

# Prevention of Cardiovascular Disease

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This is the fifth in a series of articles on presentations at the American Diabetes Association's 66th Scientific Sessions, Washington, DC, 9–13 June 2006, reviewing aspects of the interrelationships between cardiovascular disease (CVD) and diabetes, returning to the theme of obesity and further addressing benefits and adverse consequences of peroxisome proliferator-activated receptor (PPAR) $\alpha$  and  $\gamma$  agonists.

Robert H. Eckel (Denver, CO) gave the Edwin Bierman Award Lecture on the topic of prevention of CVD, beginning by remembering training with Bierman, whose career focused on the relationship of diabetes and CVD. Bierman's "rules" for trainees comprised "the principles of academic medicine at its best." He recommended a simple ethical test, never performing an experiment on others that one would not have performed on oneself. He told his fellows to always plot data before statistical analysis and to consider adjustment for basal values when a biological response was proportional to the basal. He encouraged trainees to choose both innovative projects and less novel but surer projects. Finally, he stressed the intellectual challenge of research, with ev-

ery experimental question producing more questions.

Eckel reviewed projections that obesity would dramatically increase over the next two decades (1), leading to increasing rates of development of diabetes and, as a consequence, CVD. It is relatively straightforward to make recommendations to reduce these outcomes: not smoking cigarettes, increasing physical activity, and following a balanced diet—not with "the concept of good foods and bad foods" but rather following "overall healthy eating patterns"—including fruits, vegetables, and whole grains and limiting cholesterol, saturated fats, and trans fats (vegetable oils processed by hydrogenation to increase solidity and shelf-life), as well as substituting unsaturated oils and fish, maintaining normal blood pressure by limiting salt and alcohol, and eating fruits, vegetables, and low-fat dairy products. Eckel pointed out that these are evidence-based recommendations from surveys, rather than from randomized controlled clinical trials, and reviewed some of the supporting data. In the prospective Breast Cancer Detection Demonstration Project, 42,254 women completed a food frequency questionnaire and were followed for a median of 5.6 years, with those in the top quartile of recommended diet having one-third lower all-cause mortality than those in the lowest quartile, and similar benefits were seen in reduced rates of cancer and of CVD (2). These findings were extended by the Nurses' Health Study of 84,129 women with 14 years of follow-up, showing that those with normal weight, having at least a one-half portion of an alcoholic beverage daily, with at least a half hour of physical activity daily, and following a healthy diet—although comprising only 3% of

the studied population—had >80% reduction in coronary events (3).

Physical activity, Eckel pointed out, has anti-atherosclerotic effects on lipids, blood pressure, adiposity, insulin sensitivity, inflammation, myocardial oxygen demand, endothelial dysfunction, arrhythmia, platelet adhesiveness, and fibrinolysis. A study of 19,125 men, between the ages of 20 and 79 years followed for more than a decade, compared those whose lipid levels were at the National Cholesterol Education Program Adult Treatment Panel (ATP) III goal with 4,573 subjects who were classified as requiring pharmacologic lipid-lowering treatment, who had a sixfold increase in CVD, and with 3,420 subjects in the ATP III lifestyle intervention group, with a doubling of CVD. In each group, those who were unfit based on maximal exercise time had at least a doubling of mortality (4), leading Eckel to conclude "being fit ultimately trumps a lot of other factors." In women, meta-analysis similarly suggests benefit both of vigorous exercise and of walking (5).

The prevention and treatment of obesity should be straightforward, Eckel suggested. "To lose weight you need to eat less than you burn," although the inaccuracy of self-reported calorie intake has obscured this simple relationship. Relatively modest weight reduction is needed, with studies suggesting that blood pressure improves with loss of 5% of body weight, glucose tolerance with 5–10%, lipids with 10%, left ventricular function with 5%, and obstructive sleep apnea with 5%, although benefits may be particularly evident during active weight reduction rather than when the patient is weight stable at a lower level. There currently is no evidence that weight reduction prevents CVD, but there is evidence of reduced diabetes risk in individuals with impaired glucose tolerance in the Diabetes Prevention Program (6) and in the Finnish Diabetes Prevention Study (7). An important question is how long weight loss will last following intervention, although the Finnish Study recently reported that benefits were sustained 3 years after completion of the 4-year active lifestyle modification program (8). Considering obesity not to be a disease, but rather an evolved survival mechanism addressing circumstances of food lack, Eckel pointed

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**Abbreviations:** ADA, American Diabetes Association; ATP, Adult Treatment Panel; CETP, cholesterol ester transfer protein; CHD, coronary heart disease; CVD, cardiovascular disease; FFA, free fatty acid; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; NT-proBNP, NH<sub>2</sub>-terminal pro-brain natriuretic peptide; PPAR, peroxisome proliferator-activated receptor; PROactive, PROspective pioglitAzone Clinical Trial in macroVascular Events; TZD, thiazolidinedione; UKPDS, UK Prospective Diabetes Study; VAHIT, Veterans Affairs High-Density Lipoprotein Intervention Trial.

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out that limited data suggests only 6% of individuals who lose weight maintain this over 15 years of follow-up (9). The Look AHEAD (Action for HEalth in Diabetes) Study will assess 11.5 years' effects of a 4-year weight loss program in 5,000 overweight and obese individuals with type 2 diabetes (10).

Eckel suggested that prevention of obesity and additional weight gain and more aggressive treatment of risk factors must be emphasized and that there is "no better place to begin than with children." There are 8–9 million overweight children in the U.S. The American Heart Association Alliance for a Healthier Generation is working to limit portion sizes and sodas for high schools, to advertise to children healthy lifestyle approaches, and "to get kids more engaged and more involved in their own health." Physicians need to be engaged in assessing their patients' lifestyles.

Addressing the identification of individuals at risk of weight gain, Eckel reviewed his study of the strong correlation between more positive carbohydrate balance on a high-carbohydrate diet and a lesser degree of increase in fat mass over 4 years (11), suggesting that carbohydrate balance may in some fashion feed back to the brain. Eckel concluded that lifestyle is of great importance for CVD prevention. When asked about factors determining who loses weight and maintains weight loss, Eckel answered, "Don't be a pessimist, be a realist." Those who do maintain weight loss follow a healthy diet, he stated, noting that "overall, the dietary recommendations are pretty clear," as well as exercising at least 60 min daily. He pointed out, however, that "reimbursement for those types of efforts [in encouraging lifestyle practice change] is not there." He also suggested the need to consider "intervening earlier with blood pressure, and lipids, and diabetes."

Many studies presented at the meeting addressed themes of Eckel's presentation. Analyzing the treatment of risk factors among individuals with diabetes, Piatt and Zgibor (abstract 9) compared 59 male and 59 female diabetic patients, finding that 90 and 97%, respectively, had hypertension and 81 and 86% dyslipidemia, with similar frequencies of treatment, but that approximately twice as many male as female subjects achieved blood pressure  $\leq 130/85$  mmHg and that approximately three times as many achieved non-HDL cholesterol  $\leq 130$  mg/dl (abstract numbers refer to the

American Diabetes Association Scientific Sessions, Diabetes 55 [Suppl. 1], 2006). Only 25% of male and 31% of female subjects were treated with aspirin in this population. Ngo-Metzger et al. (abstract 1,162) reported a larger study of 22,510 type 2 diabetic individuals, finding that A1C and insulin use patterns were similar across sex but that 68% of male and 60% of female subjects had LDL cholesterol  $< 130$  mg/dl, suggesting that there may be sex differences in quality of diabetes care.

### Metabolic syndrome/pre-diabetes

Metabolic syndrome has been an important, although somewhat controversial, concept in the assessment of CVD risk. Saely et al. (abstract 692) followed 241 women for 4 years following coronary angiography. Metabolic syndrome was present in 84 subjects based on the ATP III definition and in 115 based on the International Diabetes Federation 2005 definition, with only moderate concordance between the definitions; the former was associated with a significant 2.1-fold increase, while the latter showed an insignificant 21% increase in vascular events. Koehler et al. (abstract 6) studied 4,020 type 2 diabetic individuals aged 35–80 years to compare the predictive power of the diagnosis of metabolic syndrome, present in 74%, with that of its component traits for CVD outcomes, which had occurred in 16%. Metabolic syndrome was predictive of CVD, but stepwise regression analysis of the component traits showed that hypertension was most strongly predictive, increasing the likelihood of CVD 4.2- and 7.7-fold in men and women, respectively, with the various metabolic syndrome components quite heterogeneous in strength of association with CVD. Other insulin resistance-associated characteristics may also play a role in CVD. Ioachimescu et al. (abstract 914) reported that each 1 mg/dl higher serum uric acid was associated with a 25% greater likelihood of mortality among 535 type 2 diabetic individuals, adjusted for age, sex, smoking, alcohol use, diuretic use, weight, BMI, waist circumference, blood pressure, CVD, glomerular filtration rate, LDL cholesterol, HDL cholesterol, triglycerides, A1C, and fasting glucose, leading to the suggestion that intervention studies might be appropriate in determining whether uric acid is a potential therapeutic target rather than solely a marker of risk.

Misra et al. (abstract 947) performed a randomized, population-based study of

1,038 Asian-Indian immigrants in seven U.S. sites, finding that 18% had diabetes, an additional 31% had impaired fasting glucose (IFG), and 32% had ATP III-defined metabolic syndrome, confirming this to be a high-risk ethnic group. Chowdhury et al. (abstract 888) analyzed data from the 1999–2002 National Health and Nutrition Examination Survey, finding that, of 3,030 participants aged 20–75 years without diagnosed diabetes, the 954 with IFG (100–125 mg/dl) compared with those having fasting glucose  $< 100$  mg/dl were aged 49 vs. 41 years, female sex in 38 vs. 56%, blood pressure  $\geq 130/85$  mmHg or antihypertensive medication use in 48 vs. 31%, waist circumference  $> 102/88$  cm (male/female) in 56 vs. 37%, obesity in 38 vs. 23%, HDL cholesterol  $< 40/50$  mg/dl (male/female) in 44 vs. 33%, LDL cholesterol  $\geq 130$  mg/dl in 48 vs. 37%, and triglycerides  $\geq 150$  mg/dl in 44 vs. 26%, suggesting the importance of IFG as a marker of high prevalence of modifiable CVD risk factors. The association between the risks of developing diabetes and CVD may be related to insulin deficiency as well as to insulin resistance. Curtis et al. (abstract 241) reviewed findings of the National Heart, Lung, and Blood Institute Cardiovascular Health Study of 4,555 type 2 diabetic individuals followed for 6 years, calculating from fasting insulin and glucose values the homeostasis model assessment (HOMA)-B and HOMA-S indexes of  $\beta$ -cell function and insulin sensitivity, respectively. Controlling for HOMA-S, for each 20% decrease in HOMA-B, the likelihood of developing coronary heart disease (CHD) and mortality increased 9 and 10%, respectively. Yeung et al. (abstract 84) analyzed diabetes risk among 11,297 participants in the Atherosclerosis Risk in Communities Study, finding that among those with a parental history of diabetes, the highest and intermediate tertiles of familial risk of CHD were associated with 76 and 28% increased risks of developing type 2 diabetes, respectively. With a negative parental history of diabetes history, there was no significant association between familial coronary disease risk and diabetes development.

Levitzy et al. (abstract 1) studied the relationship between CVD risk and fasting glucose, adjusting for traditional CVD risk factors, in 4,058 Framingham offspring, with mean age 49 years. A total of 53% were women, with 78 CHD and 128 CVD events. There was no increased risk

at glucose levels 100–109 mg/dl, while CHD and CVD increased 2.5- and 2.1-fold, respectively, at glucose 110–125 mg/dl, comparable with the increases in risk for glucose  $\geq 126$  mg/dl. Among men, 213 CHD and 295 CVD events occurred, without increases in adjusted risk among those in either IFG category. Of course, the “adjustment” performed for traditional CVD risk factors makes the authors’ conclusion that IFG is not a risk factor somewhat problematic. Suruliram et al. (abstract 702) found that, among 106 consecutive individuals hospitalized with acute coronary syndrome with a mean age of 67 years without known diabetes or glucose intolerance and with creatinine  $<1.7$  mg/dl, an oral glucose tolerance test on day 7 showed 26% with diabetes, only 18% of whom would be identified from the fasting glucose. A total of 36% had impaired glucose tolerance, and 3% had IFG. Abnormal glucose tolerance was associated with elevated troponin T, and those with diabetes were more likely to have dyslipidemia, suggesting the importance of glycemia assessment. In an interesting extension of the association between pre-diabetes and diabetes complications, Jia et al. (abstract 916) reported prevalences of retinopathy among 260 diabetic and 169 impaired glucose tolerance individuals in Shanghai, China, diagnosed using digital fundus photography, of 21 and 7%, respectively, and of urine albumin-to-creatinine ratio  $\geq 30$   $\mu\text{g}/\text{mg}$  in 22 and 11%; the latter associated with abdominal obesity, systolic blood pressure, and history of CVD, suggesting that microvascular, as well as macrovascular, complications may precede the diagnosis of diabetes.

Several studies presented at the meeting addressed the topic of whether individuals with diabetes are resistant to the therapeutic effect of aspirin. Pitocco et al. (abstract 311) compared platelet sensitivity in 42 type 2 diabetic versus 53 nondiabetic individuals receiving aspirin, showing 16 vs. 7% maximal platelet aggregation in response to arachidonic acid with a similarly enhanced response to collagen, although not to ADP. Collagen-induced platelet thromboxane A<sub>2</sub> was 8.3-fold higher in samples from the diabetic individuals and was decreased to levels of the nondiabetic group with the administration of aspirin *in vitro*, with administration of a cyclooxygenase-2 further reducing thromboxane A<sub>2</sub> in the diabetic samples, and with cyclooxygenase-2 detectable in platelets from all the

diabetic but just two of the nondiabetic patients, suggesting that orally administered aspirin does not effectively decrease platelet function in individuals with type 2 diabetes. Cohen et al. (abstract 889) measured platelet function with the PFA-100 platelet function analyzer in 48 type 2 diabetic individuals who had taken aspirin during the prior 24 h, finding aspirin resistance in 23% of individuals, associated with higher A1C, higher BMI, and higher depression scores, which they speculate might reflect the role of abnormal serotonin uptake both in abnormality of platelet function and in mood disorders.

### Thiazolidinediones and dyslipidemia

Ronald Goldberg (Miami, FL) discussed the question of whether thiazolidinediones (TZDs) should be used for lipid management. In the Strong Heart Study of  $>4,000$  American Indians, there was a strong relationship between the number of risk factors present at baseline and the 10-year CVD risk. In the UK Prospective Diabetes Study (UKPDS), when newly diagnosed type 2 diabetic individuals were compared with nondiabetic individuals, there was low HDL (39 vs. 43 mg/dl in men and 43 vs. 55 mg/dl in women) and high triglyceride (159 vs. 103 and 159 vs. 95, respectively). These abnormalities develop in the setting of insulin resistance, with consequent increase in circulating free fatty acids (FFAs), promoting hepatic synthesis of large VLDL particles having increased apolipoprotein C-III, increasing the plasma triglyceride pool. This in turn enhances the rate of exchange from triglyceride- to cholesterol-rich particles via cholesterol ester transfer protein (CETP), leading to triglyceride-rich LDL particles, which are better substrates for hepatic lipase leading to accumulation of small dense LDL particles, with hepatic lipase also upregulated by insulin resistance. A similar pathway leads to accumulation of small dense HDL particles via CETP.

Insulin sensitizers may then be particularly beneficial. Studies using NMR lipoprotein subclass analysis comparing insulin resistant and insulin sensitive individuals without diabetes, as well as type 2 diabetic individuals, show that insulin resistance leads to decreased LDL and HDL size with an increased number of LDL particles, with increased VLDL size and particle numbers, which is associated with hypertriglyceridemia (12). In the UKPDS, LDL and HDL cholesterol were the first- and second-ranked CVD predic-

tors, respectively, while triglyceride levels were not significantly associated with CVD in multivariate analysis. Goldberg reviewed ATP III and American Diabetes Association (ADA) recommendations. ATP III suggests that all diabetic individuals should achieve LDL cholesterol  $<100$  mg/dl, with the goal for higher-risk individuals that LDL cholesterol be  $<70$  mg/dl, while the ADA recommends at least a 30–40% LDL cholesterol reduction for individuals with CVD. The ATP III recommends triglyceride lowering to be the first priority for levels  $>500$  mg/dl, with fibrates recommended as first-line drugs, while for triglyceride levels, 200–500 mg/dl the non-HDL cholesterol becomes the goal at levels  $<130$  or 100 mg/dl, depending on the degree of risk, and the ATP III recommends that for low levels of HDL cholesterol, consideration be given to use of niacin or fibrates. The ADA guidelines suggest a triglyceride goal  $<150$  mg/dl, recommending that measures be taken to raise HDL cholesterol to levels  $>40$  and 50 mg/dl in men and women, respectively, and suggests using apolipoprotein B rather than cholesterol as a risk predictor.

The National Health and Nutrition Examination Survey 1999–2002 data show that 70% of individuals with diabetes have LDL cholesterol  $>100$  mg/dl and that 30–40% have triglyceride levels  $>200$  mg/dl, while 70% have HDL below average and many well-below average (13). Thus, there is need to more widely use the powerful LDL-lowering agents currently available, but Goldberg commented that “perhaps most important is the challenge raised by low HDL,” with “urgent need for the development of HDL-raising drugs.” In this context, he reviewed potential lipid benefits of the TZDs. With the first available agent, troglitazone, LDL cholesterol increased up to 15%, without change in apolipoprotein B levels, suggesting increase in LDL size (14). Meta-analyses suggest 15–20 vs. 0–5 mg/dl increase in LDL cholesterol with rosiglitazone versus pioglitazone (15,16), leading to Goldberg’s “direct head-to-head comparison,” in which 45 mg pioglitazone daily versus rosiglitazone 4 twice daily led to an LDL increase of 12 vs. 21 mg/dl, with apolipoprotein B unchanged versus increasing 11 mg/dl (17). The two agents led to identical decreases in A1C and fasting insulin levels and significantly increased LDL size, with significant increases in large and decreases in small LDL particle masses, although the

quantitative effects differed between the two agents. Goldberg pointed out that similar shifts in particle sizes are seen with fibrates.

Little change in triglyceride level was seen with troglitazone or, in meta-analysis, with rosiglitazone, while a decrease in triglyceride was seen with pioglitazone. In the head-to-head study, triglycerides decreased 12% with pioglitazone, while increasing 14% with rosiglitazone, with VLDL particle concentration not changing versus increasing. HDL cholesterol showed a trend to increase with troglitazone and increased with both pioglitazone and rosiglitazone in the meta-analysis and in the head-to-head study, with particular effect on large HDL particles, an effect opposite of that reported in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VAHIT) with gemfibrozil, which increased the number of small particles (18). Goldberg noted that nondiabetic individuals with metabolic syndrome treated with pioglitazone show increased HDL cholesterol but that it is not known whether this occurs with rosiglitazone.

Thus, Goldberg summarized, TZDs increase LDL cholesterol levels, noting that there may be a relationship between this phenomenon and higher baseline triglycerides, as well as differences between specific agents, and that increases in LDL particle size may offset the apparent adverse effect. He further noted that TZD effects on triglycerides "are modest" and unlikely to have major impact on CVD and that the rise in HDL of 5–15% represents redistribution from small to larger particle sizes. The mechanisms of these changes are uncertain, with the reduction in triglyceride potentially decreasing CETP effects on HDL and LDL particles, enhancing the efflux of cholesterol, or with TZDs perhaps reducing hepatic lipase, another potentially cardioprotective action. There is no evidence that TZDs influence the effects of statins, with studies of rosiglitazone plus atorvastatin suggesting that the benefit of statins is preserved with this agent (19).

"Perhaps the HDL story is the more compelling one," Goldberg noted, pointing out that although its mechanism is not understood, there is a great deal of information suggesting this to be an important CVD risk factor. In the VAHIT study, the rise in HDL cholesterol with gemfibrozil was the only significant predictor of CVD prevention, despite the quantitatively greater fall in triglycerides, but the in-

crease in HDL cholesterol itself explained only 20% of the gemfibrozil benefit. Goldberg suggested that nonlipid vascular protective effects occur in a similar fashion with TZDs. TZDs may then be reasonable agents for hyperglycemic individuals with reduced HDL cholesterol, although one needs randomized controlled trial evidence with demonstration of vascular protective effects rather than simply lipid changing effects.

### Diabetic dyslipidemia

Mechanisms underlying the lipid abnormalities in type 2 diabetes were studied by a number of investigators at the ADA meeting. Tay et al. (abstract 282) administered intravenous lipids with and subsequently without glucose to seven nondiabetic individuals for 2 days, leading to doubling in FFAs. Euglycemic clamp insulin sensitivity decreased, with increases in triglycerides from 114 to 172 mg/dl and (with glucose) to 243 mg/dl, with larger VLDL particle size, decreases in HDL concentration and particle size, increases in blood pressure from 109 to 119 mmHg and 123 mmHg (systolic) and from 62 to 68 and 69 mmHg (diastolic), with C-reactive protein increasing 2- and 1.6-fold, respectively, suggesting that elevations in FFAs to levels seen in obese individuals reproduces abnormalities seen in metabolic syndrome. Smiley et al. (abstract 283) administered intravenous lipid plus heparin to 12 normotensive diabetic individuals for 48 h, showing a 13/6 mmHg elevation in blood pressure and 14% reduction in brachial artery flow-mediated dilatation. After a 6-week period of treatment with 8 mg rosiglitazone daily, although FFA levels increased to a similar degree, the lipid plus heparin infusion failed to increase blood pressure or flow-mediated dilatation. These authors (abstract 699) studied 19 normotensive obese diabetic and 13 normotensive obese nondiabetic individuals with the lipid infusion protocol, showing that along with a similar increase in blood pressure, serum insulin and C-peptide levels increased more than threefold, with tripling of C-reactive protein and doubling of tumor necrosis factor- $\alpha$  levels, suggesting that FFAs reduce insulin sensitivity, increase blood pressure, have proinflammatory effects, and cause endothelial dysfunction, while TZDs potentially prevent these adverse effects. De Serna et al. (abstract 476) studied 12 type 2 diabetic individuals with placebo and, following 1 week of 120 mg nateglinide

three times daily, 5 mg glyburide twice daily, and 5 mg glipizide extended release (XL) daily, finding relatively abrupt increases in plasma FFAs from 3 through 6 h after a standardized lunch meal, with the greatest increase in the nateglinide group, suggesting a mechanism of postprandial worsening in insulin resistance.

Moon et al. (abstract 263) studied the association of insulin resistance with hepatic steatosis, despite increased hepatic triglyceride secretion, showing evidence that in the liver, insulin promotes lipogenesis with relative decrease in apolipoprotein B secretion in an animal model, potentially contributing to this phenomenon. Duez et al. (abstract 264) reported that intestinal apolipoprotein B48 particle production was almost doubled in nondiabetic individuals with hyperinsulinemia, suggesting that gut, as well as hepatic lipid handling, must be considered in assessing the lipid abnormalities of insulin resistance. Beysen et al. (abstract 266) studied 12 type 2 diabetic individuals receiving metformin and sulfonylurea with mean A1C 8.2% after a 20-week course of treatment with pioglitazone versus rosiglitazone, showing similar 1.1–1.3% fall in A1C, with triglyceride decreasing from 218 by 18 mg/dl versus increasing from 219 by 34 mg/dl. A significant reduction in *de novo* lipogenesis, another potential mechanism of dyslipidemia, was seen only in the pioglitazone group, with neither agent changing VLDL triglyceride production or clearance.

Porchay-Balderelli et al. (abstract 4) studied the CETP TaqIB single nucleotide polymorphism in 3,115 type 2 diabetic individuals with high cardiovascular risk, based on urinary albumin  $\geq 20$  mg/l, with a mean age of 65 years, followed for 4 years. The HDL concentration was 1.25, 1.33, and 1.39 mmol/l in B1 homozygotes, B1:B2 heterozygotes, and B2 homozygotes, respectively. Adjusting for age, sex, and BMI, sudden death occurred in 7% of B1 homozygotes but in 4.8% of those with one or two B2 alleles, an association not explained by further adjustment for HDL cholesterol. Kretowski et al. (abstracts 669) noted the association of apolipoprotein A-IV with coronary artery disease in individuals with type 2 diabetes and studied the Gln360His polymorphism in 484 type 1 diabetic individuals and 501 nondiabetic control subjects, finding the histidine allele to be associated with 34% progression of coronary artery calcification over a mean 2.6 years in the diabetic but not in the nondiabetic

individuals. Alaupovic et al. (abstract 855) studied the relationship between the ATP III metabolic syndrome criteria and lipoproteins among 1,134 adult and 545 adolescent Oklahoma Cherokee individuals without diabetes, finding a particularly strong association with apolipoprotein C-III levels, suggesting that its effects on particle clearance and arterial wall binding may be relevant to insulin resistance and atherosclerosis progression in this population.

### PROactive Trial

The concepts developed by Goldberg were extended in a symposium on the potential applicability of PPAR agonists to CVD. Charles Burant (Ann Arbor, MI) discussed potential effects of PPAR $\gamma$  agonists on cardiovascular events, giving his interpretations of the PROactive (PROspective pioglitazone Clinical Trial in macroVascular Events) Trial. Clearly, glycemic and lipid control can impact cardiovascular risk. The PPAR $\gamma$  agents have effects on triglycerides, LDL size, and inflammatory mediators, although worsening obesity is a potential adverse effect. In the PROactive Trial, diabetic individuals with a history of macrovascular disease were treated under International Diabetes Federation care guidelines (A1C goal of 6.5%, with LDL lowering, aspirin, and good blood pressure control) with or without pioglitazone. The primary end point was a composite of mortality, nonfatal myocardial infarction, leg revascularization, major leg amputation, and a number of additional adverse outcomes. A forced titration of pioglitazone to 45 mg daily led to >95% of patients reaching the highest dose. A total of 5,238 individuals were enrolled, with only 2 lost to follow-up. There were 177 vs. 186 deaths, without significant difference between the pioglitazone and control groups in the primary composite end point, although Burant noted that event rates only diverged during the latter half of the 34.5-month mean observation period. The principle secondary end point was the first occurrence of all-cause mortality, nonfatal myocardial infarction, and stroke, and this did show a significant 2.1% decrease with pioglitazone. An important observation complicating interpretation of the study was the increase in leg revascularization seen with pioglitazone treatment. Burant noted that loop diuretic use increased with pioglitazone treatment and that the rate of leg revascularization was particularly great in pioglitazone-treated individuals during the 1st

year of the study, suggesting that lower-extremity edema might have led clinicians to interpret leg symptoms as reflecting ischemia. A similar line of reasoning leads to the concept that some of the excess in diagnosis of heart failure may also be due to the association of TZDs with edema.

Multivariate analysis of the primary end point showed that older individuals and those who had had a stroke had higher risk, while those with statin use, a prior cardiac event, or allocated to pioglitazone had decreased events. There has been some question as to whether other treatments affected outcomes, with individuals not receiving statins or not receiving a  $\beta$ -blocker having a trend to increase in the protective effect of pioglitazone on the primary end point. A secondary analysis of individuals who had had a prior myocardial infarction showed that recurrent myocardial infarction decreased with pioglitazone treatment, although there has been controversy as to whether it was valid to perform this analysis given the negative primary outcome.

Burant noted that much of the controversy over the study has revolved around what was in essence an arbitrary decision on the part of the investigators as to the primary end point. Event rates were somewhat lower than expected, thus a larger study might have been better. Alternatively, the study might have more clearly shown the effect of pioglitazone with longer treatment exposure. More optimal risk factor reduction could have been pursued, particularly given the somewhat lower A1C, lipid levels, and blood pressure in the pioglitazone group. He concluded that, on balance, the high dose of pioglitazone was well tolerated and that the study showed benefits of TZDs in achieving target glycemic control. "It is not certain whether TZDs can prevent CVD," he stated, "beyond the effect" on metabolic parameters.

### FIELD Study

Lawrence Leiter (Toronto, Canada) discussed PPAR $\alpha$  and cardiovascular events in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and other studies. Ligands of PPAR $\alpha$  include fatty acids and eicosanoids, as well as the fibrates. PPAR $\alpha$  agonists increase apolipoprotein A-I and A-II, lipoprotein lipase, and scavenger receptor and reverse cholesterol transport, lower triglycerides, and exhibit pleiotropic effects, including evidence of reduction in inflammation. The fibrates include clofibrate, now rarely

used, gemfibrozil, most widely used in the U.S., fenofibrate, and bezafibrate. In the Helsinki Heart Study of >4,000 individuals without known heart disease treated with gemfibrozil versus placebo, a 34% reduction was found in CVD risk (20), the VAHIT individuals with CVD and isolated low HDL showed a 22% risk reduction with gemfibrozil, and the Bezafibrate Infarction Program showed a non-significant 9% reduction in CVD (21). The Diabetes Atherosclerosis Intervention Study of individuals with diabetes and preexisting coronary artery disease treated with fenofibrate versus placebo showed angiographic benefit, with a non-significant 24% decrease in clinical outcomes (22).

Diabetes and high triglyceride or low HDL-to-LDL ratio in the Helsinki Heart Study were associated with particularly great reduction in CVD. In the Bezafibrate Infarction Program, those with triglyceride levels >200 mg/dl had significant risk reduction, as did individuals with metabolic syndrome. In the VAHIT, comparison of risk reduction among individuals with versus without diabetes, and in non-diabetic individuals with versus without hyperinsulinemia, suggest that most of the benefit observed with gemfibrozil was seen in the insulin-resistant subgroup, members of which appear then to particularly benefit from use of these agents.

In the FIELD Study, 9,795 diabetic individuals not receiving lipid treatment were randomized to fenofibrate versus placebo, with coronary death/nonfatal myocardial infarction, total CVD events, and microvascular events studied (23). Two-thirds were male, 22% had prior known CVD, and only 37% had dyslipidemia as defined when the study was initiated. Statins were frequently added during the course of the study, particularly in the placebo group. A nonsignificant 11% decrease in coronary events and a nonsignificant 11% increase in coronary mortality were found. Enrolled patients without prior CVD had 19% risk reduction, while those with prior CVD did not show benefits. Rhabdomyolysis rates were low in both groups, although safety data for individuals receiving a statin with fenofibrate have not yet been reported. There is evidence of decrease in microvascular disease, with reduced requirement for laser therapy for retinopathy and a lower rate of progression of albuminuria with fenofibrate, an observation also made in the Diabetes Atherosclerosis Intervention Study (24), although fenofi-

brate was also associated with an increase in the serum creatinine level.

The event rate in the placebo group was lower than that in VAHIT and other earlier studies, suggesting that CVD risk may have improved among individuals with diabetes and explaining in part the lesser benefit seen in the FIELD Study. The investigators achieved a mean A1C of 7% and blood pressure of 136/77 mmHg, leading Leiter to comment, "this was a very well-treated cohort." He compared the FIELD Study with the Collaborative Atorvastatin Diabetes Study in which 10 mg atorvastatin daily lowered CVD risk by 37% in diabetic individuals without CHD (25). A1C was lower in the FIELD Study, but annual event rates and baseline lipids were similar in the two studies. HDL-raising and triglyceride-lowering effects were also similar in the Collaborative Atorvastatin Diabetes Study versus the FIELD Study, but there was considerably greater LDL lowering and much greater event reduction, with Leiter noting that the event reduction in the FIELD Study is approximately what would be predicted from the LDL effect.

Leiter pointed out that the increase in HDL cholesterol initially seen was significantly attenuated over the course of the study. Apolipoprotein A-II increased, but the expected increase in apolipoprotein A-I was not seen. This point was extended in a study reported at the meeting, with Hiukka et al. (abstract 860) describing changes in HDL subspecies in 165 type 2 diabetic individuals receiving fenofibrate versus placebo treatment without concomitant statin use as part of the FIELD Study. In the overall study, there was an initial 5% increase in HDL cholesterol with fenofibrate, which lessened over 5 years. In the substudy, the baseline HDL cholesterol level was 46 mg/dl, with similar levels at 5 years in the placebo versus fenofibrate groups; among individuals receiving fenofibrate, HDL2 cholesterol decreased from 18 mg/dl by 21 and 33% at 2 and 5 years, respectively, while HDL3 cholesterol increased from 28 mg/dl by 8.1 and 10.4%, and apolipoprotein A-II increased 22 and 29%. Apolipoprotein A-I did not change over time.

There were small but statistically significant increases in deep vein thrombosis, pulmonary embolus, and pancreatitis in the fenofibrate group, perhaps related to the increased homocysteine and creatinine seen with this agent. After discontinuation of fenofibrate, homocysteine and creatinine levels returned to baseline.

Leiter noted that recent homocysteine-lowering studies have not shown benefit, leading him to question whether this is actually a mechanism, although a recent meta-analysis did suggest a modest benefit of folate treatment in reducing CVD (26). There is some experimental evidence that fibrates increase cardiac myocyte fatty acid uptake, a potential explanation of the worse outcome in the FIELD Study individuals with existing CVD. Interestingly, gemfibrozil may be less potent in extrahepatic tissues, and this could protect the heart from adverse PPAR $\alpha$  effects, contributing to the greater benefit reported in VAHIT than in the FIELD Study. It is possible, then, that adverse effects of fenofibrate may attenuate the increase in HDL over time and reduce fenofibrate's benefit. On the other hand, fenofibrate does have greater safety than gemfibrozil when used in combination with statins. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Trial has ~10,000 patients and will use 20–40 mg simvastatin and fenofibrate versus placebo in a substudy, giving us additional information about this topic. At the present time, Leiter concluded, "the overall neutral effects . . . should maintain statins as the primary lipid lowering agents in patients with diabetes."

### Lipid-lowering treatment for diabetes

Many aspects of lipid-lowering treatment in individuals with diabetes were addressed in studies presented at the meeting. Ghanim et al. (abstract 857) administered 200 mg fenofibrate daily for 12 weeks to 28 hypertriglyceridemic individuals, 13 with and 15 without type 2 diabetes. In addition to the expected triglyceride-lowering effect, C-reactive protein fell 27 and 22% in those with and without diabetes, respectively, with less marked reductions in serum amyloid A and in the adhesion molecules, vascular cell adhesion molecule-1 and E-selectin, suggesting that the drug has anti-inflammatory effect. Kearney et al. (abstract 920) reported a meta-analysis of 14 randomized trials of a statin versus controls among 18,686 patients with diabetes. Each 1 mmol/l (39 mg/dl) reduction in LDL cholesterol is associated with a 21% reduction in the likelihood of nonfatal myocardial infarction or coronary death, stroke, or coronary revascularization, with similar relative benefit in the 1,466 type 1 diabetic patients as in the 17,220 type 2 diabetic patients, as well as

in those with versus without diagnosed vascular disease or hypertension. Deedwania et al. (abstract 619) analyzed the effect of 10 vs. 80 mg atorvastatin in 5,584 participants in the 4.9-year Treating to New Targets Study; 11.3 vs. 8% of those with vs. without metabolic syndrome experienced a major CVD event, comprised of CHD death, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or stroke. Among those with zero to two, three, four, and five metabolic syndrome components, as well as diabetes plus metabolic syndrome, taking 10 vs. 80 mg atorvastatin were 8.3 vs. 7.7, 11.5 vs. 8.1, 13.1 vs. 10.3, 17 vs. 11.8, and 17.8 vs. 14%, respectively, experiencing a major CVD event.

Nichols and Koro (abstract 536) compared 10,247 type 2 diabetic individuals who newly initiated statin therapy between 1997 and 2004, ascertained from the electronic records of Kaiser Permanente Northwest, and matched them to 10,247 diabetic patients not exposed to statins. Respective myopathy and myalgia incidences were 25 and 20 per 1,000 person-years in the statin group, both 37% higher than in individuals not receiving statins, with age, obesity, female sex, and use of fibrates, corticosteroids, and sulfonamides associated with increased risk. Myositis and rhabdomyolysis occurred with incidences of 0.58 and 0.39 per 1,000 person-years, with numbers insufficient to assess statin effects. No interaction was found between diabetes treatment and the statin effect. In further analysis of the latter issue, Koro and Rabatin (abstract 923) studied a pharmaceutical database including 3,823 cases of myopathy and 22,579 control subjects, with 34 and 28% receiving statins, respectively, and 6 and 5% receiving thiazolidinediones; the latter not changing the likelihood of myopathy. Fibrates increased the risk of myopathy by 22%, with increased risk of myopathy also associated with obesity, CVD, and renal and hepatic dysfunction. In neither study were gemfibrozil and fenofibrate effects distinguished.

Isley et al. (abstract 861) administered the combination of fish oil (3.3 g eicosapentaenoic acid and docosahexaenoic acid) and 3 g niacin daily versus placebo in a crossover study in eight type 2 diabetic patients on stable doses of medications, none receiving fibrates or thiazolidinediones and three treated with a statin. Triglycerides decreased 53% to

114 mg/dl, and HDL cholesterol increased 58% to 63 mg/dl, without change in LDL cholesterol, glucose, or glucose or insulin levels after a 75-g oral glucose load. Chen et al. (abstract 856) studied GW4064, an agonist of the farnesoid X receptor, for which bile acids are endogenous ligands. The agent improved all parameters in a high-fat diet mouse model of obesity, glucose intolerance, insulin resistance, and hypertriglyceridemia, with reduction in liver and muscle triglyceride content, suggesting the potential for benefits in treatment of diabetes, insulin resistance, and metabolic syndrome.

### PPARs and heart failure versus edema

Frederick Masoudi (Aurora, CO) discussed the interrelationships between PPAR $\gamma$  agonists, heart failure, and edema. Diabetes is itself an extremely powerful predictor of heart failure, as shown by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Study, in which type 2 diabetes was as important a risk factor, as was a history of coronary heart disease, and was more important than cigarette use or left ventricular hypertrophy. The prevalence of diabetes among individuals with heart failure, then, is high, comprising 20–40% of individuals with heart failure in randomized controlled trials and in community samples. Mechanisms include the associated macrovascular disease, hypertension, and obesity of diabetes, as well as coronary microvascular disease, metabolic dysfunction, and fibrosis. Heart failure incidence may be related to the degree of glycemic control among individuals with diabetes, in community studies and in the UKPDS, where each 1% increase in A1C was associated with a 14% increase in the risk of heart failure. In animal models, cardiac function worsens with diabetes. Masoudi reviewed such a study in which aminoguanidine improved cardiac relaxation, suggesting a relationship to advanced glycation end products.

Masoudi noted that there are a number of mechanisms of the association between TZDs and cardiac function abnormality, as well as benefits, including vasodilation, beneficial lipid effects, improved myocardial insulin sensitivity and FFA exposure, and decreased restenosis. The concern, however, is TZD-related fluid retention and edema. This may be due to sodium-retaining effects at the distal nephron, increased sympathetic tone, potentially occurring as a compensatory

response to vasodilatation, and increases in vascular permeability, potentially mediated by vascular endothelial growth factor. The effect of pioglitazone on the distal nephron has been demonstrated in animal models, with amiloride preventing the increase in body weight. In a model not expressing PPAR $\gamma$  in the collecting duct, the increase in plasma volume with rosiglitazone in wild-type animals was attenuated. This TZD effect may be related to the effect of insulin in increasing distal nephron sodium retention.

Clinically, Masoudi pointed out that multiple mechanisms play a role in the development of edema, and even among individuals with heart failure, edema can be multifactorial. Diabetic individuals with heart failure presenting with fluid retention are less likely to have pulmonary edema and neck vein distention when receiving TZD treatment than when not receiving TZDs. TZDs appear not to have effects on cardiac performance, with evidence of normal echocardiographic parameters of systolic performance and lowering of peripheral vascular resistance. In individuals with impaired systolic function treated for 1 year with rosiglitazone, there was no difference in ejection fraction from patients not receiving these agents. Thus, TZDs might have beneficial effects on cardiac function, and there is no evidence of adverse cardiac effect. There is, however, certainly fluid retention with TZD treatment. Insulin treatment itself is associated with increased frequency of edema, and those individuals receiving both TZDs and insulin are particularly likely to exhibit peripheral edema.

In the PROactive Trial, individuals receiving pioglitazone had greater risk of heart failure. There was a 1.6% increase in the risk of heart failure hospitalization, without increase in heart failure mortality, although the power of the trial to detect this was low. The risk of heart failure diagnosis has been reported to be increased in some but not all studies, and Masoudi's study of TZD-treated older diabetic individuals suggests reduced mortality, although with increased risk of heart failure readmission (27), further suggesting that it is not clear whether all individuals hospitalized with the diagnosis of heart failure truly have this as the etiology of their fluid retention. An audience member commented that, in fact, the health care system encourages the diagnosis of heart failure in individuals with edema to justify procedures and to allow

hospitalization. Masoudi suggested that the American Heart Association/ADA recommendations that individuals with grade III and IV heart failure avoid TZDs seems reasonable. Treatment of heart failure and TZD withdrawal usually improves the edema in TZD-treated individuals. When asked about specific treatment for edema in individuals receiving TZDs, he commented that he had "not seen any compelling data yet that using spironolactone or amiloride will necessarily be effective." A recent study, however, suggested superiority of spironolactone, and to a lesser extent of hydrochlorothiazide, to furosemide and rosiglitazone withdrawal in individuals developing fluid retention with this agent (28).

Many individuals with diabetes have underlying functional and structural abnormalities, putting them at increased risk of heart failure, particularly in the setting of myocardial infarction; thus, it is appropriate to identify individuals at particularly high risk, perhaps with brain natriuretic peptide measurement. In a study presented at the meeting, Grimmshave et al. (abstract 660) noted that NH<sub>2</sub>-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of adverse outcome in individuals with heart failure, in those with acute coronary syndrome, and among diabetic individuals with nephropathy. NT-proBNP was measured in 285 type 1 diabetic individuals, 19% with hypertension, 18% with microalbuminuria, and 7% with known CVD, finding it to be associated with female sex, age, nephropathy, peripheral neuropathy, and myocardial infarction and angina. Over 5 years of follow-up, NT-proBNP was associated with mortality, even with exclusion of the 90 individuals with known CVD, hypertension, and diabetic nephropathy. Okada et al. (abstract 682) found a negative correlation between circulating CD34<sup>+</sup> cells, endothelial progenitors involved in the maintenance of vascular endothelial dysfunction and neovascularization, and NT-proBNP concentration in 37 type 2 diabetic individuals, mean age 70 years, suggesting a role in the development of cardiac dysfunction in individuals with type 2 diabetes.

### Dual PPAR $\alpha/\gamma$ agonists

Bart Staels (Lille, France) discussed the dual PPAR $\alpha/\gamma$  agonists. PPAR $\gamma$  receptor activation plays a role in fat metabolism in adipose tissue, appearing to explain the effects of TZDs on glucose homeostasis by increasing adiponectin and decreasing in-

sulin resistance—promoting cytokines, as well as by decreasing FFA release, while PPAR $\delta$  and  $-\alpha$  act in muscle and liver, respectively, mainly to stimulate fatty acid oxidation. All appear to have antiinflammatory effects, appearing in part to involve effects on T-cell and macrophage AP1 and nuclear factor- $\kappa$ B (29). PPAR $\alpha$  agonists act to stimulate HDL metabolism and reverse cholesterol transport, as well as increasing hepatic fatty acid oxidation. Staels pointed out that bezafibrate is not a PPAR $\alpha$  agonist alone but a triple agonist of all three PPARs. The idea of the dual PPAR $\alpha/\gamma$  agonists is that the  $\alpha$  agonists lowers triglyceride and small dense LDL cholesterol, possibly activating adiponectin receptors, while  $\gamma$  agonists increase adiponectin and decrease FFA release, with the combined agents having greater anti-inflammatory potency. The lesser effect of fibrates on HDL in diabetic than in nondiabetic individuals further suggests the need to potentiate the lipid benefit of  $\alpha$  agonists; with  $-\gamma$  agonists improving hepatic insulin sensitivity, leading to greater PPAR $\alpha$  effect. Furthermore,  $\beta$ -cell function may improve with dual agonist therapy, as PPAR $\alpha$  and  $-\gamma$  are both expressed in the  $\beta$ -cell, and lipotoxicity models show that rosiglitazone improves basal and stimulated insulin release and that fibrates improve basal insulin release. Both PPAR $\alpha$  and  $-\gamma$  improve vascular endothelial nitric oxide synthase, and atherosclerosis might be reduced in a complementary fashion by the inhibitory effects of PPAR $\gamma$  agonists on matrix metalloproteinases and of PPAR $\alpha$  agonists on tissue factor. Pioglitazone has been shown to decrease carotid intima-media thickness independent of glycemic control, and in animal models of restenosis, PPAR $\alpha$  agonists decrease neointima formation, again suggesting potential combined benefit. In the FIELD Study, fenofibrate appeared to be more effective in individuals without prior CVD, while pioglitazone in the PROactive Trial appeared of greater benefit in individuals with more evidence of prior CVD, another potential combined benefit of treating both targets.

“Nevertheless,” Staels commented, “there are a number of safety issues” with the class of combined PPAR $\alpha/\gamma$  agonists, both preclinical and clinical. The major preclinical issue has been carcinogenicity in rodent models, as well as some evidence of increased heart weight. In clinical use, PPAR $\gamma$  agonists cause edema, although not convincingly causing other

evidence of heart failure, and PPAR $\alpha$  agonists might cause myopathy by altering fatty acid oxidation in muscle and in liver, although there is no evidence that this occurs either in animal models or in humans. In studies of muraglitazar, ragaglitazar, tessaglitazar, and other compounds in development, glucose homeostasis and dyslipidemia benefits have been at least as great as those with TZDs, but safety issues have halted development. Ragaglitazar did cause weight gain and edema in phase 2 clinical trials, but its development was stopped because of rodent toxicity with urothelial cancer. MK 767 led to the development of hemangiosarcoma in rodents. A Takeda compound elevated liver enzymes. Muraglitazar and tesaglitazar appeared to be safe in preclinical testing, although prolonging the QT interval in canine studies. In humans, however, muraglitazar caused weight gain, edema, and appeared to increase development of CVD (30), while tesaglitazar development was stopped because of increased creatinine. Staels was encouraged that no “common denominator” led to discontinuation of development of these drugs. All the agents act differently, with weak  $\alpha$  agonist effects and effects on  $\gamma$ , which differ between the agents, although all are PPAR $\gamma$  dominant. Staels suggested that there might still be “pros for the dual PPAR agonists,” as agents with greater benefit on combined dyslipidemia/insulin resistance, as well as greater anti-inflammatory effect, and with less risk of drug-drug interaction than would be seen with use of PPAR $\alpha$  and  $-\gamma$  agonists separately. He commented that it may be possible to design selective PPAR modulators free of adverse effects such as edema; thus, it may be premature to completely abandon research in development of these agents.

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