

Atypical Antipsychotic Agents, Retinopathy, Nephropathy, and Cardiovascular Disease

ZACHARY T. BLOOMGARDEN, MD

This is the seventh and final in a series of articles on presentations at the American Diabetes Association Annual Meeting, San Diego, California, 10–14 June 2005.

Diabetes and atypical antipsychotic agents

John Newcomer (St. Louis, MO) discussed changes in adiposity and insulin sensitivity with the atypical antipsychotic agents ziprasidone, risperidone, aripiprazole, quetiapine, clozapine, and olanzapine, addressing the diabetes risk seen during treatment. Among persons with schizophrenia, approximately half are obese, half to three-quarters smoke, 10–14% have diabetes, particularly with co-existing depression, and there are also increased prevalences of hypertension and dyslipidemia. Metabolic syndrome, Newcomer stated, is present in ~40% of persons with schizophrenia. Persons with schizophrenia have increased rates of cardiovascular disease (CVD). The mortality due to myocardial infarction is 19% greater among persons with any mental illness and is 34% greater among persons with schizophrenia (1) than in a control population. CVD, then, is of similar importance to suicide as a cause of death in these patients, whose overall mortality is increased by half, leading to a 20% shorter lifespan than in persons without schizophrenia (2).

A major issue is weight gain with the atypical antipsychotic agents. Although weight gain occurs with conventional antipsychotic agents such as haloperidol, greater weight gain definitely occurs with chlorpromazine, olanzapine, and clozapine and may occur with risperidone and quetiapine. A meta-analysis of weight

change during randomized, controlled, 10-week trials showed that olanzapine and clozapine were associated with a 4-kg weight gain, while haloperidol and risperidone were associated with a 2-kg weight gain (3). Quetiapine leads to ~4-fold and olanzapine ~10-fold weight gain, while other antipsychotic agents give 2-fold greater rates of weight gain than those seen in nontreated schizophrenic persons. In 1-year studies, ziprasidone, risperidone, quetiapine, and olanzapine are associated with weight gains of ~1, 2, 4, and 6 kg. The degree of weight gain appears to be dose related, with olanzapine doses >10 mg daily associated with a 12-kg weight gain. These figures appear to be confirmed by randomized controlled trials comparing aripiprazole with olanzapine, showing weight loss with the former (perhaps because of withdrawal of prior drugs that had caused weight gain) and weight gain with the latter agent. Initial studies also show weight loss with ziprasidone treatment when changing to this agent from olanzapine or, to a lesser extent, from risperidone. In contrast, discontinuing high-potency conventional antipsychotic agents does not lead to significant weight change.

An important metabolic consequence of the use of these agents is diabetes, and there is some evidence that new-onset diabetes in this setting may also occur in the absence of weight gain. Animal models show dose-dependent worsening in insulin sensitivity with atypical antipsychotic agent administration, further suggesting that increases in fat mass alone may not fully explain the findings. The Food and Drug Administration's Medwatch program and published cases report develop-

ment of ketoacidosis in some cases, suggesting the potential of serious metabolic derangement, with a warning label to this effect now included in the package inserts for all the atypical antipsychotic agents (4).

In an analysis of an Iowa Medicaid database of persons with schizophrenia followed during 1990–1998, 552 persons treated with clozapine were compared with 2,461 treated with conventional antipsychotic drugs, with persons using other atypical antipsychotic agents and those with baseline diabetes, dyslipidemia, and hypertension excluded from the analysis (5). Diabetes, hyperlipidemia, and hypertension showed no difference in the overall group, but among persons age 20–34 years, 5 vs. 2% developed diabetes, with similar findings for hyperlipidemia. A Veterans Administration dataset of medications administered during a 4-month period in 1999 compared 15,984 persons with schizophrenia treated with conventional antipsychotic drugs versus 22,648 treated with atypical antipsychotic agents: 1,207 persons received clozapine, 10,970 olanzapine, 9,903 risperidone, and 955 quetiapine. There were significant adverse effects of atypical antipsychotic agents in persons <60 years of age, although this was not found in analysis of older persons. Clozapine, olanzapine, and quetiapine were associated with increased diabetes risk, while this was not observed with risperidone (6). Analysis of the U.K. general practice medical database from 1987 to 2000, including >30 million patient-years of observation, was used to compare olanzapine, risperidone, other atypical antipsychotic agents, and conventional antipsychotic medications, excluding persons with preexisting diabetes or hyperlipidemia (7). Adjusted for treatment with α - and β -blockers, thiazide diuretics, corticosteroids, phenytoin, female sex hormones, and valproate, there was a 1.1-fold increased risk with conventional antipsychotics but a 6-fold increased risk with olanzapine. For hyperlipidemia, conventional antipsychotic agents led to 1.5-fold increased risk, olanzapine to a 5-fold increased risk, and ris-

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.

Abbreviations: ARB, angiotensin receptor blocker; CAC, coronary artery calcium; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DPP, Diabetes Prevention Program; ESRD, end-stage renal disease; IMT, intima-media thickness; TZD, thiazolidinedione; VEGF, vascular endothelial growth factor.

DOI: 10.2337/dc06-zb06

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peridone to no increase in risk. In a 2-million member, managed-care system database, there was a 1.4-fold increase in diabetes risk with olanzapine, while risperidone, quetiapine, and conventional antipsychotic agents did not significantly increase diabetes (8). Another study, which compared 19,153 persons receiving olanzapine with 14,793 receiving risperidone, showed a 1.2-fold increase in diabetes with the former agent, adjusting for age, sex, and haloperidol use, with particular increase in risk during the first 3 months of use (9). Analysis of a pharmaceutical benefit plan dataset suggested increased diabetes risk with both conventional and atypical antipsychotic agents (10). Newcomer presented a meta-analysis of 16 databases showing clozapine and olanzapine to increase diabetes risk 1.4- and 1.25-fold compared with risperidone.

In addition to increasing weight and being associated with increased risk of diabetes, Newcomer described a study in which triglyceride levels increased with olanzapine and quetiapine at 3 and 6 weeks, also with increase in fasting insulin, with a 26-week study comparing placebo, aripiprazole, and olanzapine showing the latter to be most likely to cause and to exacerbate the abnormalities of the metabolic syndrome. A joint panel of the ADA, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity has issued a consensus statement concluding that "there is considerable evidence" that treatment with atypical antipsychotic agents may lead to rapid weight gain and recommending that patients be monitored for this as well as for diabetes and CVD with personal and family history, as well as baseline and follow-up measurement of weight and height, waist circumference, blood pressure, and fasting glucose and lipids. The panel also concluded that the agents differ in their risk profiles, so that clozapine and olanzapine, while effective treatment options, are associated with greater risk of weight gain, diabetes, and lipid disorders (11).

Retinopathy

Richard Hamman (Denver, CO) discussed the development of retinopathy in the Diabetes Prevention Program (DPP), noting that little is known about the time to onset of diabetic retinopathy in persons with new-onset type 2 diabetes and noting the paucity of studies among persons

with IGT. There is evidence that retinopathy is preceded by ~5 years of hyperglycemia (12). Using the DPP database, it was possible to study the level of glycemia at which retinopathy occurs and the time course of development of retinopathy in early type 2 diabetes. A total of 3,234 persons with IGT and fasting blood glucose 95–125 mg/dl participated in the DPP. At the conclusion of the DPP, an outcome study was carried out in the 2,731 persons agreeing to participate, 1,854 without and 877 with diabetes. Retinal photos were performed in a subset of 12% of DPP participants. Retinopathy was found in some persons during the initial year following diabetes development. The development of "any retinopathy," excluding hemorrhage and exudates, occurred in 9.6 and 15.4% of persons without and with diabetes, with changes suggestive of diabetic retinopathy in 7.6 and 12.5%; 6.6 and 10.6 had microaneurysms, and 1% and 1.9 had mild to moderate nonproliferative diabetic retinopathy. Overall, diabetic retinopathy was seen in 7.6% of participants without diabetes, in 8.9% of those with diabetes for 0–1 year, and in 13.5% at 1–2 years. There were no differences in risk factors among persons without diabetes who developed retinopathy. For those with diabetes, blood pressure levels were higher and HbA_{1c} (A1C) levels 6.26 vs. 6.06% among those with versus without diabetic retinopathy, respectively. Thus, retinopathy may be seen early in the course of type 2 diabetes at only modestly elevated levels of glycemia, arguing against the concept that this complication requires a long duration of diabetes with marked hyperglycemia.

A number of presentations at the ADA meeting illustrated further clinical information about retinopathy. White et al. (abstract 919) reported the effect of prior intensive therapy on retinopathy in 1,246 adult and 195 adolescent Diabetes Control and Complications Trial (DCCT) participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study. At 10 years, three-step progression of retinopathy was seen in 48 vs. 75% of adults with former intensive versus conventional treatment and for 73 vs. 86% of adolescents, despite A1C levels in all groups of ~8.2% after the conclusion of the DCCT. The lesser benefit of prior intensive treatment in adolescents may be due to their higher mean A1C levels during the DCCT. Genuth et al. (abstract 925) reported the relationship between retinopathy and glycation and

advanced glycation products in skin collagen from skin biopsy performed near closeout of the DCCT in 184 persons at 10-year follow-up. Those whose retinopathy progressed had higher levels of furiosine and carboxymethyllysine, suggesting that glycation of long-lived collagen molecules may play a role in the "metabolic memory" of persistent benefit of intensive treatment during the DCCT. Klein et al. (abstract 1042) performed ambulatory blood pressure monitoring in 233 persons with type 1 diabetes, showing an association of nighttime but not daytime systolic and diastolic blood pressure with severity of retinopathy. Nishimura et al. (abstract 1885) followed 1,061 persons with type 1 diabetes from the U.S. and 1,408 from Japan diagnosed in 1965–1979 through 1995. Twenty five-year photocoagulation rates were 50 and 49%, but 15-year rates decreased from 23 and 18% in those diagnosed from 1965 to 1969 to 14 and 16% in those diagnosed from 1975 to 1979. After 25 years, 20 and 27% of the two groups required renal replacement therapy, but 15-year rates decreased from 6 and 13% in those diagnosed from 1965 to 1969 to 3 and 4% in those diagnosed from 1975 to 1979. Cagliero et al. (abstract 25) compared 31 persons with type 1 diabetes with no or minimal retinopathy and with A1C 7.4% with 29 age-matched control subjects, showing no difference in laser Doppler retinal blood flow characteristics, further suggesting that current approaches to treatment may lessen future complications.

Growth factors and retinopathy pathogenesis. Hernandez et al. (abstract 29) measured vitreous somatostatin in 22 persons with proliferative retinopathy versus 22 control subjects, finding that the 28-amino acid molecular species had levels of 350 vs. 595 pg/ml. A relationship between deficit of this natural antiangiogenic factor and retinopathy suggests potential new therapeutic approaches. Yokota et al. (abstract 906) administered the angiotensin receptor blocker (ARB) olmesartan to streptozotocin-induced diabetic rats, showing evidence that retinopathy decreased. In cultured porcine retinal pericytes, glycated albumin up-regulated expression of platelet-derived growth factor β and vascular endothelial growth factor (VEGF) mRNA, and olmesartan inhibited this, suggesting a mechanism of therapeutic benefit. Khan et al. (abstract 910) administered C-peptide in a rat model of type 1 diabetes, showing

decreased VEGF expression. In vitro, exposure of vascular endothelial cells to high levels of glucose with C-peptide attenuated increased VEGF expression as well, suggesting this β -cell secretory product to have potential benefit in retinopathy, as has also been suggested for neuropathy and nephropathy. Growth factors also play a role in the development of diabetic nephropathy. Zhang et al. (abstracts 863 and 864) found that streptozotocin-induced diabetic rats had increased renal VEGF and intercellular adhesion molecule-1, as well as decreased renal levels of angiostatin, an antiangiogenic plasminogen fragment. They speculated that decreased matrix metalloproteinase-2 results in decreased release of angiostatin, which may physiologically inhibit high glucose-induced expression of fibronectin, VEGF, and transforming growth factor- β , contributing to inflammation and fibrosis. Pigment epithelium-derived factor, another angiogenic inhibitor, was also decreased by high glucose concentrations, another potential cause of transforming growth factor- β overexpression and fibronectin production, contributing to glomerular mesangial expansion.

Sun et al. (abstract 907) reported that aspirin in anti-inflammatory doses prevented the development of acellular capillaries in the retina of streptozotocin-induced diabetic rats, without an effect of clopidogrel, an inhibitor of ADP-induced platelet aggregation, and without change in prostaglandin E2 levels, suggesting the mechanism to involve neither platelet effects nor change in prostaglandin levels. Zheng and Kern (abstract 929) administered aspirin, sodium salicylate, or sulfasalazine to diabetic rats, all agents reducing retinal vascular cell death and acellular capillaries, with the authors suggesting an nuclear factor κ B-mediated effect. Kowluru and Basak (abstract 908) found that retinal levels of the mitochondrial enzyme superoxide dismutase were inhibited \sim 30% in streptozotocin-induced diabetic rats, with a three- to fourfold increase in apoptotic capillary cells and acellular capillaries; these abnormalities were prevented by dietary α -lipoic acid supplementation.

Nephropathy

Burrows et al. (abstract 821) used data from the U.S. Renal Data System to analyze the rate of development of end-stage renal disease (ESRD) from 1990 to 2002, during which time the annual ESRD inci-

dence among persons with diabetes increased from 16,649 to 43,638. The increase in ESRD incidence was associated with increasing prevalence of diabetes, with the age-adjusted incidence increasing from 277.8 in 1990 to 344.4 in 1996 but subsequently decreasing to 234.6 per 100,000 diabetic population in 2002. Although decreasing 32 and 38% between 1996 and 2002 for persons aged 45–64 and <45 years, respectively, the rate was stable for persons aged 65–74 and increased 15% for those >75 years of age. Unnikrishnan et al. (abstract 836) and Rema et al. (abstract 32) performed a population-based survey of 26,001 persons aged ≥ 20 years in Chennai, India. Diabetes had been diagnosed among 1,529 persons in the survey. Two urine albumin determinations were performed in 1,374 persons, with 18% having microalbuminuria on both occasions. Of 872 persons with diabetes, four-field retinal stereo color photography showed a 17% prevalence of retinopathy and there was electrocardiographic or historical evidence of coronary disease in 18%, with the two conditions showing significant correlation. Overall, diabetic nephropathy, retinopathy, and coronary disease each affect \sim 1% of the region's population, with Mohan et al. (abstract 1017) further reporting that the study showed 6 and 9% of the region's adult population to have diagnosed and undiagnosed diabetes.

Pavkov et al. (abstract 1066) followed 1,926 Pima Indians with diabetes for a mean of 13.7 years, reporting a 7.5-fold greater age- and sex-adjusted likelihood of ESRD among those developing diabetes at age <20 than at ≥ 20 years. Mortality was 2.7- and 1.9-fold greater for the younger- and older-onset diabetes groups than for 3,053 persons without diabetes. Boright et al. (abstract 845) studied apolipoprotein E polymorphisms in the 14-year DCCT/EDIC follow-up of 1,347 Caucasian persons with type 1 diabetes, finding that the T/T and T/C genotypes of the marker rs7412 were associated with 44% greater likelihood of development of persistent microalbuminuria than the C/C genotype, indicating an association with the e2 haplotype, although this was not significant in multivariate analysis with triglyceride, total cholesterol, and HDL. Ng et al. (abstract 798) performed a meta-analysis of 47 studies of 14,727 subjects addressing the association of the ACE insertion (I)/deletion (D) polymorphism with diabetic nephropathy, showing the

II genotype to be associated with a 22% lower risk of nephropathy, with the association seen particularly among type 2 diabetic Chinese, Japanese, or Koreans. So et al. (abstract 866) followed 2,089 Chinese type 2 diabetic patients for 45 months, with higher ACE activity in DD carriers. ACE inhibitor/ARB treatment reduced mortality by approximately half for II and ID compared with no effect in persons with the DD genotype, with the likelihood of renal failure among macroalbuminuric persons decreasing 70 vs. 60%. Canani et al. (abstract 824) studied the A54T polymorphism of intestinal fatty acid-binding protein-2, responsible for absorption of long-chain fatty acids, and associated with insulin resistance and hypertriglyceridemia, in 1,042 Brazilians and in 483 persons from Massachusetts with type 2 diabetes. The TT genotype was associated with a doubling of the likelihood of albuminuria, of proteinuria, and of ESRD.

A number of studies suggest the need for revised approaches to the characterization of persons with diabetes and renal disease. Placha et al. (abstract 812) studied 63 families with 426 diabetic and 431 nondiabetic persons, showing 26% heritability of urinary albumin excretion and 39% heritability of serum cystatin C, a measure of glomerular filtration that may be more accurate than creatinine clearance. However, albuminuria and cystatin C showed linkage with different sites, on chromosomes 7q and 22q and chromosome 7p, respectively, and did not correlate with each other. Bakris et al. (abstract 219) studied 21,897 persons age 53 years participating in the Kidney Early Evaluation Program, finding that among those with hyperglycemia, the urine albumin-to-creatinine ratio was >20 mg/g in 49, 56, 75, and 80% of those with creatinine clearance estimated from the Modification of Diet in Renal Disease (MDRD) formula 60–89, 30–59, 15–29, and <15 ml/min per 1.73 m², respectively. Severe renal function impairment may then be present without albuminuria. Middleton et al. (abstract 220) studied 7,596 adults with diabetes in Salford, U.K., finding that 28% had creatinine clearance <60 ml/min per 1.73 m², of whom 51% had albuminuria and 18% had serum creatinine >1.7 mg/dl. Clinicians should, then, estimate creatinine clearance in order not to overlook persons with noteworthy degrees of renal impairment. Silveiro et al. (abstract 225) followed 160 persons with type 2 diabetes and urine albumin <20

$\mu\text{g}/\text{min}$ for a mean period of 8 years, showing that urine albumin $>8.5 \mu\text{g}/\text{min}$ was a predictor for progression to nephropathy, suggesting that the currently used microalbuminuria cutoff may be too high. Rigalleau et al. (abstracts 794 and 805) compared creatinine clearance determination from the Cockcroft and Gault formula with isotopic determination in 122 persons with diabetes and renal damage, showing that the formula lead to a 14% underestimate in persons with normal BMI but to 15 and 55% overestimates in persons who were overweight and obese, respectively. The MDRD formula was more accurate, although also somewhat overestimating low creatinine clearance.

Jimenez-Corona et al. (abstract 1067) studied 1,296 Pima Indians without diabetes, of whom 128 developed $>30 \text{ mg}/\text{g}$ creatinine albuminuria over 4.7 years of follow-up. This degree of albuminuria occurred twice as often in women, 24% more often per 10 cm waist circumference, and 13% more often per 10-mmHg increase in blood pressure. Among 446 with diabetes who had normal urinary albumin excretion ($<30 \text{ mg}/\text{g}$) at baseline, 149 developed albuminuria during a similar period of follow-up, with 14% greater incidence per 10 mmHg blood pressure, but other risk factors were different from those of those without diabetes: 48% per 100 mg/dl fasting glucose, 23% per 10-mg/dl-lower HDL cholesterol, and curiously 9% less per 50 mg/dl triglyceride.

Tuttle et al. (abstract 223) followed 123 persons with type 2 diabetes and albumin-to-creatinine ratio 200–2,000 mg/g, despite treatment with ACE inhibitors, ARBs, or both for at least 6 months, showing a 24% 1-year fall in albuminuria with the protein kinase C β inhibitor ruboxistaurin. Nicholas et al. (abstract 224) reported a 48% decrease in albuminuria in a diabetic mouse treated with rosiglitazone, while no change was seen in insulin-treated mice with similar improvement in glycemia. Lim et al. (abstract 456) compared 50 mg losartan with 20 mg quinapril daily in a cross-over study of 40 previously untreated type 2 diabetic persons with albuminuria, showing similar decrease in blood pressure but a greater reduction in albuminuria with the ARB agent. Ljubic et al. (abstract 813) treated 69 type 2 diabetic persons with lisinopril, 48 with losartan, and 36 with both for 1 year. Pulse pressures were 65, 71, and 75 mmHg, decreasing 8, 11, and 24 mmHg, respectively, with lisinopril

but not losartan associated with decrease in C-reactive protein (CRP) and the combination most potent in reducing albuminuria.

Moltich et al. (abstract 810) compared 65 persons with type 1 diabetes for >20 years without versus 42 with urine albumin excretion $\geq 30 \text{ mg}/\text{g}$ creatinine, showing a 30% decrease in likelihood of nephropathy for every 10-mg/dl increase in HDL cholesterol. Hor and Baldwin (abstract 825) reported 7-year follow-up of 104 persons with diabetes following renal transplantation, finding that, in persons both with preexisting (60%) and new-onset posttransplant (40%) diabetes, blood pressure and glucose control reduced the likelihood of elevation in the albumin-to-creatinine ratio, which in turn was associated with greater likelihood of stable renal function.

Donnan et al. (abstract 685) studied the 1993–2001 cohort of 4,442 persons with type 2 diabetes from Tayside, Scotland. A total of 931 of subjects had coronary heart disease (CHD) events, with anemia and, particularly, the change in hemoglobin risk factors independent of creatinine clearance. Middleton et al. (abstract 831) found a 25% prevalence of anemia among 7,596 persons with diabetes in Salford, U.K., with 42% prevalence among persons with creatinine clearance $<60 \text{ ml}/\text{min}$ per 1.73 m^2 . The presence of albuminuria was independently associated with a 72% increase in likelihood of anemia, with lower diastolic blood pressure and diabetes duration additional risk factors. Fischer et al. (abstract 832) found anemia in 26% of 160 type 1 and in 22% of 348 type 2 diabetic persons. Urine albumin excretion was increased in 48 vs. 29%, respectively. Evidence of iron deficiency was present in 26% of type 1 vs. 13% of type 2 diabetic persons with anemia. Kyriacou et al. (abstract 837) studied 321 persons with chronic kidney disease, 22% with diabetes, finding 22 vs. 8% of nondiabetic patients having hemoglobin $<11 \text{ g}/\text{dl}$, with low creatinine clearance and low albumin additional risk factors, the latter suggesting a relationship to malnutrition and/or inflammation.

CVD

Relationship between diabetes treatment and CVD. Johannes et al. (abstract 1053) compared subsets of 16,685 persons with diabetes starting a thiazolidinedione (TZD) with 19,938 starting metformin or a sulfonylurea, matching for age, CHD risk factors, insulin, and other

antidiabetic medication use, showing 22.35 vs. 21.55 episodes of myocardial infarction or coronary revascularization per 1,000 person-years over a mean 15-month follow-up period. Inzucchi et al. (abstract 256) studied 24,953 Medicare beneficiaries with diabetes discharged from the hospital after myocardial infarction, 8,872 discharged on an antihyperglycemic agent, 3,515 sulfonylurea, 3,509 insulin, 1,273 metformin, 819 TZD, and 139 both metformin and TZD. Mortality rates were similar for all monotherapies but were reduced 48% in those taking both sensitizers. TZDs were, however, associated with 17% increased risk of readmission for heart failure. Abdalla et al. (abstract 703) reported 5-year mortality for diabetic and nondiabetic persons from a national cohort of 203,656 Medicare patients aged ≥ 65 hospitalized with confirmed acute myocardial infarction between 1994 and 1995, with the 32% having diabetes having 44% increased mortality after adjusting for demographics, past medical history, procedures during hospitalization, medications on admission/discharge, and quality of care. Silver et al. (abstract 684) found that 21 and 16% of 92 and 114 persons with type 1 and type 2 diabetes were resistant to aspirin, a prevalence similar to that in other high-risk persons, suggesting that aspirin should remain the primary antiplatelet agent for persons with diabetes but that consideration should be given to determination of aspirin resistance to identify persons who would benefit from additional antiplatelet therapy. Albert et al. (abstract 689), studying 10 persons with poorly controlled diabetes and 10 nondiabetic control subjects, failed to find any decrease in aspirin's platelet effect. Khanolkar et al. (abstract 729) found, interestingly, that peroxisome proliferator-activated receptor α is highly abundant in platelets and that clofibrate reduced ADP-induced platelet aggregation in vitro, suggesting an antithrombotic effect of fibrate therapy. Khanolkar et al. (abstract 546) reported a 33% decrease in platelet aggregation among 35 persons treated with rosiglitazone versus the sulfonylurea gliclazide in combination with metformin. Platelet reactivity decreased following in vitro incubation of whole blood with rosiglitazone.

Scheen et al. (abstract 704) performed a meta-analysis of stent use for coronary artery disease (CAD) in persons with diabetes. Ten studies assessing performance of bare-metal stents showed a

64% increase in likelihood of restenosis, and 6 studies of paclitaxel- or sirolimus-eluting stents, although reducing restenosis 85% during the 1st year, still showed a 96% increase in likelihood of restenosis in the diabetic subgroup. Katayama et al. (abstract 709) administered 30 mg pioglitazone daily versus placebo to 30 persons without diabetes following coronary stenting. Intravascular ultrasound at 6 months showed 20 vs. 36% restenosis with 50% reduced intimal area, suggesting the agent to reduce neointimal hyperplasia after stent implantation even without diabetes.

CVD risk factors. Schaan et al. (abstract 724) categorized 145 persons undergoing coronary angiography by fasting blood glucose, finding that as glucose increased from <88 to 88–99, to 100–125, and to >125 mg/dl, coronary disease extent by the Humphries score increased from 27 to 30, to 36, and to 50 and by the Califf score from 39 to 50, to 60, and to 69, respectively, suggesting an association with glycemia even within the normal range. Drexel et al. (abstract 740) followed 750 persons following coronary angiography, showing 4-year event rates of 15, 20, and 31% with fasting glucose ≤ 100 , 101–125, and ≥ 126 mg/dl, respectively, with factor analysis suggesting the glycemia-related increase to be associated with low HDL/high triglyceride.

Several studies presented findings showing the relationship of risk to metabolic syndrome. Wong et al. (abstract 255) characterized 5,298 persons with type 2 diabetes, finding that 72% had World Health Organization metabolic syndrome. Compared with diabetic persons without the syndrome, there was a 17.2 vs. 11.6% prevalence of ischemic heart disease, 7.6 vs. 4.7% history of coronary artery bypass graft, and 6 vs. 3.9% history of stroke. Metabolic syndrome was associated with more than a doubling of ischemic heart disease risk among persons age 40–50 years. Franklin et al. (abstract 1018) studied 2,753 participants in the Fourth National Health and Nutrition Examination Survey (NHANES) 1999–2000 not receiving antihypertensive medications. Isolated diastolic comprised 21%, systolic-diastolic 23%, and isolated systolic 56% of hypertension, but the likelihood of the three hypertension types was increased 11-, 5-, and 2-fold, respectively, in persons with versus without metabolic syndrome. Diastolic hypertension, although less common, may then be particularly associated with metabolic

syndrome. Landsman and Alexander (abstract 646) used Third NHANES data to assess the relationship of diabetes, metabolic syndrome, and CRP to CHD among persons aged ≥ 50 years, showing CHD in 8 and 9% and CRP >3 mg/l in 25 and 25% of those with and without diabetes without metabolic syndrome, but, in CHD, in 19 and 14% of those with and without diabetes with metabolic syndrome and elevated CRP in 48 and 44% of those two groups. Among those with CRP >3 mg/l, 22% of those with diabetes, and 14% of those without diabetes had CHD. For those with metabolic syndrome without diabetes, the prevalence of CHD was 14 vs. 12% for high versus low CRP; for those with both metabolic syndrome and diabetes, the prevalence of CHD was 22 vs. 16% for high versus low CRP.

Several additional potential CVD risk factors were presented in other studies. Watanabe et al. (abstract 648) studied 12 persons with type 2 diabetes during a hyperinsulinemic-euglycemic clamp, showing increase in QT dispersion, the difference between the maximum and the minimum QT interval on a 12-lead electrocardiogram, a measure of the spatial inhomogeneity of cardiac repolarization, while there was no change in the coefficient of variation of RR intervals, a measure of cardiac autonomic neuropathy, and no association of the increase in QT dispersion with fall in serum potassium. Ljubic et al. (abstract 670) randomized 283 persons with type 2 diabetes to a 1-year period of treatment with atorvastatin, simvastatin, pravastatin, lisinopril/losartan, aspirin, or a control group receiving none of these. CRP levels decreased with atorvastatin, simvastatin, and lisinopril/losartan; homocysteinemia with simvastatin and pravastatin; and fibrinogen only with atorvastatin. Hermans et al. (abstract 679) assessed variants of the C₆₇₇T methylene-tetrahydrofolate reductase gene polymorphism in 133 type 2 diabetic persons with homocysteine >12 μ mol/l, finding 55 with the CT and 25 with the TT genotype, with a 23% prevalence of stroke, while only 6% of the 53 with the CC genotype had had this complication, although the homocysteine levels did not differ between the three groups. Lin et al. (abstract 672) reported that plasma cardiotrophin-1, a newly isolated cytokine related to interleukin-6 that induces cardiac myocyte hypertrophy, was 31, 100, and 269 pg/ml in nondiabetic, type 2 diabetic normotensive, and type 2 diabetic hypertensive persons,

correlating in multivariate analysis with blood pressure and with apolipoprotein B. Keenan et al. (abstract 727) performed a 10-cM genome screen on 177 diabetic and 317 nondiabetic family members for linkage with CRP and interleukin-6, both showing higher levels in persons with diabetes and both showing significant heritability; with gene linkages found on chromosomes 1q41 for interleukin-6 and 5p15 for CRP.

Avignon et al. (abstract 674) studied 20 type 2 diabetic persons with asymptomatic angiographically proven coronary disease and 20 age-, sex-, and duration-matched type 2 diabetic persons with negative exercise electrocardiogram and myocardial scintigraphy, showing association of coronary disease with plasma levels of osteoprotegerin, an inhibitor of osteoclast formation that may play a role in atherosclerosis. Young et al. (abstract 688) reported that of 236 asymptomatic persons with type 2 diabetes, 15% had “minor T-wave abnormality,” which was associated with a 2.6-fold increase in the likelihood of the presence of reversible myocardial perfusion imaging defect, suggesting silent myocardial ischemia. The presence of T-wave abnormality had a 26% sensitivity, 88% specificity, positive predictive value of 30%, and negative predictive value of 85% in the population studied. Abnormal Valsalva ratio, a measure of cardiac autonomic neuropathy, was also significant in multivariate analysis, predicting a fivefold increase in likelihood of silent ischemia. Moriaj et al. (abstract 692) studied 170 type 2 diabetic persons, finding a 2.2-fold increase in CVD risk for those who were *Helicobacter pylori* positive, associated with an HDL cholesterol of 50 vs. 54 mg/dl in those who did not have serologic evidence of infection, with antibiotic treatment associated with 9.4% lowering of total cholesterol. Leitão et al. (abstract 838) studied 1,349 persons with type 2 diabetes, finding cigarette use to be associated with increased coronary disease, despite lower weight and blood pressure.

Noninvasive CVD assessment. In a study of 335 nondiabetic Mexican-American persons whose parents had CAD, compared with 146 spouses without such history, Quinones et al. (abstract 691) reported that premature parental CAD (before age 55 years for fathers or 65 for mothers) was associated with carotid intima-media thickness (IMT) of 0.670 vs. 0.636 mm in those without such parental history. Fasting insulin was a sig-

nificant risk factor, along with systolic blood pressure, parental history, cigarette use, age, and sex. Araki et al. (abstract 253) reported that carotid artery stiffness, measured by ultrasound, showed negative correlation with plasma adiponectin in 98 persons with type 2 diabetes and 116 nondiabetic persons. Ahmad et al. (abstract 660) compared 81 persons with newly diagnosed type 2 diabetes with nondiabetic control subjects, showing an increase in carotid IMT and in the inflammatory markers CRP, tumor necrosis factor- α , and fibrinogen in diabetes, but no association of IMT with inflammation. Sanchez et al. (abstract 651) reported abnormal, large proximal upper-extremity artery elasticity in 28% of 50 nondiabetic persons versus 46% of 56 persons with diabetes. Teramura et al. (abstract 662) studied 1,542 Japanese adults, 654 with type 2 diabetes, showing that modified metabolic syndrome, based on BMI >23.8 kg/m² for men and >27.7 kg/m² for women rather than on waist circumference, was present in 40 and 9% of men and of women, showing association with carotid IMT and carotid stiffness, with hyperglycemia and blood pressure correlating with both measures and with low HDL cholesterol and blood pressure correlating with carotid stiffness. In a study of 99 potential nucleotide polymorphisms contributing to CVD in 2,126 persons with diabetes, Yamasaki et al. (abstract 708) reported that combinations of genes rather than individual polymorphisms appeared to lead to increased carotid IMT, with, for example, diabetic persons with the methylene-tetrahydrofolate-reductase gene 677TT genotype, interleukin-10 gene -819TT genotype, and thrombospondin-1 gene 2210AA genotype showing fivefold greater increase in carotid IMT than nondiabetic persons. Hosoi et al. (abstract 714) measured carotid IMT in 274 persons with type 2 diabetes, finding it to be associated with the total-to-HDL cholesterol ratio, systolic blood pressure, and peak plasma glucose during a 3-day hospitalization, but not with A1C.

Urbina et al. (abstract 208) studied 969 adolescents, finding that among those with BMI below the 85th percentile for age, sex, and ethnicity, having fasting insulin below versus above the 90th percentile was associated with brachial artery distensibility of 7.1 vs. 6.8 mmHg, while overweight or obese adolescents with lower versus higher insulin had brachial artery distensibility of 6.2 vs. 5.9 mmHg,

suggesting that both insulin resistance and obesity contribute separately to the early development of atherosclerosis. Suzuki et al. (abstract 677) followed 28 type 2 diabetic persons with ankle-brachial systolic pressure index >0.9 for 3–4.8 years, showing correlation of mean A1C, but not of blood pressure, lipids, or cigarette use, with the annual rate of change in brachial-ankle pulse-wave velocity and resistive index, suggesting an effect of glycemia on arterial stiffness. Porramatikul et al. (abstract 680) reported a $\sim 50\%$ increase in arterial stiffness, based on the augmentation index derived from pulse-wave analysis, in persons with type 2 diabetes, impaired glucose tolerance, or metabolic syndrome, correlating with age, sex, triglyceride, and diastolic blood pressure levels. Yoshimura et al. (abstract 711) measured popliteal artery blood flow volume with gated two-dimensional cine-mode phase-contrast magnetic resonance imaging in 229 persons with type 2 diabetes without known CVD, reporting that 3.2-year follow-up revealed those whose flow volume was <73 ml/min per 1.73 m² had an 11.2-fold greater risk of events than those with greater flow rates, suggesting this to be a potential screening tool for systemic atherosclerosis as well as that of the lower extremities. Jerums et al. (abstract 221) performed a renal duplex scan and transthoracic echocardiogram in 197 persons with type 2 diabetes, showing that the renal parenchymal resistance index, a measure of compliance of the intrarenal arteries, correlated with measures of left-ventricular diastolic dysfunction.

Adiponectin and CVD. Jazri et al. (abstract 254) reported that the presence of the G allele of the adiponectin T45G polymorphism was associated with a 70% increase in the likelihood of myocardial infarction, controlling for sex, age, BMI, A1C, albuminuria, and blood pressure in a cohort of 3,123 persons with type 2 diabetes followed for 47 months. Kang et al. (abstract 687), however, found no effect of the adiponectin T45G polymorphism on carotid IMT, although carotid IMT was higher in patients with the SNP276 GG genotype, who had 33% lower adiponectin levels than those with other genotypes.

Abdella et al. (abstracts 641 and 642) evaluated 102 persons with type 2 diabetes, showing age-adjusted negative correlation of adiponectin with BMI, waist, CRP, and leptin but not with insulin or homeostasis model assessment of insulin resistance. In a larger group of 141 per-

sons with diabetes, 55 with CHD, resistin correlated with obesity, insulin resistance, and CHD risk factors but not independently with CHD. Moriuchi et al. (abstract 2003) reported increased adipocyte adiponectin production with pioglitazone and with the angiotensin 2 receptor antagonist telmisartan, but not with candesartan, noting that there is also evidence that telmisartan may directly activate peroxisome proliferator-activated receptor γ .

Burnett et al. (abstract 1068) compared resistin levels in Native Americans with versus without prior myocardial infarction, showing diabetes prevalence of 67 vs. 41% and resistin levels 3.4 vs. 2.8 ng/ml, more strongly associated with albuminuria >300 mg/g creatinine than with history of myocardial infarction. Kanaya et al. (abstract 982) studied 2,848 white and black adults aged 70–79 years, finding that for African Americans, doubling of adiponectin unexpectedly increased the likelihood of CHD 8% among those with normal or impaired glucose tolerance and 15% among those with diabetes but that there was no relationship between adiponectin and CHD among Caucasians.

Glycation and CVD. Koyama et al. (abstract 252) reported that the soluble variant of the receptor for advanced glycation end products (sRAGE), which acts as a circulating “decoy receptor” for AGE, was 0.18 vs. 0.25 ng/ml in 210 persons with type 2 diabetes compared with 134 nondiabetic control subjects, showing modest negative correlation with body weight, blood pressure, glucose, A1C, and insulin resistance, with levels 0.17 vs. 0.22 ng/ml in persons with versus without plaque in the carotid and femoral arteries. For each 0.1-ng/ml increase in sRAGE, there was a 54% reduction in the likelihood of arterial plaque independent of age, sex, BMI, systolic blood pressure, smoking, non-HDL cholesterol, HDL cholesterol, and A1C.

Wilson et al. (abstract 1892) noted that different persons glycate proteins at different rates and that higher glycation rates may predict increased risk for long-term complications independently of glycemic control. They used home glucose monitoring data to calculate mean glucose area under the curve (AUC) using the trapezoidal rule in 123 persons averaging at least four tests per day, suggesting that a measure of glycation might be the residual from a regression of A1C versus glucose AUC, showing within-individual correlation of this measure on three occa-

sions at 3-month intervals. The approach failed to show good correlation when 3-day continuous glucose monitoring data were used rather than the meter glucose values. Cohen et al. (abstract 405) studied genetic determinants of hemoglobin glycation by measuring the difference between A1C measured directly and calculated from serum fructosamine in 40 and 47 pairs of monozygotic and dizygotic healthy female twins, respectively, showing higher correlation in the monozygotic group, suggesting that 68% of the difference is heritable, with postulated mechanisms including variations in intracellular glucose concentrations or in rates of nonenzymatic glycation or deglycation. Kim et al. (abstract 1001) compared the difference between U.K. Prospective Diabetes Study (UKPDS) participants' actual A1C and that predicted from regression of A1C on fasting plasma glucose, which they termed the hemoglobin glycation index, with the development of 309 microvascular events (first-to-occur of retinopathy requiring photocoagulation, vitreous hemorrhage, or fatal or nonfatal renal failure) in 3,421 participants in the UKPDS. The glycation measure showed similar predictive power as the fasting glucose or A1C, with blood pressure and male sex also significant risk factors, while, peculiarly, obesity and cigarette smoking were protective in their model.

Schindhelm et al. (abstract 661) measured the reactive dicarbonyl 3-deoxyglucosone, a major intermediate in the formation of AGE, following two high-fat or -carbohydrate meals in eight women with type 2 diabetes versus nine control subjects. Baseline 3-deoxyglucosone was 215 vs. 162 nmol/l with further increase to 303 vs. 184 nmol/l after carbohydrate, while the high-fat meals were not associated with increased levels. Friedman et al. (abstract 706) reported increase in mRNA expression of intracellular adhesion molecule-3, integrin $\beta 1$ and $\beta 2$, and CD69, as well as protein expression of CD69, in mononuclear cells after ingestion of 75 g glucose.

Negrean et al. (abstract 722) and Stirban et al. (abstract 723) compared effects of meals with high versus low AGE content in 10 persons with type 2 diabetes, showing a 46 vs. 20% decrease in brachial artery flow-mediated vasodilatation, the effect of the former markedly attenuated by administration of the liposoluble vitamin B₁ analog benfotiamine. Uribarri et al. (abstract 1783) reported a correlation

of dietary AGE intake with serum AGE, LDL-apolipoprotein B-AGE, CRP, and insulin levels in 90 healthy nondiabetic persons, suggesting that dietary AGEs contribute to circulating prooxidant AGEs and influence inflammation and insulin sensitivity.

Qi et al. (abstract 1005) measured adiponectin levels in 780 persons with diabetes in the Health Professionals' Follow-up Study, finding that levels were 18% higher in persons in the lowest versus highest quintile of glycemic load, with dietary fiber and magnesium also associated with higher adiponectin. Martinez-Larrad et al. (abstract 1027) studied 571 persons without diabetes, finding cigarette smoking to be associated with lower adiponectin levels after adjustment for age, sex, HDL cholesterol, triglycerides, and insulin sensitivity.

Type 1 diabetes and CVD. Karantza et al. (abstract 261) compared carotid IMT in 90 type 1 diabetic patients aged 12–21 years with 16 control subjects, showing greater IMT in diabetic patients than nondiabetic control subjects in males, correlating with A1C, cigarette exposure (either smoking or "second hand"), and apolipoprotein B but not correlating with fibrinogen, von Willebrand factor antigen, plasminogen activator inhibitor 1, interleukin-6, or homocysteine. Pitocco et al. (abstract 658) compared 27 persons with type 1 diabetes with 27 age- and sex-matched persons with type 2 diabetes, showing 0.9 vs. 2.1 mg/l CRP, with no relationship to clinical variables in type 1 diabetes, although there was an association of CRP with BMI in type 2 diabetes. Karantza et al. (abstract 1888) studied 74 type 1 diabetic adolescents, finding that those with CRP <1, 1–3, and >3 mg/l had LDL 99, 121, and 110 mg/dl, apolipoprotein B 77, 96, and 96 mg/dl, and triglyceride 71, 103, and 155 mg/dl, respectively, with significant differences between the groups with CRP <1 and 1–3 mg/l but not between those with CRP 1–3 and >3 mg/l. HDL cholesterol was similar in the three groups. Picardi et al. (abstract 716) reported that 43 persons with type 1 diabetes had median CRP 0.43 vs. 0.69 mg/l at diagnosis vs. 1 year subsequently. Devaraj et al. (abstract 249) measured inflammatory markers in 50 persons with type 1 diabetes vs. 50 nondiabetic control subjects, showing CRP 2.6 vs. 1.2 mg/l, with increased intercellular adhesion molecule and monocyte interleukin-6 and superoxide release, suggesting type 1 diabetes to be associated with inflamma-

tion. Gabbay et al. (abstract 713) studied 481 persons with type 1 diabetes age 19.7 years, finding that as diabetes duration increased from <5, to 5–10, to 10–15, and to >15 years, the mean waist circumference increased from 72, to 75, to 76, and to 79 cm, the prevalence of hypertension increased from 8 to 14, to 19, and to 47%, and the prevalence of metabolic syndrome increased from 9 to 15, to 30, and to 44%, respectively. McGill et al. (abstract 250) studied 427 ketosis- or antibody-positive (GAD or insulinoma-associated protein 2) persons with type 1 diabetes, comparing 64 patients with World Health Organization metabolic syndrome versus duration-matched patients without the syndrome. For those with diabetes >20 years, BMI was 27 vs. 24 kg/m², blood pressure 140/80 vs. 120/71 mmHg, HDL 50 vs. 59 mg/dl, triglyceride 203 vs. 88.5 mg/dl, and urine albumin 60 vs. 7 mg/l. Metabolic syndrome increased the likelihood of stroke 23-fold, ischemic heart disease 2.4-fold, peripheral arterial disease 7.3-fold, and retinopathy 3.7-fold, although the authors recognized that one cannot determine from these data whether the increased risk is related to insulin resistance or rather to the effect of the various risk factors. Penno et al. (abstract 862) studied 978 persons with type 1 diabetes, finding 13% with metabolic syndrome, with hypertension the most common defining abnormality. Microalbuminuria was present in 27% of those with compared with 18% of those without metabolic syndrome, as well as macroalbuminuria in 21 vs. 5%, with the syndrome also correlating with retinopathy.

Maahs et al. (abstract 682) measured coronary artery calcium (CAC) with computerized tomography twice over a mean of 2.5 years in 466 type 1 diabetic patients. Among 81 persons with elevated urinary albumin, worsening CAC was 4.3-fold more likely in those not receiving ACE inhibitor or ARB treatment but was not significantly increased for those receiving this treatment. Other predictors of CAC progression were age, diabetes duration, baseline CAC, HDL cholesterol, and systolic blood pressure. Wadwa et al. (abstract 725), from the same group, reported that arterial stiffness was associated with blood pressure, age, diabetes duration, and A1C but not with CAC, suggesting the latter to reflect a different aspect of coronary disease.

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