

# Diabetes 2005

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## New Paths to Glycemic Control



Important data on diabetes presented at the 65th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$10 certificate 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 2005** 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 important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, 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.

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The pathophysiology of Type 2 diabetes involves both insulin resistance as well as progressive  $\beta$ -cell dysfunction. Until recently, the treatment of Type 2 diabetes has focused predominately on improving insulin sensitivity (metformin, thiazolidinediones) and/or augmenting insulin availability (secretagogues, insulin injections). The closer researchers look, the more it becomes apparent that there are other fundamental hormonal derangements in this condition that may play a more central role in its development and progression than initially considered. A good example is the growing appreciation of the adipocyte and its altered secretory function in the obese state. Another exciting area involves glucoregulatory hormones of pancreatic and gut origin. Glucagon, for instance, is a powerful islet cell product that increases hepatic glucose production, while also modulating insulin secretion. Another islet peptide, amylin, has several effects, including reduction of glucagon secretion, delay of gastric emptying, and probably central effects to decrease caloric intake. The incretins, peptide hormones secreted by enteroendocrine cells of the gastrointestinal tract, augment insulin secretion in a glucose-dependent fashion, while simultaneously having many of the aforementioned effects attributed to amylin. The development of analogs or agonists of these glucoregulatory hormones or agents that delay their degradation has been an area of active investigation for the past five years. Numerous presentations at this week's meeting discussed the use of these new medications alone or in combination with other orally administered antihyperglycemic agents or insulin.

### Incretins: Insulinotropic Peptides

Incretins modulate pancreatic islet secretion as part of the "enteroinsular axis." Two incretins have been discovered to affect glucose metabolism: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Of the two, GLP-1 has garnered the majority of investigative interest as it is clearly deficient in persons with Type 2 diabetes and therefore may be a more significant target. (GIP, in con-

trast, is normal in Type 2 diabetes, although some resistance to its effect may be present.) The use of GLP-1 agonists, analogues, or agents that slow GLP-1's inactivation by dipeptidyl peptidase IV (DPP-IV) may offer an effective alternative to insulin therapy in patients uncontrolled with traditional oral antihyperglycemic agents. The former are injectables, whereas the latter have the advantage of being available in pill form.

Exenatide, a GLP-1 agonist initially discovered in the saliva of the gila monster, was found by Heine and colleagues (9-OR) to provide similar glycemic control with weight loss, rather than gain, as compared to glargine in Type 2 diabetic patients uncontrolled on metformin plus sulfonylurea therapy. In a 26-week study, investigators randomized 551 patients to exenatide 5  $\mu$ g twice daily for four weeks, then 10  $\mu$ g twice daily or insulin glargine once daily. At study conclusion, similar reductions in HbA1c levels were observed in both treatment groups (~1.0% from baseline levels of ~8.2%), as were the percentages of patients with HbA1c levels  $\leq$  7% (48% exenatide, 46% glargine). A significant difference was observed in weight change: those treated with exenatide lost 2.3 kg while those given insulin gained 1.8 kg. Nocturnal hypoglycemia was significantly less frequent with exenatide compared with glargine (0.9 vs. 2.4 mean events/patient year,  $p < 0.001$ ). The effects of exenatide in combination with metformin, or a sulfonylurea, or both on HbA1c and weight loss were found to be durable in an 82-week study by Blonde *et al.* (477-P). In the trial, 393 patients who completed one of three 30-week treatment arms (placebo, exenatide 5  $\mu$ g, or exenatide 10  $\mu$ g administered subcutaneously twice-daily) were entered into an open-label extension and given exenatide 5  $\mu$ g twice daily for four weeks followed by 10  $\mu$ g twice daily for 48 weeks. At week 30, patients treated with exenatide exhibited a dose-dependent reduction of HbA1c and weight, with these reductions sustained at week 82 (Figure 1). Mild to moderate nausea was the most frequent adverse event. Exenatide was recently made available on the US market as Byetta®.

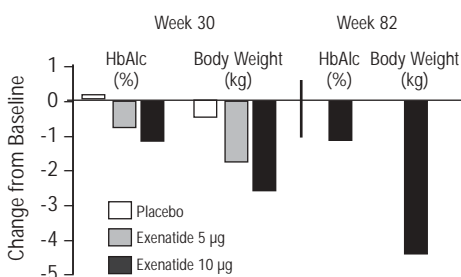
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## New Paths to Glycemic Control Continued from page 1

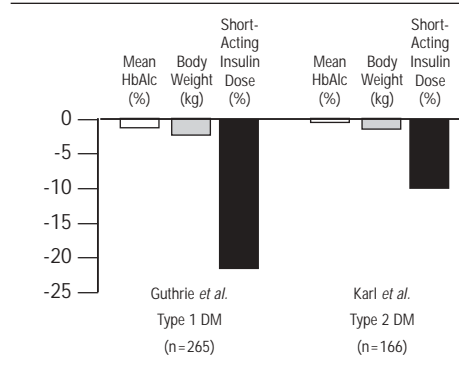
In a placebo-controlled study, an investigational long-acting (half-life of 10 days) GLP-1 analogue, CJC-1131, significantly reduced HbA1c, without increasing the risk for hypoglycemia, in patients previously inadequately controlled by metformin alone or metformin plus a sulfonylurea (10-OR). The effects of CJC-1131 on HbA1c were dose dependent (-0.6% with low-dose [ $2.1 \pm 1.06 \mu\text{g/kg}$ ] and -1.1% with high-dose [ $2.6 \pm 0.97 \mu\text{g/kg}$ ]). Gastrointestinal intolerance, primarily during the first four weeks of treatment, and moderate nausea were the most frequent adverse events.

Brazg and American collaborators (11-OR) assessed the effect of MK-0431, an orally active selective DPP-IV inhibitor, in a group of patients with inadequate control of their Type 2 diabetes despite a stable dose of metformin. In the two-period crossover trial, 28 patients (baseline HbA1c 6.5%-9.6%) receiving metformin were randomized to the DPP-IV inhibitor followed by placebo, each administered for four weeks, or vice versa. As compared to metformin plus placebo, treatment with metformin plus the DPP-IV inhibitor produced significantly greater reductions in fasting plasma glucose (-20.3 mg/dl,  $p < 0.001$ ), mean daily glucose (-28.0 mg/dl,  $p = 0.046$ ), and fructosamine levels (-33.7 mmol/l,  $p = 0.003$ ), a marker of blood glucose control over a two- to three-week period. Treatment with the DPP-IV inhibitor produced no weight gain and no increased incidence of gastrointestinal or hypoglycemic events. In a 12-week dose-ranging efficacy study that enrolled 743 patients (baseline HbA1c 6.3% - 11.0%) by Scott and colleagues of New Zealand (41-OR), MK-0431 at doses ranging from 5 to 50 mg twice daily produced placebo-subtracted differences in HbA1c that ranged from -0.4% to -0.8% in a dose-dependent manner. Treatment with the DPP-IV inhibitor produced no significant weight change and was well tolerated with few reported episodes of hypoglycemia.

**Figure 1. Effects of Exenatide**



**Figure 2. Effects of 26 Weeks of Pramlintide on HbA1c, Body Weight, and Short-Acting Insulin Dose**



## Pramlintide: A Synthetic Amylin Analog

Amylin, like insulin, is secreted by the pancreatic  $\beta$  cells with absolute amylin deficiency present in those with Type 1 diabetes and a relative deficiency occurring in those with Type 2 disease. The synthetic amylin analog, pramlintide, restrains hepatic glucose production by suppressing postprandial glucagon secretion in both Type 1 and Type 2 patients. It has also been recently released in the US as Symmlin®.

In an open-label study, Guthrie and associates (478-P) evaluated the safety and efficacy of pramlintide on HbA1c, body weight, and short-acting

insulin use in 265 patients with Type 1 diabetes (mean age 43 years, BMI 29 kg/m<sup>2</sup>, HbA1c 8.0%, diabetes duration 21 years). Pramlintide dose was escalated from 15 to 60  $\mu\text{g}$  as tolerated, with patients titrating their insulin to achieve glycemic targets. At week 26, significant reductions in mean HbA1c, body weight, and short-acting insulin dose were observed (Figure 2). Mean postprandial glucose trended lower (12-21 mg/dl) across meals. Similar effects on HbA1c, body weight, and short-acting insulin dose were observed in a study of 166 patients with Type 2 diabetes (mean age 54 years, BMI 39 kg/m<sup>2</sup>, HbA1c 8.3%), enrolled in a 26-week open-label study by Karl and US colleagues (48-OR) (Figure 2). In these patients, the mean postprandial glucose trended lower (40-49 mg/dl) across meals. In both studies, mild to moderate nausea and vomiting were the most frequently reported adverse events. Although performed using a non-validated questionnaire, many patients reported better control over their blood sugar levels, weight, and ability to cope with their disease.

As reported in previous editions of this newsletter, we continue to feel that these novel agents will have an important place in the management of diabetes. They have multiple complementary effects to improve glucose metabolism without the weight gain often associated with other agents (Table 1). Obviously the availability of pramlintide

	<i>GLP-1 Agonists</i>	<i>DPP-IV Inhibitors</i>	<i>Pramlintide</i>
Action	Activate GLP-1 receptors	↓ metabolism of endogenous GLP-1	Synthetic analogue of amylin
Metabolic effects	- ↑ insulin secretion (glucose-dependent) - ↓ glucagon secretion - Slow gastric emptying - ↓ food intake - ? $\beta$ -cell preservation	- ↑ insulin secretion - ↓ glucagon secretion - Slow gastric emptying - ? $\beta$ -cell preservation	- ↓ glucagon secretion - Slow gastric emptying - ↓ food intake
Benefits in clinical trials	- ↓ FPG, PPG, HbA1c - Weight loss	- ↓ FPG, PPG, HbA1c - Weight neutral	- ↓ PPG, HbA1c - Weight loss
Side effects	Nausea	Nausea	Nausea
Formulation	SQ injections (2/day)	Oral	SQ injections (3/day)
Availability/Indications	Exenatide, in Type 2 diabetes inadequately controlled on metformin and/or sulfonylureas	Investigational only	Type 1 and Type 2 diabetes inadequately controlled by multidose insulin

FPG=fasting plasma glucose, PPG=postprandial glucose, SQ=subcutaneous

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## **New Paths to Glycemic Control** *Continued from page 2*

and GLP-1 agonists only by injection will limit their use, as will concerns about side effects, such as nausea. (Of note, long-acting GLP-1 agonists are currently in development, which might require only

weekly or even monthly injections.) The DPP IV inhibitors are particularly attractive since they are now oral, although their effects on body weight and HbA1c appear to be less than the GLP-1 agonists. Both GLP-1 agonists and the DPP IV inhibitors may eventually be particularly useful in early diabetes or even pre-diabetes, since both

appear to enhance  $\beta$ -cell function and there is some data to suggest that they may also lead to  $\beta$ -cell preservation. Their precise role, however, in patient care will depend on a number of factors, including our clinical experience with them over the next several years.



## MOMMY and ME-tformin



Pregnancy is a well recognized insulin-resistant state, with increased levels of estrogens, human placental lactogen and cortisol, as well as a variety of other placenta-derived peptides impeding insulin action. Gestational diabetes mellitus (GDM) is characterized by insulin-resistance and relative  $\beta$ -cell decompensation. Metformin easily crosses the placenta, is secreted into breast milk, and is considered a highly controversial therapeutic agent in insulin-resistant pregnant women. In oral and poster presentations, the physiologic effects of pregnancy on insulin sensitivity were described, and in a symposium entitled "Metformin in Pregnancy—Is It Safe? Does it Work?," leading authorities attempted to elucidate the role of metformin in these patients.

### **Physiologic Effects of Pregnancy on Insulin Sensitivity**

The changes in insulin sensitivity that occur during pregnancy may be in part due to changes in adipose tissue and adiponectin levels according to the findings of Catalano *et al.* from Cleveland (1917-P). Ten healthy women were evaluated prior to conception and again in early (12-14 wks) and late (34-36 wks) pregnancy. Maternal adiponectin decreased by 20% ( $p=0.01$ ) in late, as compared to early, pregnancy (12.5 to 10.0  $\mu\text{g/l}$ ). There was a strong positive correlation between adiponectin concentrations and insulin sensitivity, as measured by the euglycemic insulin clamp technique, at all three timepoints, but most especially during late gestation. However this correlation was no longer significant after adjustment for maternal fat mass, with an impressive negative correlation between adiponectin and maternal body fat ( $p=0.008$ ).

Weight gain, even during the years prior to pregnancy, increases the risk for diabetes as well as GDM as revealed in a study by Henderson *et al.* from California (1914-P). The investigators

examined the relationship between the rate of weight change during the six years before pregnancy and GDM in a case control (114 GDM cases and 94 controls), multicenter cohort of 13,798 women aged 20-44 years who delivered between 1996 and 1998 and were screened for GDM at 24-28 weeks. Women were categorized according to quartiles of rate of weight change. Compared to women who lost weight (-8.2 to -0.67 kg/year), women whose weight changed by -0.67 to +0.39 kg/year had an increased risk of GDM (OR = 2.3). Women who gained 0.39 to 1.62 kg/year had a corresponding relative risk of 3.4 for GDM, and women in the highest quartile (+1.8 to +8.4 kg/year) had a striking relative risk of 5.7 for GDM, compared to women in the lowest quartile.

### **Metformin During Gestation**

In the opening presentation of the symposium, Dr. Clifford Bailey from Birmingham, UK, an international authority on metformin, reviewed the drug's cellular and metabolic mechanisms of action. Briefly, metformin counters insulin resistance by both insulin-dependent and -independent actions and may therefore have a potential role in the pregnant, insulin-resistant woman. It also appears to exert favorable cardiovascular effects without causing hypoglycemia or weight gain. Among women with insulin-dependent GDM, the addition of metformin often results in a 30% to 60% reduction in insulin dose. In those with a history of GDM, metformin therapy is thought to delay the onset of diabetes as well as its associated complications.

### **Determining Drug Safety During Pregnancy**

Safety is of significant concern when prescribing any agent during pregnancy, as reviewed during a symposium presentation by Dr. Gerry Briggs from California. Of all fetal structural defects, expo-

sure to drugs or chemicals is implicated in only 3% of cases, with over 40% being of unknown cause. Among diabetics, determining teratogenicity is especially difficult as these patients already have a three- to seven-fold higher background rate of structural defects (between 9% and 14%). In the case of metformin, rat and rabbit studies using doses of metformin two- to 10-times higher than those administered to humans produced no evidence of impaired fertility, structural defects, fetal abnormalities, or any effects on lactation. Embryo toxicity has been seen in rats at a dose of  $\geq 10$  times the human doses based on body surface area, thus placing metformin in the "moderate risk" category.

### **Metformin in PCOS and GDM**

In subsequent symposium presentations, Drs. Charles Glueck of Cincinnati and Janey Rowan of New Zealand reviewed the results of studies using metformin in women with polycystic ovary syndrome (PCOS) and GDM. Glueck reported that 80% of non-ovulatory women with PCOS responded to metformin. Among the non-responders, the addition of pioglitazone further promoted ovulation. Additional studies have found that metformin treatment significantly decreases the risk of spontaneous abortions (14% among those treated with metformin vs. 68% in controls) as well as reduces the development of GDM by 50% with no increased incidence of pre-eclampsia. It also promotes lactation in women with inadequate breast milk production and produces no difference in infant height, weight, or motor social development scores during 18 months of follow-up. In a study comparing metformin with a sulfonylurea or insulin, a higher risk of pre-eclampsia was noted in the metformin group; however, these women were older and heavier than those in the other treatment groups. The reduction in spontaneous

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## Mommy and ME-tformin

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abortion rates with metformin is thought to be associated with a decrease in the activity of plasminogen activator inhibitor-1 (PAI-1) activity, an antifibrinolytic factor that is an independent determinant of miscarriage.

Children born to women with GDM are at three to four-fold higher risk of developing obesity and diabetes. The ability of metformin to modify insulin sensitivity suggests that it may play a protective role when used in GDM. Rowan described the results of a retrospective study performed in a diverse ethnic population of diabetic/insulin-resistant women that found a lower risk of hypoglycemia in neonates of mothers given metformin compared to those given insulin and glibenclamide. This finding suggests that the use of metformin during pregnancy, although it is not FDA-approved for this indication, may improve the metabolic milieu of both the mother and fetus.

**Table 2. Mortality Risk by Diabetes and Child-Bearing Category**

	Mortality Rate Ratio	95% CI	p-value
Nondiabetic, parous	1.00	(reference group)	
Nondiabetic, nulliparous	2.43	1.26 – 4.67	<0.01
Diabetic, nulliparous	1.87	0.93 – 3.77	0.08
Diabetic, parous	2.38	1.45-3.94	<0.01
Diabetic in pregnancy	2.81	1.73-4.59	<0.01

## Long-Term Effects on Mortality

Little is known about the long-term impact of diabetes during pregnancy on maternal mortality. Curtis *et al.* from Phoenix studied this association in a longitudinal health study involving Pima Indians, a population known to have a high prevalence of both insulin resistance and Type 2 diabetes (158-OR). Women between the ages of 20-34 years during the period 1965-1979 (n=840) were followed until death or through 2001. Diabetes and parity were determined at

baseline and then up until age 35, after which time these variables were fixed for analysis. As shown in Table 2, the highest mortality was seen in women with a history of pregnancy complicated by diabetes before the age of 35 years, as compared to those who had given birth but did not develop diabetes. Of note, nulliparous, nondiabetic women also had increased mortality rates.

GDM is clearly important to identify and treat. The role of metformin in this regard continues to evolve.



## Feeling Low?



Hypoglycemia poses the major barrier to tight glycemic control of diabetes. Numerous presentations highlighted the risk factors associated with this feared complication and its potential prevention.

Few studies have evaluated potential risk factors for occurrence of severe hypoglycemia in insulin treated Type 2 diabetes subjects. Akram *et al.* from Denmark evaluated 401 patients who completed a questionnaire about occurrence of hypoglycemia awareness and socio-demographic factors (632-P). In the preceding year total number of episodes of severe hypoglycemia was 178, corresponding to an incidence rate of 0.44 episodes/person-years. The risk of any severe event was increased with impaired hypoglycemia awareness (OR 2.95), long duration of insulin therapy (OR 1.97/10 years), and marital status (OR 2.39), while treatment with an angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) decreased the risk (OR 0.5). For those who had one event, the risk of repeated events was increased with presence of neuropathy (RR 2.99) and macrovascular complications (RR 2.0), while diabetes duration prior to insulin commencement decreased the risk (RR 0.35/10 years). Thus, the incidence of severe hypoglycemia in insulin-treated Type 2 diabetes is one third of that in Type 1 diabetes, and impaired awareness is the most important risk factor.

Severe hypoglycemia in Type 1 diabetes has been associated with high renin-angiotensin system (RAS) activity. Hoi-Hansen *et al.* from

Denmark studied nine patients with high RAS activity and nine patients with low RAS activity (mean age 40 years, diabetes duration 18.3 yrs, HbA1c 8.3%) to test whether high activity may predispose to cognitive dysfunction during hypoglycemia (622-P). In a cross-over study, patients were subjected to hypoglycemia and euglycemia using IV insulin infusion or IV insulin-glucose infusion, respectively. Cognitive function and hypoglycemic symptoms were recorded during the experiment. Despite a similar hypoglycemic stimulus (nadir plasma glucose ~43 mg/dl), only the group with high RAS activity showed significant deterioration in cognitive performance (reaction time for tasks requiring use of working memory). The high RAS group reported a lower increase in autonomic symptoms scores during hypoglycemia. The investigators concluded that in patients with Type 1 diabetes high RAS activity is associated with increased cognitive dysfunction and a blunted autonomic symptom response during mild hypoglycemia compared to patients with low RAS activity.

In another study, the same researchers, Hoi-Hansen *et al.* from Denmark, assessed the relationship between conventional risk factors for hypoglycemia and the occurrence of silent hypoglycemia using continuous glucose monitoring (CGMS<sup>®</sup>) (621-P). A cohort of 119 patients with Type 1 diabetes (mean age 46 years, diabetes duration 22 years, HbA1c 8.3%, 89% on multiple injections, 21% treated with ACEI or ARB) partici-

pated in six days of continuous glucose monitoring. Valid monitoring time was 621 days, with total number of episodes less than 40 mg/dl of 3.9 per week, including silent hypoglycemia (3 per week), symptomatic hypoglycemia (0.8 per week), and severe hypoglycemia (0.06 per week). There was no relationship between hypoglycemia and known risk factors, such as HbA1c, hypoglycemia awareness, diabetes duration, age, C-peptide status, ACE activity, and late diabetic complications. Patients not being treated with an ACEI or ARB had two times more episodes of silent hypoglycemia (p<0.01), as compared to patients taking one of these medications. After excluding patients on ACEI/ARB treatment, patients with impaired awareness were 1.6 times more likely to have episodes of silent hypoglycemia as compared to patients with normal awareness. In conclusion, silent hypoglycemia is quite common and was not related to known risk factors of severe hypoglycemia. ACEI/ARB therapy may confer protection against silent hypoglycemia.

To avoid severe hypoglycemia, frequent glucose monitoring is mandatory. In addition, comprehensive diabetes education is important, particularly in insulin-treated patients, so that dosing can be modified appropriately during periods of increased physical exertion and decreased caloric intake. The data provided this week concerning the RAS system are quite interesting.



## Late Breaking Clinical Trials

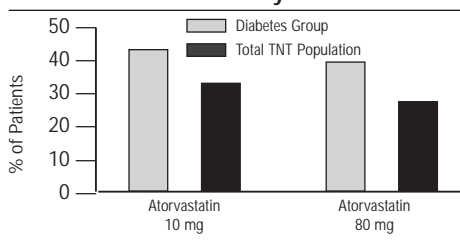


Results and/or updates on five clinical trials were featured in a crowded Sunday afternoon symposium. The first, *Intensive Lipid Lowering with Atorvastatin in Patients with Diabetes and Stable Coronary Disease*, was presented by Dr. James Shepherd of Glasgow. Results of the Treating to New Target (TNT) study were presented earlier this year at the annual meeting of the American College of Cardiology and revealed that atorvastatin 80 mg reduced the relative risk of vascular events by 22% in all patient types. At this meeting, Dr. Shepherd shared the results for the diabetes subset of TNT. A total of 1,501 patients with diabetes randomized to receive atorvastatin 10 mg daily (n = 753) or atorvastatin 80 mg daily (n = 748) were followed for 4.9 years. The average LDL-cholesterol at the completion of the trial was 100 mg/dl and 77 mg/dl in the 10 mg and 80 mg atorvastatin groups, respectively. Patients receiving 80 mg had a 25% relative risk reduction in the time to first major cardiovascular event (p = 0.026). The total number of events were 135 in the 10 mg group and 103 in the 80 mg group. Cerebrovascular events decreased by 31% in the 80 mg group (p = 0.037). As would be expected, event rates were higher in the diabetes subset versus total TNT group (Figure 3). Dr. Shepherd remarked that this trial confirms that aggressive lipid lowering therapy should become standard for all patients with diabetes.

In the second late-breaking trial, Dr. David Kendall of Minnesota shared information related to two double-blind, randomized studies evaluating muraglitazar, a dual PPAR  $\alpha/\gamma$  agonist. The first, a two-year trial, demonstrated maintenance of an average HbA1c of 6.5%, a decrease in triglycerides ranging from 13-39%, and an increase in HDL-cholesterol of greater than 20% at muraglitazar doses of 0.5 mg to 20 mg. The second trial compared muraglitazar 5 mg daily to pioglitazone 30 mg per day, each in combination with metformin. The muraglitazar group demonstrated a statistically significantly greater improvement in HbA1c, triglycerides, and HDL-cholesterol when compared with pioglitazone (p < 0.001, each parameter). One criticism of the trial is the 30 mg pioglitazone dose (versus 45 mg) was used as the comparator. Despite the trial limitations, muraglitazar appears to be promising new therapeutic agent.

Dr. Richard Herman, University of Colorado, presented retinopathy screening results from the *Diabetes Prevention Program (DPP)*. This study was designed to address: (1) the level at which diabetic retinopathy (DR) occurs; and (2) the time course of development of DR in Type 2 diabetes.

**Figure 3. Vascular Event Rates in the TNT Study**



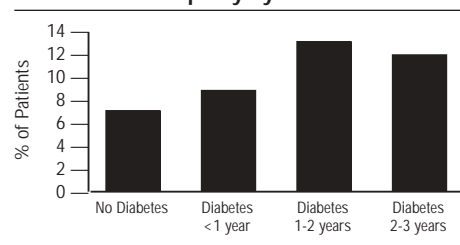
Patients previously enrolled in the DPP, now DPP Outcomes Study (DPPPOS) were followed for development of DR. The prevalence of non-proliferative retinopathy was significantly higher in patients with diabetes versus those without (15.4% vs. 9.6%, p < 0.015). Similarly, proliferative diabetic retinopathy was greater in those with diabetes (12.5% vs. 7.6% in non-diabetics, p = 0.028). Prevalence of DR by duration of diabetes did not show a linear relationship (Figure 4).

The study indicates that even individuals with impaired glucose tolerance can have detectable DR, suggesting that DR may begin before the clinical diagnosis of diabetes. The study also demonstrates that DR occurs very early in the clinical course of Type 2 diabetes.

Rimonabant, a cannabinoid receptor-1 antagonist previously shown to decrease food intake and body weight in laboratory animals and humans, was evaluated in obese or overweight patients with Type 2 diabetes. Dr. Andre Scheen of Belgium presented results of the RIO-Diabetes trial, a randomized, double-blind study, showing a statistically significant improvement in several parameters with rimonabant 20 mg as compared with placebo (Table 3). Scheen also reported that rimonabant was well tolerated with an incidence of adverse drug events similar to placebo.

Cutting edge trial results culminated with the update provided by Dr. David Nathan from

**Figure 4. Prevalence of Diabetic Retinopathy by Disease Duration**



Harvard who reported on *Effects of Intensive Diabetes Management on Cardiovascular Events in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)*. He reminded the audience that it has been greater than 22 years since the DCCT and 12 years since the results demonstrated intensive insulin control prevents long-term microvascular complications. DCCT evolved into EDIC, a long-term observational group that has shown a persistent benefit of intensive insulin therapy despite convergence of HbA1c values at year five. The primary outcome of the current study is aggregate cardiovascular events between the groups previously identified as intensive versus conventional insulin control. The 20-year cumulative incidence of a first event was 6% in the intensive group and 11% in the conventional group (p = 0.018). Overall risk reduction for the intensive arm was a statistically significant 47%. Even when adjusted for differences in renal disease and microalbuminuria, risk reduction was still impressive at 38% and 42%, respectively. HbA1c during the DCCT was the major independent predictor of cardiovascular events. The mechanism remains to be established for the continued protective effects or "metabolic memory," as the benefit of early intensive insulin therapy on cardiovascular disease has persisted for almost two decades.

**Table 3. Rimonabant versus Placebo in Patients with Type 2 Diabetes**

Parameter	Placebo	Rimonabant 20 mg	p-value
Body weight (kg)	-1.4	-5.3	<0.001
Waist circumference (cm)	-1.9	-5.2	<0.01
Patients with >5% weight loss	19.5%	55.9%	<0.001
Patients with >10% weight loss	21.4%	3.0%	<0.01
HbA1c (%)	+0.1	-0.6	<0.001
HDL-cholesterol (mg/dl)	+3	+6	<0.001
Triglycerides (mg/dl)	+4	-31	<0.001

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