

Diabetes 2006

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The Diabetes "Grey Zone"



Important data on diabetes presented at the 42nd Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2006**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc. E-mail or fax delivery to your office of **Diabetes 2006** will be followed by a **Diabetes 2006** booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing fee to the Yale Office of Continuing Education, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

Diabetes 2006 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians.

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Type 1 diabetes develops in the aftermath of an immune-mediated destruction of pancreatic β -cells. We now recognize that this abnormal immune response is induced and promoted by the interaction between genetic and environmental factors. Type 1 diabetes used to be defined in terms of the absolute need for insulin therapy (insulin-dependent diabetes) or, before that, the age of onset of the disease (juvenile-onset diabetes). More recently these criteria have been discarded in favor of the term "Type 1 diabetes" when it became apparent that not everyone with autoimmune diabetes developed the disease during childhood or was in absolute need of insulin replacement therapy. Individuals who are found as adults to have diabetes-associated antibodies (particularly those to glutamic acid decarboxylase [GAD] and insulinoma-associated antigen [IA]-2 autoantibodies), but who may not require insulin treatment have been classified as having "latent autoimmune diabetes of adulthood" (LADA), also sometimes referred to as "slowly progressing insulin-dependent diabetes" or "Type 1-1/2" diabetes.

LADA is defined by three principal features including: adult age at diagnosis, the presence of diabetes-related autoantibodies, and delay in the need for insulin therapy. Some groups have attempted to tighten the criteria by restricting the diagnosis to ages 30-70 years and to those individuals who have not needed insulin therapy for at least six months after diagnosis. However, these criteria haven't been completely accepted. What is clear to all practicing physicians, especially in the northern hemisphere, is that we are seeing many more such patients. Not surprisingly, this week's meeting generated interesting data in this field.

In an attempt to determine the characteristics of LADA in the Italian population, Buzzetti *et al.*, presenting on behalf of the NIRAD (Non Insulin Requiring Autoimmune Diabetes) Group, characterized the pathogenetic markers GAD and IA-2 in patients enrolled in their study (abstract 288). The cohort consists of 4,250 consecutive Type 2 diabetic patients enrolled between 2001 and 2004 in 83 diabetes centers in Italy. Patients were screened for the presence of various markers

of autoimmune diabetes: 4.5% of patients had either antibodies to GAD or IA-2A (4.4% anti-GAD, 0.9% anti-IA-2A, and 0.9% with both). Analysis of GAD titers was independent from diabetes duration and showed a bimodal distribution, with one subgroup having high and one having low-titers. Compared with classical Type 2 diabetes, high-titer GAD antibody patients showed significantly higher fasting blood glucose, HbA1c, and TPO antibodies, and lower age of diabetes onset, BMI, waist circumference, triglycerides, and prevalence of the metabolic syndrome (all $p < 0.001$). These features suggest a more profound degree of insulin deficiency. Patients with low GAD antibody titers differed in a similar way from the classical Type 2 patients, but less significantly. The data from NIRAD shows that a subset of adult patients with a diagnosis of Type 2 diabetes who are antibody positive differ phenotypically from patients with ordinary Type 2 diabetes, contributing to their increased risk of ketosis and their more rapid progression to needing insulin replacement therapy.

"Action LADA" is a major multinational European project designed to identify the prevalence of LADA in adults. The results of this multicenter study were presented by Hawa *et al.*, UK (abstract 290). Entry criteria for the study included diagnosis of diabetes between 30 and 70 years of age, duration of disease less than five years, and no insulin requirements for the first six months. GAD antibodies were measured using a radioimmuno-precipitation assay. LADA samples were identified according to the selection criteria, and GAD antibodies were identified in 551 (10.6%) samples. Data from a single center in England were then analyzed, revealing that age at diagnosis was lower in GAD-positive vs. GAD-negative patients (43 vs. 49 years, $p < 0.001$) and a higher percentage had progressed to insulin therapy (32 vs. 7%, $p < 0.001$). There were no gender differences. These findings highlight the importance of identifying LADA, in that it may represent between 5-15% of patients given a presumptive diagnosis of Type 2 diabetes.

Limited information is available on the prevalence and predictive role of these autoantibodies

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among adults at risk for diabetes. Dablea *et al.* of the US presented data from the Diabetes Prevention Program (DPP) (abstract 307). The DPP measured baseline GAD and IA-2 antibodies in 3,050 impaired glucose tolerance (IGT) subjects aged 25-84 years, randomized to intensive lifestyle, metformin, or placebo and followed for 3.2 years. Cox models assessed the effect of antibodies on diabetes risk. A total of 367 subjects (12%) had positive samples (9.5% of non-Hispanic whites, 9.7% of Hispanics, 16.0% of African-Americans, 14.1% of Asians, and 29.6% of Native Americans). Race/ethnicity differences were mostly due to the prevalence of IA-2. Although antibody-positive patients in the placebo group had a 40% higher diabetes risk, overall, the investigators found that they did not clearly predict the development of diabetes (HR 1.8 [95% CI 0.96-1.46]). Metformin and intensive lifestyle interventions were equally effective in delaying the development of diabetes in both antibody-positive and -negative patients. (We would note here that caution may have to be used with metformin because of the theoretical risk of severe metabolic acidosis in those individuals who progress to insulin-independence, although we are also aware of preliminary trials in adolescents with Type 1 diabetes showing a benefit on glycemic control with metformin.)

Timar *et al.* of Romania took a slightly different look at the "grey zone" between Type 1 and Type 2 diabetes by analyzing the prevalence

Table 1. Characteristics of Type 1 Diabetic Patients With and Without Metabolic Syndrome

	Metabolic Syndrome	Without Metabolic Syndrome
Number (Men/Women)	100/112	282/230
HbA1c (%)	8.4±2.5	7.4±1.9
Systolic Blood Pressure (mmHg)	142.3±24.2	132.5±19.1
Diastolic Blood Pressure (mmHg)	92.4±10.7	81.3±9.3
Total Cholesterol (mg/dl)	231.2±42.3	203.4±38.2
LDL-cholesterol (mg/dl)	121.2±26.1	113.1±24.3
HDL-cholesterol (mg/dl)	33.6±8.7	46.7±9.9
Triglycerides (mg/dl)	274.8±56.4	168.8±42.3

Data are mean ± standard deviation.

Note: p<0.001 for each comparison by unpaired Student's t test.

of the metabolic syndrome in patients with a diagnosis of Type 1 diabetes. The study enrolled 724 patients with a mean age 42.3±7.8 years and median duration of diabetes 23.4±7.2 years. Metabolic syndrome was identified according to the new International Diabetes Federation (IDF) criteria, and absolute 10-year coronary heart disease (CHD) risk, using a standardized method. The metabolic characteristics of Type 1 diabetic patients with and without metabolic syndrome are shown in Table 1. Ten-year CHD risk was 12.1% in patients with vs. 8.3% in those without metabolic syndrome. The researchers concluded that metabolic syndrome is more prevalent in individuals with Type 1 diabetes than the general population and increases the cardiovascular risk of these patients. This study might suggest that some forms of LADA may be precipitated by the devel-

opment of obesity and insulin resistance. On the other hand, the study may simply indicate that even patients with Type 1 diabetes are not immune to those forces leading to weight gain in society.

What became clear from this session at the EASD is that while individuals with LADA possess many of the features of Type 1 diabetes, there is no clear strategy for the management of this condition. By better defining LADA, appropriate clinical trials can then be conducted. For instance, as autoimmune diabetes is predominantly a defect in insulin secretion, should all individuals with LADA be treated with insulin irrespective of their degree of hyperglycemia? Alternatively, is this a condition in which immunomodulation may play a therapeutic role. Some exciting trials are already being conducted in this area and we hope to report on some of these to you in the future.



TZDs: Effects Beyond Glucose



Investigations into the clinical and metabolic outcomes of thiazolidinedione (TZD) therapy continue to proliferate. This week's presentations included updates on the first clinical trial using this class of anti-hyperglycemic drugs with a cardiovascular disease (CVD) endpoint. Also, more information became available on their effects on dyslipidemia, inflammatory mediators, and fatty liver disease.

CV Events and TZDs

In some of the most clinically-relevant presentations, two subgroup analyses of the PROactive trial (Dormandy, *Lancet* 2005) evaluated the impact of pioglitazone on recurrent MI and recurrent stroke. PROactive was a double-blind cardiovascular outcome study in which 5,238

patients were randomized to pioglitazone or placebo added to their other baseline diabetes regimen. The mean follow-up was 34.5 months.

In one of two studies reporting on the PROactive subpopulation with a history of previous stroke within six months of randomization, Erdmann and international colleagues identified a significantly lower incidence of fatal or non-fatal MI in the pioglitazone-treated group (5.3 vs. 7.2%, Hazard Ratio [HR]=0.72, p=0.045). The results were unaffected by gender, age, or diabetes duration (abstract 1159). Similarly, Dormandy and European colleagues demonstrated that, in patients with previous stroke, there were statistically significant benefits of pioglitazone therapy in the endpoints of 1) fatal or non-fatal stroke and 2) cardiovascular death, MI, or stroke (abstract 120). A trend toward benefit was observed in the the

study's primary and principal secondary endpoints (Table 2). TZD therapy had no effect on stroke incidence in the patients with no history of stroke. In each subanalysis, the researchers attributed the positive outcomes to the pleiotropic effects of pioglitazone, including those on dyslipidemia and inflammation.

We would point out that subanalyses from larger clinical trials should be considered hypothesis-generating only, since the studies are not powered to detect a difference in subpopulations. So, while these findings are interesting, they should be confirmed in separate clinical trials. In this regard, the Insulin Resistance Intervention after Stroke (IRIS) study is currently underway and will examine the effect of pioglitazone on subsequent vascular events in non-diabetic insulin-resistant patients.

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CVD Risk Factors

Characterization of the beneficial lipid effects of TZDs was explored in another sub-analysis of the PROactive trial. Spanheimer and US colleagues focused on the lipid-altering effects, conducting four treatment-group comparisons: (1) pioglitazone vs. placebo; (2) pioglitazone vs. placebo ± insulin at baseline; (3) pioglitazone vs. placebo, each with metformin or sulfonylurea; and (4) pioglitazone vs. placebo, each with metformin and sulfonylurea therapy (abstract 109). A statistically significantly greater mean decrease in triglyceride and increase in HDL-cholesterol levels were observed in all comparisons between a pioglitazone-assigned group and the placebo comparator. Although an increase in LDL-cholesterol was observed with pioglitazone, the LDL:HDL-cholesterol ratios were generally improved in the pioglitazone-containing cohorts. The researchers concluded that pioglitazone offers benefits on lipids beyond those derived from concomitant glucose-lowering and lipid-altering regimens. Whether this may explain the findings of PROactive remain controversial.

The impact of gender on TZDs' effects was studied by Park and Korean colleagues (abstract 752). Measurements were assessed in 47 women and 46 men receiving pioglitazone at 3, 6, and 12 months of treatment. There were statistically significant decreases in fasting plasma glucose and HbA1c following six months of pioglitazone therapy in each gender group ($p < 0.01$), with the decrements relative to baseline being more pronounced in women than in men. Both men and women exhibited significant improvements in HDL-cholesterol ($p < 0.01$), while only women exhibited significant benefits on triglycerides (from 226 ± 226 to 148 ± 90 mg/dl, $p < 0.05$), serum leptin levels (from 14.0 ± 8.0 to 17.2 ± 10.1 mg/ml, $p < 0.01$), and C-reactive protein (CRP; from 2.2 ± 3.6 to 0.8 ± 0.7 mg/dl, $p < 0.05$). However, after six months of treatment, only women exhibited significant increases in body weight and body mass index. Overall, it appeared that the effects of TZD therapy—both positive and negative—may be enhanced in women.

Both the TZDs and statins are known for their effects on anti-inflammatory markers such as high sensitivity- (hs-)CRP, but it is not known whether these effects are additive. Hanefeld and German colleagues evaluated the effects of pioglitazone and simvastatin in combination versus the TZD alone or the statin alone on hs-CRP in non-diabetic patients with cardiovascular disease

Table 2. Effect of Pioglitazone Therapy on Cerebrovascular and Cardiovascular Endpoints

	No. of Events (%) in Patients with Prior Stroke			No. of Events (%) in Patients without Prior Stroke		
	Pioglitazone (n=486)	Placebo (n=498)	HR (95% CI)	Pioglitazone (n=2,119)	Placebo (n=2,135)	HR (95% CI)
All-stroke	27 (5.6)	51 (10.2)	0.53 (0.34 - 0.85)	59 (2.8)	56 (2.6)	1.06 (0.73 - 1.52)
Cardiovascular	63 (13.0)	88 (17.7)	0.72 (0.52 - 1.00)	194 (9.2)	225 (10.5)	0.86 (0.71 - 1.04)
Primary endpoint*	98 (20.2)	126 (25.3)	0.78 (0.60 - 1.02)	416 (19.6)	446 (20.1)	0.94 (0.82 - 1.07)
Principal secondary endpoint†	76 (15.6)	98 (19.7)	0.78 (0.58 - 1.06)	225 (10.6)	260 (12.2)	0.86 (0.72 - 1.03)
All-cause death	46 (9.5)	49 (9.8)	0.96 (0.64 - 1.44)	131 (6.2)	137 (6.4)	0.96 (0.75 - 1.22)

* All-cause death, non-fatal MI (including silent MI), acute coronary syndrome, cardiac intervention including CABG or PCI, stroke, major leg amputation, bypass surgery or revascularization in the leg.

† All-cause death, non-fatal MI (excluding silent MI), or stroke.

and high hs-CRP (abstract 89). In this double-blind, placebo-controlled trial, patients were randomized to one of the three treatment arms and treated for 12 weeks. A statistically significant decrease from baseline in hs-CRP was observed in all three groups, with pioglitazone plus simvastatin having a seemingly additive effect on hs-CRP (from 3.49 ± 1.97 to 2.06 ± 1.42 mg/l, $p < 0.01$). Pioglitazone in combination or as monotherapy produced decreases in HOMA, with the correlation between the changes in insulin sensitivity and hs-CRP being significant ($r = 0.43$; $p < 0.05$).

Kadoglou and colleagues from Greece assessed the combined effects of a TZD and exercise on blood pressure, dyslipidemia, and other cardiovascular risk factors (abstract 111). A total of 100 overweight (BMI > 27 kg/m²) patients with poorly-controlled Type 2 diabetes (HbA1c $> 7\%$) and metabolic syndrome receiving stable doses of metformin and a sulfonylurea were randomized to one of four groups: (1) add-on rosiglitazone + exercise; (2) add-on rosiglitazone; (3) exercise; and (4) control. At the end of the six-month study, glycemic control and blood pressure measures improved in each of the groups with the exception of controls. Significant reductions ($p < 0.05$) in total cholesterol and LDL-cholesterol were seen in the add-on rosiglitazone + exercise group as well as the exercise (control) group. The impact of add-on rosiglitazone therapy + exercise appeared simply additive with respect to increase in HDL-cholesterol and decrease in hs-CRP, but actually synergistic relative to insulin resistance, triglycerides, and VO₂ max (i.e., the maximum volume of oxygen that the body can consume during intense exercise breathing room air at sea level, a measure of physical fitness).

Fatty Liver

Two studies evaluated the impact of a TZD on nonalcoholic steatohepatitis (NASH). In the first, 48 patients with impaired glucose tolerance/Type 2 diabetes and NASH as well as 12 matched-controls were randomized to receive pioglitazone or placebo for six months by Belfort and US colleagues (abstract 255). Significant decreases in the levels of inflammatory markers were observed in those treated with pioglitazone versus placebo (hs-CRP, $p < 0.04$; TNF-alpha, $p < 0.01$; VCAM, $p < 0.01$; ICAM, $p = 0.001$). Steatosis and necroinflammation decreased by ~50% in the pioglitazone group ($p < 0.0001$ and $p < 0.01$, respectively vs. placebo).

In a related investigation, Ratziu *et al.* of France conducted a one-year, randomized, double-blind trial in 63 patients with biopsy-proven NASH comparing rosiglitazone (8 mg daily) and placebo (abstract 1162). Histologic response (improvement in steatosis $> 30\%$) was significantly greater in the rosiglitazone group (47%) versus placebo (16%, $p < 0.004$) and among rosiglitazone-treated patients, occurred more frequently in those without a diagnosis of diabetes (61% non-diabetes, 11% diabetes, $p < 0.01$). A biochemical response (normalization of ALT) was observed in 38% of rosiglitazone and in 7% of placebo patients ($p = 0.005$). Among those treated with rosiglitazone there was no difference in biochemical response between those with or without diabetes. The anti-steatogenic effect of TZD therapy was correlated with ALT improvement ($r = 0.35$, $p < 0.05$), β-cell function (by the "QUICKI" formula; $r = 0.66$, $p < 0.01$), and insulin sensitivity (by HOMA) ($r = -0.55$, $p = 0.04$). Larger studies are now underway to further assess this apparent benefit on this extremely common condition.

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Impact on Insulin Dosing

The impact of a TZD on insulin requirements were evaluated by various groups of investigators. Schmitz and colleagues conducted a subgroup analysis utilizing subjects from PROactive treated with insulin at baseline (abstract 806). The researchers compared insulin dosing and glycemic control in those assigned to pioglitazone (n=864) versus placebo (n=896). At baseline both groups were receiving similar mean daily doses of insulin (47 units/day) and had comparable HbA1c values (8.5%). Analysis after nearly three years demonstrated a significant decline in insulin dose in the pioglitazone group (42 units/day versus an increase to 55 units/day for placebo, $p < 0.0001$). Despite less insulin used, HbA1c values were diminished to a greater degree in the pioglitazone group (-0.93%) versus in the placebo arm (-0.45%, $p < 0.0001$). Insulin was discontinued altogether in a greater number of patients in the pioglitazone group (9%) vs. placebo (2%, $p < 0.0001$) as well. A significant increase in edema (31% vs. 18%, $p < 0.0001$) and hypoglycemia (41% vs. 29%, $p < 0.0001$) in the pioglitazone group did mitigate these apparent benefits; otherwise safety profiles were comparable.

Attempting to better understand the mechanism for decreases in insulin requirements,

Table 3. Impact of Rosiglitazone on Metabolic Indices and Markers of β -Cell Function in Patients with Type 2 Diabetes

Parameter	Insulin Only (Baseline)	Rosiglitazone + Insulin x 3 months	p-value
Triglycerides (mg/dl)	176.2 ± 106.8	143.3 ± 64.1	$p = 0.049$
HDL-cholesterol (mg/dl)	44.9 ± 9.0	53.1 ± 11.0	$p < 0.001$
Free fatty acids (mmol/l)	663.14 ± 88.18	499.48 ± 94.36	$p < 0.001$
Diastolic blood pressure (mmHg)	77.14 ± 12.45	74.50 ± 5.92	$p = 0.008$
C-peptide at 30 minutes (mmol/l)	0.63 ± 0.23	0.84 ± 0.33	$p = 0.002$
AUC C-peptide at 30 minutes (mmol/min/l)	15.51 ± 6.05	19.85 ± 7.19	$p < 0.001$
Glucagon-like peptide-1 at 30 minutes (GLP-1) (pmol/l)	24.45 ± 1.23	25.60 ± 1.13	$p < 0.001$
AUC GLP-1 at 120 minutes (pmol/min/l)	2601.43 ± 184.41	2686.29 ± 71.07	$p < 0.001$

Wu *et al.* from China studied the effects of rosiglitazone and insulin on islet β -cell function and on serum levels of glucagon-like peptide-1 (GLP-1) in patients with Type 2 diabetes (abstract 75). Fourteen subjects received rosiglitazone 4 mg daily along with usual insulin therapy and were compared with a matched control group (n=14). Several indices, including measures of early-phase insulin secretion and other markers of β -cell function, demonstrated a statistically significant improvement in the rosiglitazone-treated group (Table 3), but not in controls. From

these data, the researchers concluded that TZDs may enhance islet β -cell function including early-phase insulin secretion, which may be partially due to an increase in GLP-1 secretion, at least in patients requiring insulin.

This week's EASD meeting was particularly rich in new information concerning the TZD class (see Issue 2; *Life is But a DREAM*). Presently, they are considered mainly anti-hyperglycemic drugs. Whether their use will ever expand to include diabetes prevention, NASH, or a cardiovascular indication remains highly controversial.



Emerging Therapies and Technologies



Given the multifactorial nature of Type 2 diabetes, successful treatment requires consideration of several pathophysiological defects leading to hyperglycemia. Today, we have many different classes of anti-hyperglycemic drugs at our disposal, most of which have unique mechanisms of action. As our appreciation of the complexity of this disease grows, the availability of an even wider array of therapeutic agents is expected. Several presentations this week highlighted several new and potentially exciting developments in the field. Over the coming years, some of these may translate into even more options for our patients with diabetes.

One novel category of drugs under development by several companies is the fructose 1,6-biphosphatase (FBPase) inhibitors, which reduce activity of one of the key gluconeogenic enzymes, thereby controlling hepatic glucose production—often inappropriately augmented in Type 2 diabetes. Bruce *et al.* from the US reported their preliminary results on CS-917, a FBPase

inhibitor (abstract 37). Thirty-nine subjects (30 men, nine women) with Type 2 diabetes were randomized to receive placebo or one of four oral doses of CS-917 (50-400 mg), escalating over 14 days. The mean age of the patients was 52-62 years and the mean fasting glucose 205-249 mg/dl. Compared with placebo, active therapy resulted in statistically significantly decreased fasting plasma glucose. At the highest dose, nausea and vomiting were reported in two subjects and two others had mild, isolated, and asymptomatic elevation of post-prandial lactic acid levels. At the lower doses, the drug appeared to be reasonably well tolerated without serious adverse events or hypoglycemia.

Kim *et al.* from South Korea tested pinitol (3-O-methyl-D-chiro-inositol) in Type 2 diabetic patients (abstract 857). This agent has been shown to enhance insulin action and improve glycemic control. Sixty-six patients on oral hypoglycemic agents for three months or more were

enrolled. They were randomly assigned to two groups and given 400 mg pinitol or placebo three times daily for 12 weeks, added to their baseline therapy. In the active therapy group, HbA1c, fasting glucose, and HOMA-IR decreased significantly as compared to placebo ($p < 0.05$). In a subgroup analysis, those with HbA1c > 8% and those with the greatest insulin resistance seemed to experience the most prominent effects. No toxicity was detected during this short-term study. Depending on the outcomes of further studies, this new insulin sensitizing agent may hold some promise.

One new drug class that is somewhat closer to market is the DPP-4 inhibitors. These oral agents reduce the activity of dipeptidyl peptidase 4, the enzyme that rapidly degrades the endogenous incretins, GLP-1 and GIP (see *Diabetes 2006*, Volume 14, Issue 2.) Two such drugs, sitagliptin and vildagliptin, are currently under review at the FDA. Dozens of abstracts were presented this week on this drug category.

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Emerging Therapies

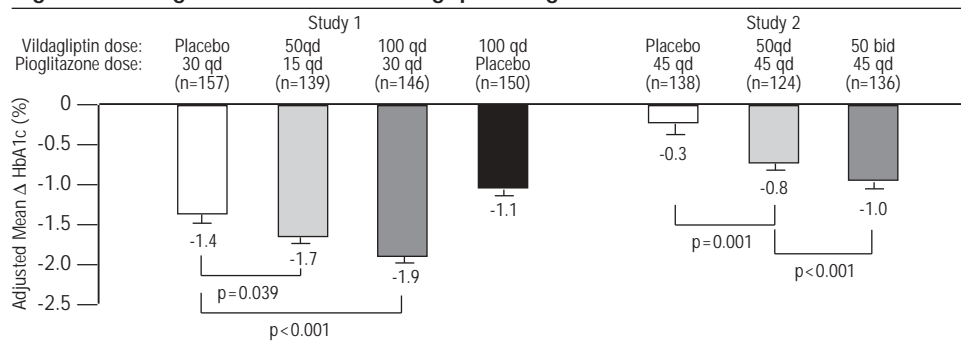
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Aschner *et al.* from the US (abstract 5) randomized 741 patients (aged 18-75 years, with HbA1c 7.0-10.0%) to one of two doses of sitagliptin (100 or 200 mg once daily) or placebo. After 24 weeks, both sitagliptin groups experienced significant lowering of HbA1c (-0.79% and -0.94%, respectively [placebo-adjusted]; $p < 0.001$). Fasting glucose was reduced by only 18-22 mg/dl, however, consistent with a predominately post-prandial effect of the drug. This was confirmed during a mixed meal tolerance test, during which the two-hour glucose fell by 54 mg/dl in the high-dose group. Additionally, the investigators demonstrated improvement in β -cell function using the HOMA- β equation and C-peptide levels.

Similar results were reported by Meininger and Israeli collaborators (abstract 6) in a 24-week sitagliptin-metformin combination therapy trial involving 701 subjects inadequately treated with metformin alone (>1500 mg/day with HbA1c $\geq 8\%$). With 100 mg of sitagliptin, the placebo-adjusted HbA1c was reduced by 0.65% ($p < 0.001$). Rosenstock and American colleagues (abstract 39) added this same dose to pioglitazone therapy in 354 patients with HbA1c 7-10%. Placebo-adjusted HbA1c in the active therapy group was lowered by 0.70% ($p < 0.001$). In addition, use of sitagliptin nearly doubled the chance that a patient would achieve an HbA1c of <7% (45% vs. 23%, $p < 0.001$).

Vildagliptin studies included a 24-week monotherapy trial by Dejager and US collaborators (abstract 791) in which 380 patients with HbA1c 7.5-10% were assigned to one of four treatment groups: vildagliptin 50 mg once daily, 50 mg twice daily, 100 mg once daily, or placebo. The

Figure 1. Change in HbA1c From Vildagliptin-Pioglitazone Combination



differences from the change in HbA1c with placebo were $-0.5 \pm 0.1\%$ ($p = 0.006$), $-0.5 \pm 0.1\%$ ($p = 0.006$), and $-0.6 \pm 0.1\%$ ($p = 0.001$) in the three respective sitagliptin groups.

Bosi and international colleagues (abstract 793) performed a 52-week trial with 526 drug-naïve patients, randomizing them to vildagliptin 50 mg bid or metformin (titrated up to 1,000 mg bid). HbA1c was reduced by $1.0\% \pm 0.1\%$ with vildagliptin and $1.4\% \pm 0.1\%$ with metformin. The study did not establish "non-inferiority" to metformin (which in clinical trial-speak means greater effect with metformin than with vildagliptin.) In a similar group of drug-naïve patients Baron *et al.* of the US and Switzerland (abstract 801), found various combinations of vildagliptin with pioglitazone effective (Figure 1). The baseline HbA1c in each of these DPP-4 trials was in the 8-8.5% range. The drugs were well tolerated without weight gain.

Advances are also being made in monitoring technologies. Gal and Harman-Boehm from Israel have developed a non-invasive glucose monitoring device, GlucoTrack™, that employs three tech-

nologies (sonography, conductivity, and heat capacity) to quantify the current glucose level, with the results from each compared using an algorithm (abstract 959). To date, the device has been used by 69 patients, with a total of 174 points measured: 83.3% fell in Zone A of the Clarke Error Grid (indicating good correlation with the meter) and 16.7% in Zone B (indicating discordance between device and meter that would not lead to any treatment errors.) If such reliability is confirmed in larger studies and in a variety of patient types, such non-invasive glucose measuring devices could radically change the current approach to diabetes care, especially in insulin-treated patients.

Managing patients with Type 2 diabetes will continue to become more complex as some of these drugs (and technologies) become available—the DPP-4 inhibitors should be available soon. As new agents emerge, it is important to understand their mechanisms of action, indications, efficacies, and potential side effects so that their uses may be optimized.



So Many Posters, So Little Time...



Update on Pancreatic Transplantation

Coppelli *et al.* from Italy presented three-year follow-up results for 63 patients with Type 1 diabetes who underwent pancreas transplantation for extremely labile glycemic ($n = 9$) or progressive diabetic complications ($n = 54$) (abstract 240). In their single-center experience, overall patient survival was 98% and graft survival (as defined by insulin-independence) was 89%, 87%, and 80% at years 1, 2, and 3, respectively. With successful transplantation came sustained euglycemia (mean HbA1c 5.3%, 5.3%, and 5.4% at the end of each of the

three successive years), reduction in cardiovascular risk factors (blood pressure, total and LDL-cholesterol, fibrinogen), three-fold reduction from baseline in proteinuria, either stabilization or improvement in retinopathy (82% of patients), and significant improvement in neuropathy parameters.

Combination Lipid Therapy

Catapano and multinational investigators conducted *post-hoc* analyses of data from a double-blind, six-week study in which 2,959 patients were randomized to one of six treatment groups

(three doses of ezetimide/simvastatin [10/20, 10/40, or 10/80 mg] and three doses of rosuvastatin [10, 20, or 40 mg]) (abstract 114). In the subgroup of 367 patients with diabetes and the subgroup of 811 patients with metabolic syndrome and no diabetes, statistically significantly greater reductions from baseline ($p < 0.001$) in LDL-cholesterol (treatment difference of -4.3% and -3.2% for diabetics and patients with metabolic syndrome, respectively; mean across dose groups) and triglycerides (treatment difference of -3.0% and -2.7%, respectively) were observed with the combination drug.

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