972
14. Nichols GA, Hillier TA, Erbey JR, Brown JB: Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care* 24:1614–1619, 2001
15. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ: Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol* 38:421–428, 2001
16. Malmberg K: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 314:1512–1515, 1997
17. Ilercil A, Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Howard BV: Associations of insulin levels with left ventricular structure and function in American Indians: the Strong Heart Study. *Diabetes* 51: 1543–1547, 2002
18. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822–1826, 1997
19. Bastyr EJ 3rd, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE: Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA_{1c}. *Diabetes Care* 23:1236–1241, 2000
20. de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237–1241, 1995
21. DECODE Study Group: Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. *Lancet* 354:617–621, 1999
22. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ: Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 42: 1050–1054, 1999
23. Liao D, Shofer JB, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY: Abnormal glucose tolerance and increased

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risk for cardiovascular disease in Japanese-Americans with normal fasting glucose. *Diabetes Care* 24:39–44, 2001
24. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J: Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39:1577–1583, 1996
25. Yano K, Grove JS, Reed DM, Chun HM: Determinants of the prognosis after a first myocardial infarction in a migrant Japanese population. The Honolulu Heart Program. *Circulation* 88:2582–2595, 1993
26. Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T: Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD Study. Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes. *Diabet Med* 17:835–840, 2000
27. Service FJ, Hall LD, Westland RE, O'Brien PC, Go VL, Haymond MW, Rizza RA: Effects of size, time of day and sequence of meal ingestion on carbohydrate tolerance in normal subjects. *Diabetologia* 25:316–321, 1983
28. Stern MP, Williams K, Haffner SM: Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Ann Intern Med* 136:575–581, 2002

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