Cardiovascular Disease in Diabetes

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This is the fifth of a series of articles based on presentations at the American Diabetes Association (ADA) Scientific Sessions held 5–9 June 2009 in New Orleans, Louisiana, pertaining to cardiovascular disease (CVD) studies in diabetes.

Pre-diabetes and atherosclerosis

Steven Haffner (San Antonio, TX) gave the Edwin Bierman lecture, discussing the relationship between aspects of pre-diabetes and its relationship to atherosclerosis. He noted that one-third of persons without a prior diagnosis of diabetes who had glucose tolerance testing after myocardial infarction had diabetes and that another third had pre-diabetes as defined by impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) (1). In his analyses, pre-diabetes was defined based on finding individuals who on follow-up were documented to develop diabetes, which is in some ways preferable to a definition based on risk of diabetes because of IFG or IGT, as many such individuals do not actually develop diabetes. The development of diabetes should, furthermore, be distinguished from CVD risk. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) data, as an example, suggest IGT to convey higher risk than IFG (2,3). Various statistical methods can be used to understand the relationships between pre-diabetes and preheart disease; the complexity of this relationship is further increased by the finding that many CVD risk factors, such as cigarette use and low HDL cholesterol, are also risk factors for diabetes.

Haffner's San Antonio Heart Study shows that risk factors for conversion to diabetes were age, obesity, fasting and 2-h glucose, fasting insulin, and, more strongly, insulin sensitivity calculated from the minimal model. For each 1-SD increase in BMI, there is a 1.4-fold increase in risk of diabetes, with similar risk from higher glucose levels, while a 1-SD increase in insulin sensitivity is associated with a 20% reduction in risk, with greater acute insulin response also predictive of lower diabetes risk. In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study, IFG and IGT each were associated with a ~7%, and the presence of both with a ~14% annual conversion rate to diabetes (4). Higher levels of triglyceride, blood pressure, insulin, weight, and lower HDL cholesterol are associated with both diabetes and macrovascular disease, the latter showing evidence of beginning prior to the onset of the former (5), with data from the Nurses' Health Study also showing increased CVD rates prior to onset of diabetes (6); the implication is that CVD prevention might be gained with diabetes prevention. Waist, triglyceride, and fasting glucose were not, but HDL cholesterol, blood pressure, and the presence of diabetes have been shown as predictors of CVD (7). Studies from Haffner's group suggest that IGT and the metabolic syndrome predict CVD and that persons with both abnormalities are at particularly high risk, so that one could consider them candidates for treatment (8). There is also emerging evidence that microvascular disease begins prior to the onset of diabetes, and studies show this to occur with microalbuminuria (9), decreased renal function (10), and retinopathy (11). Diabetes appears to develop both in the setting of insulin resistance (IR) and of decreased insulin secretion, with evidence that it is the former that is responsible for CVD risk (12). Similarly, the proinflammatory state appears to be associated with IR, whether measured comparing C-reactive protein (CRP) levels with the number of metabolic syndrome components (13,14) or compared with more direct measures of IR. Insulin-sensitive individuals developing diabetes have normal CRP levels, even with adjustment for BMI (15). Fatty liver measures are also associated with diabetes, appearing to be as powerful risk factors as CRP, although statistically independent (16). Additional risk factors for diabetes are sex hormone binding globulin, plasminogen activator inhibitor-1, and prevalent coronary heart disease (CHD) itself—all related to IR.

Haffner concluded that pre-diabetes should be considered an atherogenic state, particularly related to IR rather than to decreased insulin secretion, and that measures to prevent diabetes should in theory reduce CVD, regardless whether such approaches reduce conversion to diabetes, but noted that to date none of these strategies have actually been shown to lead to fewer cardiovascular (CV) events, with the intensive lifestyle intervention of the Diabetes Prevention Program (DPP) leading to weight loss and diabetes prevention but not as yet showing evidence of changing event rates, although follow-up will be available in 2014 and may modify this view. He pointed out that risk of diabetes is more related to glucose and obesity levels, but that those who are at particularly high diabetes risk may not be at high CVD risk, and hence that the studies thus far carried out have not had sufficient statistical power to demonstrate CVD benefit. Another issue is that "it's harder . . . now that we have many more interventions," aggressively and routinely treating lipids, blood pressure, and cigarette smoking. The correct approach to address this is not clear. It would certainly be safe to carry out long-term behavioral intervention in communities with indirect atherosclerosis assessments, such as measures of carotid intima-media thickness (CIMT), and one also could study very high-risk populations, such as those having acute coronary syndrome. In low-risk populations, annual CVD event rates are likely to be ~0.5%, so that one would need to follow ~25,000 persons per group for a decade to show a 15% risk reduction. Before initiating such a long-term type 2 diabetes prevention study, there must be absolute certainty that the intervention is safe. Haffner asked whether it is truly necessary to demonstrate that preventing diabetes will prevent macrovascular disease. He noted that we could "forget about CHD and focus on microvascular events." Possible therapeutic strategies beyond be-

havioral intervention for pre-diabetes include metformin and intensification of CV risk factor management; but at this point, Haffner considered there to be insufficient data to justify other pharmacological agent treatments.

In studies presented at the ADA Scientific Sessions related to diabetes risk, Selvin et al. (abstract 244) reported factors associated with development of diabetes at 6 years in 11,889 persons whose glucose tolerance tests did not show diabetes at 0 and 3 years, finding that baseline A1C (in the normal range) more strongly predicted diabetes than glucose levels after adjustment for age, sex, race, BMI, smoking status, hypertension, triglycerides, physical inactivity, and family history of diabetes. Mullican et al. (abstract 245) found that systolic and diastolic blood pressure 130–139 mmHg and/or 85–89 mmHg, respectively, was associated with increased risk of development of diabetes after adjusting for IR, obesity, IGT, and family history of diabetes. Hu and Tuomilehto (abstract 950) reported 13.3-year follow-up of 27,806 persons and found that high-normal blood pressure, hypertension with systolic <160 and diastolic <100 mmHg blood pressure levels, and hypertension at greater blood pressure levels were associated with 1.2-, 1.8-, and 2.2-fold increases in likelihood of diabetes, respectively, independent of age, smoking status, education, physical activity, alcohol, coffee and tea consumption, and BMI. The relationship appeared to be among normal weight and overweight and obese persons. Alssema et al. (abstract 246) found that male sex and smoking, when added to the Finnish risk score, which includes age, BMI, waist, exercise, diet (fruits and vegetables), blood pressure, history of elevated glucose, and family history of diabetes, were associated with diabetes risk, but that hip circumference, use of lipid-lowering medication, and self-reported shortness of breath during walking were risk factors.

Type 1 and type 2 diabetes and atherosclerosis

John D. Brunzell (Seattle, WA) suggested an approach to managing CVD risk by regarding type 1 and type 2 diabetes in a similar fashion. The paradigm has changed, he said, and type 1 diabetic persons "really look a lot more like type 2 . . . in a particular subset." In the UK Prospective Diabetes Study (UKPDS) analysis of CVD risk factors, LDL cholesterol was

first and HDL cholesterol was second, as a risk factor (17). Although LDL levels are not increased in diabetes, LDL subfractions need to be evaluated in assessing CVD risk in type 2 diabetes, with many methodological approaches confirming that small, dense (sd)-LDL particles have the strongest association with CVD (18). In type 2 diabetes, triglyceride levels are increased and HDL cholesterol is decreased, particularly in the HDL_2 subfraction, with non-HDL cholesterol more useful than LDL as a therapeutic goal. Brunzell noted that the shift to sd-LDL, increased VLDL, and decreased HDL cholesterol is similarly present in nondiabetic IR persons, with central obesity and chronic kidney disease also contributing to their dyslipidemia and increasing CVD. Statin treatment improves outcome in type 2 diabetes (19,20). Another important therapeutic agent is niacin, which lowers sd-LDL, increases HDL, and decreases triglyceride levels, although it somewhat increases glucose and A1C levels (21).

Brunzell discussed the high mortality in type 1 diabetes in the Steno, EURODIAB, and Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) studies, particularly with development of renal disease (22,23). Further observations of this were given at the ADA Scientific Sessions by Secrest and Orchard (abstract 93). During a 14-year follow-up of 658 type 1 diabetic persons, 125 had coronary disease, myocardial infarction, or coronary death with serum creatinine, as well as HDL cholesterol and angina, predicting these events. Brunzell noted that at follow-up of the DCCT cohort, the intervention was found to reduce CVD by half, in part by preventing the development of renal disease and in part directly from glycemic improvement (24). The DCCT revealed, however, two complications of intensive type 1 diabetes treatment: hypoglycemia and weight gain. Intensive glycemic treatment in this study did not lead to weight gain in the same fashion in all study participants. Those in the top weight gain quartile averaged ~35 pounds (25), considerably more than the weight gain in the lower quartiles. This subgroup had slightly higher baseline A1C, but their on-study A1C was similar to that in those with lesser or no increase in weight. Their sd-LDL and triglyceride levels were elevated, with increased intraabdominal fat. Intensive treatment is itself associated with a decrease in VLDL cho-

lesterol and no overall change in HDL, but Brunzell showed evidence that HDL decreased in those who gained weight, while it increased in those who did not. Those gaining weight were more likely to have a type 2 diabetic parent and had higher prevalence of the peroxisome proliferator–activated receptor-γ coactivator gene polymorphism associated with IR. With greater weight gain, there was higher blood pressure and more development of microalbuminuria. Those who developed microalbuminuria had increased VLDL cholesterol, with decreased buoyant and increased sd-LDL. Although event rates were low overall, an excess of CVD occurred in those with more weight gain in the intensive treatment group during the DCCT (26). For type 1 diabetic persons whose control of glycemia comes at the expense of weight gain causing IR, then, CV risk increases.

Brunzell suggested that weight gain should be considered the major cause of dyslipidemia and CVD in type 1 diabetes, terming this "double diabetes." His studies showed a trend for CIMT to increase as a function of weight gain in the intensive treatment group, further supporting the hypothesis. Over time, with lower dietary saturated fat, better blood pressure treatment using ACE inhibitors, statin treatment, decreased cigarette use, and more intensive glycemic treatment, the causation of CVD in type 1 diabetes has changed. "In modern times, central obesity and IR lead to CVD," Brunzell said, concluding, "We need to treat the obese type 1 diabetic [patient] like type 2." He recommended statins for all type 1 diabetic persons with either obesity or microalbuminuria, as well as adding niacin, but expressed skepticism about extremely intensive glycemic treatment, interpreting recent studies in type 2 diabetes to show that such approaches do not reduce CHD.

Epidemiology and genetics

James Meigs (Boston, MA), giving the Kelly West Lecture, recalled West's 1978 book *Epidemiology of Diabetes and Its Vascular Lesions*, which discussed the causal relationship between obesity and type 2 diabetes and the notion of an identifiable state of pre-diabetes, suggesting that type 2 diabetes is preventable, with epidemiology basic to such endeavors. His research has been based on data from the Framingham Heart Study, which began ~60 years ago, with an Offspring study starting in 1972 and the third generation enrolled in

2002, allowing a multigenerational prospective cohort. Obesity prevalence has risen progressively during this period, and while normal-weight persons have had low and stable type 2 diabetes rates, the marked increase in diabetes incidence has been among obese persons. CVD rates in the U.S. have declined since the 1950s, but although decreasing, they have remained twice as high in diabetic persons. The rising prevalence of diabetes has increased its population-attributable CVD risk, while such risks from hypertension and hypercholesterolemia have decreased and that from cigarette use has been constant.

Pre-diabetes is also associated with increased CVD. Metabolic traits are intercorrelated with high co-occurrence. Factor analysis gives three domains among nondiabetic persons: high glucose/insulin, adiposity/dyslipidemia, and obesity/hypertension. Rather than diabetes causing CVD, the common soil hypothesis posits that underlying IR and obesity both lead to CVD and to diabetes. "For better or for worse," Meigs commented, this leads to the notion of metabolic syndrome. Metabolic syndrome using the National Cholesterol Education Program (NCEP) definition is a better predictor of diabetes than of CVD. There are, however, multiple potential subtypes of metabolic syndrome, those without glycemic abnormality not having increasing the likelihood of diabetes. Although IR and metabolic syndrome are independently associated with CVD, even after considering standard CV risk factors, Meigs showed evidence suggesting that these do not represent the same condition.

The perivascular fat depot represents an important site not simply storing fat but elaborating cytokines, as well as free fatty acids, acting on peripheral tissues and on the pancreatic islets, and contributing to development of diabetes and CVD. Adiponectin, resistin, and tumor necrosis factor-α were associated with IR in a study of 2,358 men and women in the Framingham Offspring Study. In the Nurse's Health Study, adiponectin was inversely associated with diabetes and resistin was not a factor for either diabetes or CVD but was associated with heart failure, whereas adiponectin was not. E-selectin, plasminogen activator inhibitor-1, and von Willebrand factor (vWF) were associated with type 2 diabetes risk, the highest quintile of the former, for example, with five-fold greater risk than the lowest quintile. Elevated vWF predicted

CVD, particularly in type 2 diabetic persons. Meigs suggested that the elevated CVD rates in diabetes beyond those predicted from standard risk factors may be found to reflect endothelial dysfunction. In a related study presented at the ADA Scientific Sessions, Lee et al. (abstract 727) noted that the cytokine erythropoietin, in addition to regulating erythropoiesis, reduces apoptosis and oxidative stress and promotes angiogenesis. Among 92 type 2 diabetic persons with mean A1C 10.4% without anemia or renal failure, erythropoietin levels correlated with CIMT and CRP.

Meigs illustrated the use of Mendelian randomization as a potential test of causality in epidemiology with genetic studies. The adiponectin gene exhibits a variety of single nucleotide polymorphisms (SNPs), with two SNPs significantly associated with adiponectin levels, but associations of these SNPs with outcome are not readily demonstrated. Similarly, the CRP gene is associated with CRP levels, but in the Framingham studies, it was not associated with CVD, with the evidence, rather, that CVD may increase CRP levels, suggesting this not to be causally related. LDL gene polymorphisms are, however, associated both with the LDL level and with CVD, suggesting causality.

There are ~20 confirmed genetic loci associated with type 2 diabetes (among millions of potential gene combinations). The Framingham SNP Health Association Resource (SHARe) study, which gives publicly available data, has been joined with 30 other cohort studies in the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). Meigs reviewed the novel finding that the fasting glucose is associated with melatonin receptor 1B, suggesting that the circadian system is involved in glucose regulation and in the pathogenesis of type 2 diabetes, what he termed "novel biology coming from modern genetics." Further genetic studies imply that many more type 2 diabetes genes will be found to be associated with fasting glucose and with insulin secretion. Addressing the concept that "personalized medicine" might give a "genetic risk profile," Meigs analyzed an 18 SNP genotype score, with those with the highest genotype score having 2.5-fold greater risk of diabetes, although comprising only 11% of the sample. If a clinical model from age, sex, family history, and metabolic syndrome components is used, the genotype score increases risk just by

~10%, with little effect on the contribution of family history, implying that these 18 SNPs are only a subset of those important for diabetes development. The genotype score did not allow greater discrimination than the simple clinical model, and there was no clear evidence that knowing one's genetic risk was beneficial, as although those having a high score appeared to be more motivated to change lifestyle, disturbingly, "low genetic risk" reduced participants' willingness to improve lifestyle. Some genetic findings do have interesting therapeutic implications, such as the DPP lifestyle intervention reversing the risk of the TCF7L2 gene polymorphism (27).

Many interesting genetic findings were reported at the ADA Scientific Sessions. Li et al. (abstract 41-LB) confirmed earlier evidence that variants in *KCNQ1* are associated with diabetes as well as with impaired fasting glucose among 3,210 Han Chinese persons and found lower homeostasis model assessment (HOMA)-B as well, suggesting the variants to lead to reduced β-cell function. Guo et al. (abstract 47-LB) reported that among 3,501 Pima Indians variants in *KCNQ1* were associated with diabetes, with lower BMI and with reduction in insulin secretory response to intravenous glucose. Scott et al. (abstract 39) reported specific variants in the *Clock* gene to be associated with metabolic syndrome, to raise triglyceride levels, and to reduce HDL cholesterol levels, supporting epidemiologic evidence that disruption of circadian rhythms is involved in the development of obesity and type 2 diabetes. Frayling (abstract 42-LB) performed a meta-analysis of genome-wide association studies, showing that 26 loci are associated with increased diabetes risk, including polymorphisms affecting gene transcription (*TCF7L2, HHEX,* and *JAZF1*), basic cell cycling (*CDKAL1, CDKN* family, and *CDC123*), ion transport (*KCNJ11, KCNQ1,* and *SLC30A8*), circadian clock (*MTNR1B*), and phosphodiesterase and carboxypeptidase. Florez et al. (abstract 44-LB) reported a similar meta-analysis, finding loci associated with elevated fasting glucose at or near *ADCY5, MADD, ADRA2A, CRY2, FADS1, GLIS3, SLC2A2, PROX1,* and *FAM148B,* and with fasting insulin and HOMA-IR (*IGF1*), as well as the known type 2 diabetes loci *TCF7L2* and *SLC30A8* and fasting glucose loci *GCK, GCKR, G6PC2, MTNR1B,* and *DGKB/TMEM195*. The analysis suggested that genes expressed in

the islet appear to be the major variants associated with development of type 2 diabetes. Hivert et al. (abstract 46-LB) reported a genome-wide meta-analysis, finding certain glucose-dependent insulinotropic peptide receptor (GIPR) gene variants to be associated with higher 2-h glucose levels and lower 2-h insulin levels. Saxena et al. (abstract 182) reported such studies in samples from 15,234 Europid persons and found *GCKR, VPS13C* (a human homolog of yeast vacuolar sorting protein)*, TCF7L2, SLCO4C1* (a member of the organic anion transporter family), and *GIPR* loci to be associated. Garofalo et al. (abstract 4-LB) reported that polymorphisms of CREBL2, a mammalian homolog of a nutrient-responsive *Drosophila* gene, are associated with diabetes, glucose and A1C level, and obesity. Xiang et al. (abstract 86) found that variation in the HNF4A gene was associated with change in the disposition index, a measure of β-cell compensation, and Ley et al. (abstract 284) reported that the hepatocyte nuclear factor 1A (*HNF1A*) gene G319S variant was associated with increase in likelihood of diabetes, but only among active cigarette smokers.

More CVD studies

Questions of antiplatelet treatment of diabetic persons were addressed with a number of studies at the ADA Scientific Sessions. Moeremans et al. (abstract 44) analyzed the question of whether low-dose aspirin is effective for diabetic patients, calculating that with at least a 16–20% reduction in events, as little as a 4% 10-year CV event rate (typical of persons with well-controlled early diabetes) will lead to aspirin use being cost-saving. De Berardis et al. (abstract 90) reported a meta-analysis of six trials of administration of aspirin to 10,117 diabetic persons without prior CVD, finding nonsignificant 6–9% reductions in major CV events, CV mortality, and overall mortality, with a significant 43% reduction in myocardial infarction in men but a nonsignificant 8% increase in women, and nonsignificant trends to 11% increased stroke in men and a 25% reduction in stroke in women. The authors commented, "Small but clinically important benefits cannot be ruled out." Ajjan et al. (abstract 644) studied clotting and its response to aspirin among 18 type 1 diabetic patients before and after intensified insulin treatment, reducing A1C from 10.5 to 9.2%, finding that aspirin paradoxically worsened clot lysis time in the

poorer glycemic control state. Muñoz et al. (abstract 754) reported that postmenopausal type 2 diabetic women had levels of the steroid precursor dehydroepiandrosterone 50% lower than those in healthy postmenopausal women and that incubation of platelet-rich plasma from type 2 diabetic women with dehydroepiandrosterone reduced platelet aggregation and increased nitric oxide production. Stanek et al. (abstract 1034) compared 2,238 diabetic persons who had percutaneous coronary intervention with stenting treated with clopidogrel alone with 1,767 who received a proton pump inhibitor as well as clopidogrel and found a 44% greater likelihood of CV events among the latter group, who in particular had a 66% greater likelihood of developing myocardial infarction or unstable angina.

Hemoglobin is associated with oxidative stress, presumably because of its iron content. Gilliam et al. (abstract 25-LB) noted that the type 2 polymorphism of haptoglobin (Hp), a plasma protein binding free hemoglobin, leads to reduction of its protection. In type 1 diabetic patients, those homozygous for Hp1 had lower levels of oxidized LDL, urinary isoprostane, and other measures of oxidative stress than those with one or two Hp2 alleles, with a suggestion that the Hp2 allele was associated with diabetes complications. Interestingly, the Hp2 allele has been reported to be associated with benefit of vitamin E treatment (28), further supporting the relationship to oxidative stress. Victor et al. (abstract 652) reviewed studies showing that persons with the Hp 2–2 phenotype variant have reduced clearance of circulating hemoglobin as well as reduced reverse cholesterol transport by HDL, which is oxidized by Hp variant–to–glycated hemoglobin complexes. They described a high-throughput monoclonal antibody–based assay showing 98–99% agreement in comparison with reference methods in samples from 4,126 persons, suggesting that this might prove a useful test in characterizing CV risk in diabetic patients.

Cosson et al. (abstract 639) derived a risk score from 781 asymptomatic diabetic persons with ≥1 risk factor consecutively treated between 1992 and 2006 undergoing myocardial stress or dipyridamole scintigraphy, which was positive in 227. Age ≥60 years, presence of retinopathy and of nephropathy, and extracardiac atherosclerotic arterial disease were associated with 1.5- to 1.8-fold greater

risk, whereas male sex was associated with 2.4-fold greater risk, validated among 482 type 2 diabetic patients who had scintigraphy in two other centers. Nichols et al. (abstract 100) analyzed 12,278 persons entered in the Kaiser Permanente Northwest CVD database from 2000 to 2005, followed through 2008, of whom 2,384 had type 2 diabetes; adjusting for their greater use of antiplatelet drugs, angiotensin-directed agents, β-blockers and statins, their hospitalization and mortality rates were 41 and 33% greater than among nondiabetic persons. Hanefeld et al. (abstract 724) followed 4,020 type 2 diabetic persons in Germany for 3.7 years. Among 251 having a first CV event, BMI and HDL cholesterol were lower and male sex and higher blood pressure were associated with risk, but there was no association with A1C level. Bacha et al. (abstract 261) found subclinical coronary artery calcification in 52% of 27 obese adolescents with type 2 diabetes and 17 with impaired glucose regulation, but in 37% of 27 with normal glucose regulation, with visceral adipose tissue as an additional predictive factor. Davidson et al. (abstract 717) found no difference in coronary artery calcification between 146 and 153 type 2 diabetic persons receiving pioglitazone and glimepiride, respectively, followed for 18 months; progression was associated with higher baseline age, triglyceride, BMI, and visceral obesity.

Bucca et al. (abstract 876) found that among 117 type 1 diabetic persons with mean duration 28 years those with proliferative diabetic retinopathy had higher coronary artery calcification scores, controlling for male sex, duration, albuminuria, serum creatinine, and antihypertensive treatment. Souza et al. (abstract 649) found greater CIMT in 72 type 2 diabetic than in 220 nondiabetic persons, with 19.4% versus 1.4% having atherosclerotic plaques. Diabetic patients with and without plaque did not, however, differ in CIMT, suggesting that the measure may be imperfect for assessment of carotid atherosclerosis. Gastaldelli et al. (abstract 673) reported that among 1,300 nondiabetic persons a fatty liver score based on waist circumference, BMI, and triglyceride and γ-glutamyl transpeptidase levels was associated with increased CIMT and with greater 10-year CHD risk.

Geltman et al. (abstract 742) reported that 49% of patients with type 1 diabetes duration >50 years (who presumably represent a group not developing what Brunzell described as the combination of

type 1 and type 2 diabetes) had CVD, similar to the prevalence among age-matched diabetic patients in the National Health and Nutrition Examination Survey (NHANES). Risk factors included age, duration, lower HDL cholesterol, higher lipoprotein Lp(a) and pre-β2 HDL, higher CRP and vascular cell adhesion molecule, urinary albumin-to-creatinine ratio >70 μg/mg, cigarette use, male sex, and lower blood pressure, heart rate, and LDL cholesterol, but CVD was associated neither with BMI nor with A1C, although there was an association with the advanced glycation end product carboxyethyl-lysine. Colhoun et al. (abstract 98) found that levels of circulating soluble receptor for advanced glycation end products were higher in type 2 diabetic persons having CHD events, although not being associated with stroke. Levels failed to respond to atorvastatin. Aroda et al. (abstract 267) reported that skin intrinsic fluorescence, a measure of advanced glycation end products, correlated significantly with mean A1C followed for up to 21 years but not with the most recent A1C, suggesting it to be an integrated measure of lifetime glycemic exposure. Conway et al. (abstract 1046) reported skin intrinsic fluorescence to correlate with progression of coronary artery calcification among 80 type 1 diabetic persons with follow-up scanning over a 10-year period, independent of baseline score, sex, insulin dose, and hypertension.

Rubin et al. (abstract 275) assessed 5,145 participants in the Look AHEAD (Action for Health in Diabetes) trial, showing depression and use of antidepressants to correlate with CVD risk. Curtis et al. (abstract 958) found that 509 diabetic participants were more likely than 4,470 nondiabetic persons in NHANES 2005–2006 to have moderate depression, which was present in 6.2 vs. 4.9% of normal weight, 7.6 vs. 3.7% of overweight, and 9.5 vs. 6.7% of obese persons. Anderson et al. (abstract 277) compared data from two trials including 93 diabetic persons with depression who were treated with bupropion and 351 with sertraline, suggesting greater likelihood of response to bupropion. Those with fewer diabetes complications, lower pain scores, older age, and lower baseline depression levels were more likely to show improvement. Emerson et al. (abstract 1000) reported the relationship between cardiorespiratory fitness and mortality among 6,617 nondiabetic and 932 diabetic men participating in an ex-

ercise testing study. During mean 8.1-year follow-up, those with neither diabetes nor CVD, with diabetes alone, with CVD alone, or with both who had maximal metabolic equivalent units (METs) <5 had mortality 3.3-, 3.8-, 4.6-, and 5.2-fold, respectively, compared with those with neither and with METs >10; however, there was no increase in risk for those with diabetes and METs >10, and mortality for those with both diabetes and CVD was less than half as great for those with METs >10 as for those with METs <5.

Lipid treatment approaches
D'Emden et al. (abstract 662) compared effects of fenofibrate among 3,657 women compared with 6,138 men in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and noted that it reduced LDL cholesterol by 16.5 vs. 9.4%, respectively. Adjustment for CV medications, statin "drop-in," and baseline characteristics showed fenofibrate-associated CVD reductions by 29% in women but only by 13% in men, suggesting sex differences in the effect of the agent. Sathyapalan et al. (abstract 932) reported similar mean fasting LDL cholesterol (measured with a direct assay) at 65.4 vs. 64.6 mg/dl with 40 mg simvastatin compared with 10 mg atorvastatin daily in 26 type 2 diabetic patients, but that variability of 10 samples over a 5-week period was 6.6 vs. 0.4 mg/dl, suggesting that the longer half life of the latter agent might lead to less biological variation in its action, which could be therapeutically beneficial. Ballantyne et al. (abstract 933) reported the effect of extended-release niacin in 166 persons with IFG. Fasting glucose levels at 24 weeks exceeded 125 mg/dl in 18, 21, and 34% of persons receiving 0, 1, and 2 g niacin daily, respectively. Paniagua et al. (abstract 91-LB) randomized 337 persons with metabolic syndrome to a high saturated fat, high monounsaturated fat, or low fat/high complex carbohydrate with or without very long chain n-3 polyunsaturated fatty acid supplementation for 12 weeks and found reduction in metabolic syndrome by 12, 12, 10, and 25%, respectively, suggesting the supplementation to be beneficial. In the analysis of 2,396 type 2 diabetic persons screened for the Look AHEAD study, Belalcazar et al. (abstract 173) similarly found that marine n-3 fatty acid intake was associated with higher HDL cholesterol and lower triglyceride levels. Bays et al. (abstract

471) studied the effect of AEGR-733, an inhibitor of microsomal triglyceride transfer protein, which facilitates the incorporation of lipids into apolipoprotein B–containing lipoproteins, in 461 overweight persons with dyslipidemia, and reported dose-dependent weight loss of up to 3.5%, in addition to reduction in LDL cholesterol and triglyceride levels.

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