

# Diabetes 2009

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## Defining dī'ə-bē'tīs



Important data on diabetes presented at the 69th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2009**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2009** will be followed by a **Diabetes 2009** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

**Diabetes 2009** is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of  $\beta$ -cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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One of the biggest topics under discussion at this week's *Scientific Sessions of the American Diabetes Association* is the very recent International Expert Committee Report on the Role of the Glycated Hemoglobin (A1c) Assay in the Diagnosis of Diabetes, released on Friday, June 5th. The report proposes significant changes in how diabetes is diagnosed, with a move away from using fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT) and toward the hemoglobin A1c test. A special symposium was arranged on the opening day of the Sessions to present, critique, and discuss this somewhat controversial Report.

Dr. David Nathan, of the Massachusetts General Hospital, and chairman of the Expert Committee, was introduced by Dr. Vivian Fonseca of Tulane University, who chaired the session. As background, Dr. Nathan described the rationale for using the A1c, a stable measure of chronic hyperglycemia, instead of or in addition to fasting glucose or the response to an OGTT, which are more labile glycemic measures. The major impediment to using the A1c was the lack of a global standard A1c assay. Over the past several years, the American College of Pathology and the International Federation of Clinical Chemists have set a standard based on the A1c used in the Diabetes Complications and Control Trial (DCCT). This standardization is now being implemented in most developed countries, although a fair amount of variation still remains across and within some nations. Standardization will allow for the use of A1c as a diagnostic tool.

Dr. Nathan next reviewed the history of diabetes diagnostic criteria. Prior to 1979, there was no widely agreed-upon definition. It was the National Diabetes Data Group who, in 1979, set the guidelines for diagnosis, namely a FPG of  $\geq 140$  mg/dl or two plasma glucose values  $\geq 200$  mg/dl during an OGTT, to include the 2-hour value. These thresholds were chosen because they appeared to predict which patients would go on to develop clinically symptomatic disease. The intermediate category of impaired glucose tolerance (IGT) was defined as a 2-hour OGTT glucose of 140-199 mg/dl. The WHO released similar guidelines in 1980.

The definition of diabetes was revised in 1997 by the first Expert Committee (Table 1), who examined data from several epidemiological cohorts that strongly suggested an 'inflection' in the curvilinear relationship between glucose and retinopathy at approximately 126 mg/dl fasting. Accordingly, the FPG threshold for diagnosis was set at 126 mg/dl, whereas the OGTT criteria were simplified to a single 2-hour glucose of  $\geq 200$  mg/dl. For the first time, diagnostic thresholds were set at physiologically relevant points, correlating with a specific microangiopathic complication of the disease. The IGT criteria remained unchanged, but the Committee added the fasting equivalent of IGT, namely impaired fasting glucose, or IFG (100-125 mg/dl.) The WHO endorsed these guidelines in 1999.

Later, in 2003, the Expert Committee redefined the lower threshold for IFG as 100 mg/dl, data for which suggested it was more closely aligned with the OGTT 2-hour value of 140 mg/dl.

With the success of the National Glycohemoglobin Standardization Program, the Expert Committee was convened by multiple professional organizations, including the ADA, to reassess the guidelines (Table 2).

**Table 1. Current Diagnostic Criteria for Diabetes**

	Normal	Impaired	Diabetes
Fasting plasma glucose (mg/dl)	<100	100-125	$\geq 126$
2-hour OGTT (mg/dl)	<140	140-199	$\geq 200$
Random (casual) (mg/dl)	—	—	$\geq 200^*$

\* with classical symptoms of diabetes.

The Committee felt that the A1c has certain advantages over glucose. First, pre-analytically, A1c is a more stable measure than glucose after sample collection. Secondly, A1c demonstrates less intra-individual variation day-to-day when measured repeatedly as opposed to glucose.

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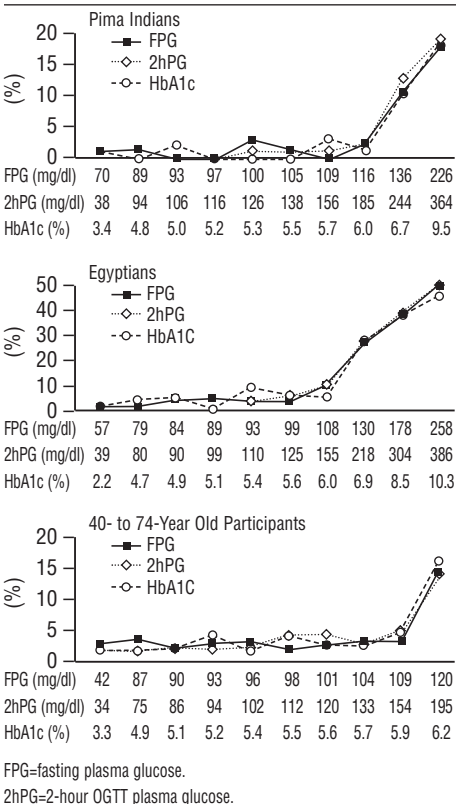
## Defining Diabetes

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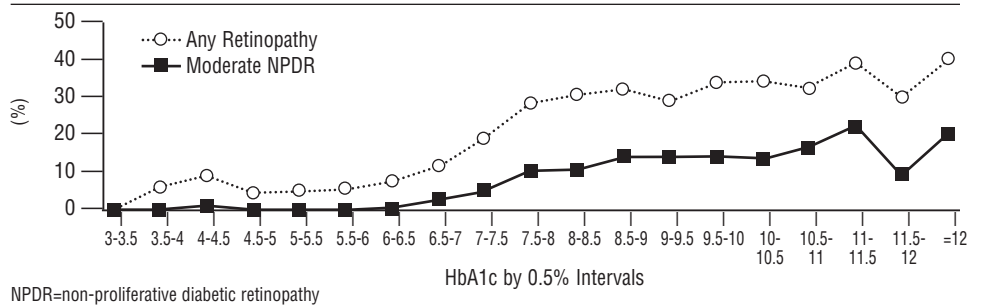
Finally, A1c holds the distinct advantage of not requiring a fasting blood draw, which is more convenient for patients.

In subsequent reanalysis of the original epidemiological data sets from the 1997 Report (Figure 1), it was apparent that a similar inflection at ~6.5% existed in the relationship between A1c and retinopathy as described for glucose. Moreover, the DETECT-2 study recently revealed very similar data (Figure 2). The receiver operating curve (ROC) analysis of this data set suggested that the optimal cut-point for detecting retinopathy was indeed an A1c of 6.5%, with an area under the curve (AUC) of 0.91. The cut-point for FPG was 117 mg/dl and for the 2-hour glucose during OGTT, 202 mg/dl, with AUCs of 0.87 and 0.89, respectively. Accordingly, since the A1c had several practical advantages over glucose, and as good if not slightly better correlation with a chronic complication, the Committee felt that it should be considered the preferred test. Importantly, the Committee did not feel that glucose testing should necessarily be abandoned, especially since some parts of the world may not have access

**Figure 1. Prevalence of Retinopathy by Deciles of Fasting Glucose, 2-Hour OGTT Glucose, and HbA1c**



**Figure 2. Prevalence of Retinopathy by 0.5% Intervals of A1c in Persons Aged 20-79 Years**



to A1c measurements, let alone standardized ones. However, it felt that patients should be tracked with a single test. Using A1c along with FPG, for instance, was likely to lead to confusion, since patients defined as having diabetes through one metric may not necessarily have it based on another.

The Expert Committee also examined a closely related issue, namely the metabolic states now referred to as 'pre-diabetes'—IGT and IFG. Because A1c is being proposed as the preferred diagnostic test, it may logically be used to identify persons at risk for diabetes, as has been done with FPG and the OGTT. Indeed, as these latter measures are used less frequently, the labels of IGT and IFG would become less germane. Since the relationship between A1c and diabetes risk is a graded one, beginning at approximately 5.0%, and without any apparent 'inflection', the Committee felt that the terminology 'pre-diabetes' was no longer appropriate. Instead, patients with high A1cs not yet in the diabetic range (6.0-6.5%) should be considered at 'higher risk.'

Dr. Nathan concluded his presentation by underscoring that the recommendations of the Expert Committee should be considered a 'catalyst' for future discussions about the method by which patients are diagnosed with diabetes. The various professional organizations, including the ADA, will now need to examine the recommendations to determine whether they should be incorporated into their own standards of care.

Over the next hour, commentary was sought from a group of international authorities. Dr. Ann Albright of the Centers for Disease Control, who participated in the Expert Committee, reflected on the public health implications of the proposed guidelines. There are few data thus far on how these new criteria would affect the prevalence of diabetes and pre-diabetic states in the US. She felt that, since the A1c test was more likely to be performed in at-risk patients, due to convenience, it may serve to facilitate enhanced diagnostic capabilities. Dr. Massimo Massi-Benedetti of Italy was highly critical of the Committee's report.

**Table 2. Recommendation of the International Expert Committee for the Diagnosis of Diabetes**

- The A1c assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.
- The A1c assay has several advantages compared to laboratory measures of glucose.
- Diabetes should be diagnosed when the A1c is  $\geq 6.5\%$ . Diagnosis should be confirmed with a repeat A1c test. Confirmation is not required in symptomatic subjects with plasma glucose levels  $> 200$  mg/dl ( $> 11.1$  mmol/l).
- If A1c testing is not possible, previously recommended diagnostic methods (eg, fasting plasma glucose or 2-hour OGTT plasma glucose), with confirmation, are acceptable.
- A1c testing is indicated in children in whom diabetes is suspected, but the classic symptoms and a casual plasma glucose  $> 200$  mg/dl ( $> 11.1$  mmol/l) are not found.

He raised several epidemiological, statistical, and practical concerns. One of his greatest worries is the possibility that two standards would emerge, A1c in developed countries and FPG in developing countries. Dr. Shashank Joshi of India was generally complementary of the Committee's efforts but also raised major concerns about the applicability of the recommendations in the third world. Finally, Dr. Harold Lebovitz of the US raised issues concerning patients with hemoglobinopathies, anemias, and liver and renal disease, in whom the A1c test is inaccurate. He also had great reservations about the abolishment of the pre-diabetes diagnosis, suggesting that a change at this point will serve only to confuse both physicians and patients alike. Dr. Lebovitz, along with both Drs. Fonseca and Nathan, called for more studies in this area to better understand the relationship between the various measures of glycemia and not only microvascular diseases, but also cardiovascular disease.

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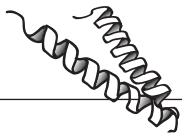
Comments from the capacity audience were next entertained. While most congratulated the Committee on its hard work and bold recommendations, several session attendees raised additional concerns about the recommendations. Issues addressed included the substantial cost differences between A1c and FPG; the implications for health insurance coverage for diabetes prevention strategies; the anticipated confusion in the medical community if the diagnostic criteria changes are adopted by professional organizations; and, the need for widespread physician and patient education to be required to ease implementation. There also appeared to be a general sense that the older terminology of 'pre-diabetes' was a useful tool to motivate patients to undertake lifestyle change and that the newer phrase 'high risk' may not carry with it the same urgency.

We feel that the Committee's recommendations are very well considered and reasonable. A1c should be used to diagnose diabetes when available, given its advantages as stated above, especially since it may be drawn in the non-fasted state. However, the implications of such a radical change on the prevalence of diabetes needs to be better understood. Our sense is that many patients previously diagnosed with diabetes by the traditional criteria may have A1c's <6.5%. Do these patients suddenly not have diabetes? For this and other reasons, the Report will likely lead to a fair amount of confusion in the healthcare community. Therefore, a more inclusive approach of using any of the three glycemic measures (A1c, FPG, OGTT) for diagnosing diabetes may be a reasonable compromise, with the diagnosis defaulting, conservatively, to the most abnormal result.

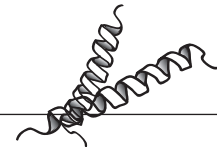
We are also concerned about losing the

'pre-diabetes' terminology, having found this to be extremely helpful in our discussions with patients—who usually respond better to concrete words and figures, as opposed to the more nebulous "risk"-based terminology. Another problematic aspect with endorsing the A1c for diagnosis is the modest paradox of endorsing the use of metformin for patients at the time of diagnosis at an A1c of 6.5%, but having the treatment guidelines set at 7.0%.

In summary, the International Expert Committee Report on the Role of the Glycated Hemoglobin (A1c) Assay in the Diagnosis of Diabetes is likely to raise significant controversy in the diabetes community for the foreseeable future. Importantly, the Report is not considered a position of the ADA, or for that matter, the EASD, IDF, or WHO. Each of these important organizations will need to examine the Committee's work and construct rational guidelines for using A1c in the diagnosis of diabetes.



## Are PPARs Par?



Now available for more than a decade in the US, the thiazolidinediones (TZDs)—peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonists—continue to be studied extensively to further characterize their clinical benefits and risks.

### The RECORD Trial

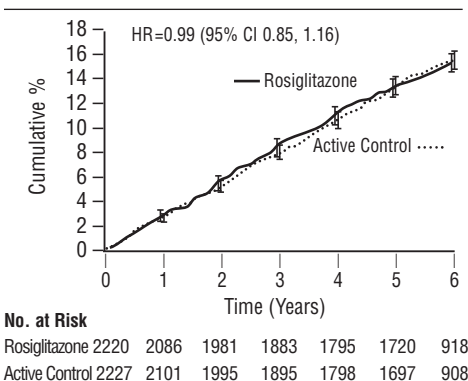
During an opening-day session at this week's meeting, Drs. Pocock (London, UK), Komajda (Paris, France), Beck-Nielsen (Odense, Denmark), and Home (Newcastle, UK) presented results of the long-awaited and recently completed RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes) trial. Inconclusive interim analysis results were reported in 2007 (Home *et al.*, *NEJM* 357:28-38) in the context of

that year's rosiglitazone controversy.

RECORD was a multicenter, open-label, 'noninferiority' trial in which patients with Type 2 diabetes inadequately controlled by metformin or a sulfonylurea were randomized to receive add-on rosiglitazone (n=2,220) or the combination of metformin and sulfonylurea (n=2,227). It was initiated at the request of European drug regulatory agencies to demonstrate the safety of this TZD. Over a mean follow-up period of 5.5 years, 321 and 323 patients in the rosiglitazone and active comparator groups, respectively, experienced the primary endpoint of hospitalization or death from cardiovascular (CV) causes (Figure 3). This met the upper confidence interval 'non-inferiority' margin of 1.20 (hazard ratio [HR], 0.99; 95% CI 0.85, 1.16).

Similar results were observed in two pre-defined sensitivity analyses (per-protocol analysis of randomized dual therapy and an analysis in which primary endpoints of non-atherosclerotic origin were excluded) as well as in analyses within each treatment stratum (ie, TZD vs. metformin on a background of sulfonylurea and TZD vs. sulfonylurea on a background of metformin). With regard to acute MI, a subject of great debate since 2007 (Nissen and Wolski, *NEJM* 356:2457-71), there was a slight but non-significant difference between treatment groups, with 8 additional events with rosiglitazone, leading to inconclusive evidence for increased MI risk. Not surprisingly, the event rate for heart failure was ~2-fold higher with a TZD (61 vs. 29 for active control; HR 2.10 [Table 3]).

**Figure 3. Kaplan-Meier Analysis of Time to Hospitalization or Death from CV Causes**



**Table 3. Hospitalization or Death from CV Causes**

Variable	Number of Patients			
	Rosiglitazone (n=2,220)	Metformin + Sulfonylurea (n=2,227)	Hazard Ratio (95% CI)	p-value
Primary endpoint*	321	323	0.99 (0.85, 1.16)	0.93
Death from CV causes	60	71	0.84 (0.59, 1.18)	0.32
Death from any cause	136	157	0.86 (0.68, 1.08)	0.19
Acute myocardial infarction†	64	56	1.14 (0.80, 1.63)	0.47
Stroke†	46	63	0.72 (0.49, 1.06)	0.10
Heart failure†	61	29	2.10 (1.35, 3.27)	0.001
Death from CV causes, myocardial infarction, or stroke	154	165	0.93 (0.74, 1.15)	0.50

\*First occurrence of a hospitalization or death from CV causes.

†Fatal and non-fatal.

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Deaths due to heart failure were also more common in the TZD group (10 vs. 2 for active control), whereas deaths due to stroke and other acute vascular events were fewer (data not shown). Of note, the event rate overall was only 2.6%, a fraction of the anticipated 11% rate that entered the power calculations. Also, there were approximately 10% more rosiglitazone-treated patients taking statins during RECORD, likely a reflection of this TZD's known effects to increase LDL-cholesterol concentrations. The investigators, however, estimated that this difference contributed a minuscule amount to the hazard ratio.

Risk of bone fracture was increased with rosiglitazone (risk ratio [RR] 1.57,  $p < 0.0001$ ), primarily in women (RR 1.82 vs. 1.23 for men; interaction  $p = 0.10$ ). (Similar results were presented by Aubert *et al.* [abstract 601-P, page 5], although the gender difference was smaller.) The excess fractures affected upper (RR=1.57,  $p = 0.0095$ ) and distal lower limbs (RR 2.60,  $p < 0.0001$ ), with no increase in hip/femur fractures.

Finally, glycemic control was improved over time in those patients randomized to rosiglitazone vs. comparator, consistent with the results from ADOPT, which demonstrated greater durability of effectiveness of this TZD vs. sulfonyleurea or metformin.

Do the RECORD results vindicate rosiglitazone as a relatively safe option for our patients with Type 2 diabetes? Since the Nissen-Wolski paper in 2007, this drug has fallen out of favor. The consistent hazard ratios ~1.0 in RECORD would appear to generally refute the suggestion from that meta-analysis that rosiglitazone increases myocardial infarction and CV mortality. We interpret the RECORD trial, despite its limitations, as demonstrating no convincing evidence of any substantial risk on coronary heart disease endpoints from this drug. The main risks, namely heart failure and bone fractures, are already appreciated.

One question that remains is why rosiglitazone does not reduce CV disease endpoints, as may have occurred with pioglitazone in the PROactive study (Dormandy, *Lancet* 2005; 366:1279-89), another safety study designed to address concerns of European agencies. Preclinical data suggested that rosiglitazone could beneficially influence important molecular events involved in the atherosclerotic process. As with many drugs, however, what appears reasonable in the preclinical setting may not translate to an actual clinical benefit to our patients. Moreover, the differences amongst the TZDs may reflect

differential effects of these nuclear receptor agonists on lipid metabolism.

## Cardiovascular Effects

In a related presentation, Reaven and American colleagues evaluated the impact of a TZD on preclinical cardiovascular disease (CVD). They assessed the long-term effects of pioglitazone on carotid intima-media thickness (CIMT) in patients with IGT who were enrolled in the ACT NOW diabetes prevention study and randomized to either pioglitazone (45 mg/day) or placebo (abstract 15LB-OR). Of 602 study participants, 490 had CIMT measured by high-resolution B-mode ultrasound carotid imaging at baseline. A total of 393 patients (194 pioglitazone and 199 placebo; age=53±12 yr; 54% female; 55% non-Hispanic White; BMI=33.2±5.3 kg/m<sup>2</sup>; HbA1c=5.4±0.4%) had 2 to 3 repeat scans. Baseline characteristics and CVD risk factors were similar between the treatment groups. The annual rate of change in CIMT—determined from mixed models fitted to CIMT data from patients who completed ≥2 scans—was 38% lower in the pioglitazone group (mean ± SE, 0.0055±0.0011 vs. 0.0089±0.0011 mm/yr,  $p = 0.025$ ) over a median follow-up period of 2.7 years. The between-treatment-group difference in CIMT progression was observed even when the participants who developed diabetes during the study were excluded from the analysis, indicating that the treatment benefit with TZD was not apparently a consequence of progressive hyperglycemia in the placebo recipients. The annual rates of CIMT change were linear (ie, persistent) and unaffected by adjustment for baseline CVD risk factors. Taken together, pioglitazone slowed CIMT progression in pre-diabetic individuals, and this anti-atherogenic effect persisted for almost 3 years. The investigators suggested, based on their findings, that use of TZD therapy early in the evolution of diabetes may have beneficial effects on CVD. Obviously, such an approach needs to be balanced against the potential risks of such therapy.

## Diabetes Progression

β-cell dysfunction is a strong predictor of progression to Type 2 diabetes in patients with the prediabetic states, IGT and/or IFG. Although TZDs have been shown to improve β-cell function in patients with Type 2 diabetes, little is known about such effects in the pre-diabetic state. Hanley and Canadian co-investigators from the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) study evaluated β-cell function—using fasting proinsulin/C-peptide

ratio (PI/C) and 'insulinogenic index' (defined as the insulin/glucose ratio during the first 30 minutes of an OGTT divided by homeostasis model of insulin resistance) (IGI/IR)—in 982 DREAM participants with IFG and/or IGT who had an OGTT at baseline, after 2 years, and at study end (abstract 968-P).

By way of background, in the DREAM study, eligible patients were randomly assigned to rosiglitazone 4 mg once daily for the first 4 months and 8 mg once daily thereafter. Patients were concurrently assigned to treatment with the ACE inhibitor, ramipril 15 mg, or placebo in a 2x2-factorial design. At the time of the DREAM study, it was hypothesized that ACE inhibition might lower glucose via direct effects on the β-cell, although studies had not been conducted in subjects with IGT and/or IFG. Patients were followed for ~3 years. As reported in 2006, rosiglitazone treatment significantly reduced the incidence of Type 2 diabetes (-62%) and increased the likelihood of regression to normoglycemia in adults with prediabetes (DREAM Investigators, *Lancet* 2006;368:1096-1105), whereas treatment with the ACE inhibitor did not (*NEJM* 2006;355:1551-62).

During their poster presentation this week, the DREAM investigators showed that subjects receiving rosiglitazone had a significant increase in IGI/IR between baseline and study end compared to the placebo group (3.57 vs. 0.27,  $p < 0.0001$ ) and a significant decrease in PI/C (-0.010 vs. -0.006,  $p < 0.0001$ ). In contrast, no significant changes in IGI/IR or PI/C were seen in subjects receiving ramipril compared to placebo (1.63 vs. 2.53,  $p = 0.98$ , and -0.007 vs. -0.008,  $p = 0.64$ , respectively). The impact of the TZD on IGI/IR and PI/C was similar among those with isolated IGT (each  $p < 0.001$ ) and more modest in those with isolated IFG (IGI/IR: 1.25 vs. 0.30,  $p = 0.03$ ; PI/C: -0.003 vs. -0.001,  $p = 0.07$ ). These findings demonstrate that the diabetes preventive effect of TZDs is, at least in part, a consequence of improved β-cell function over time.

## Lipid Effects

Given their favorable effects on hyperglycemia and dyslipidemia, Dunbar *et al.* from Philadelphia conducted a study to determine if TZD treatment might abrogate niacin-induced impairment of insulin sensitivity and glucose tolerance in patients with metabolic syndrome and associated low HDL-cholesterol (abstract 621-P). The investigators randomized 45 patients in a double-blind manner to daily extended-release niacin 2 grams with either placebo ( $n = 25$ ) or pioglitazone 45 mg ( $n = 20$ ) for 12 weeks. Study patients underwent a battery of

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tests to assess insulin sensitivity before and after the conclusion of treatment. Their results indicated that extended-release niacin impairs fasting (primarily hepatic) insulin sensitivity and insulin-independent glucose disposal (glucose effectiveness), and that the addition of a TZD appeared to prevent the development of these defects.

## Fracture Risk

TZDs have been associated with an increased fracture risk in women. Using an integrated pharmacy and medical claims database of ~13 million individuals, Aubert *et al.* from San Antonio and Boston assessed fracture risk from ongoing or newly initiated treatment with a TZD (n=69,047, mean age=56±5 years, 59% men), as compared to another antihyperglycemic agent (ie, metformin, exenatide, or a sulfonylurea) (n=75,352, mean age=56±5 years, 51% men), for diabetes (abstract 601-P). Using a logistic regression model, adjusted for age, COPD, asthma, osteoporosis, stroke, and prior fracture, the investigators found that fracture risk was increased in both men and women being treated with a TZD over the 540-day study period (Figure 4). There was no difference in fracture risk between patients taking pioglitazone vs. rosiglitazone (OR 1.03, p=0.416). In a sub-set of patients who initiated a TZD, risk was increased only in women, leading the investigators to conclude that the time to fracture following initiation of TZD may be longer in men.

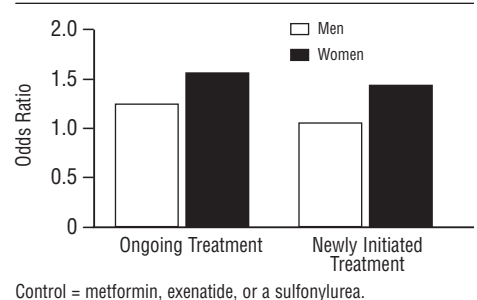
## Emerging Agents

Henry *et al.* from the US and Switzerland presented results of the SYNCHRONY study, a phase 2, dose-ranging, active-controlled trial of aleglitazar, a dual PPAR $\alpha/\gamma$  agonist, in patients with Type 2 diabetes (abstract 917-P). These

agents have previously been shown to reduce HbA1c to the same degree as PPAR $\gamma$  agonists (ie, TZDs) but with greater lipid benefits, especially on triglycerides and HDL-cholesterol. Prior members of this class, however, have been dropped in late stages of clinical development because of adverse effects, including a paradoxical increase in CV events. Following a 4- to 5-week placebo run-in period, 332 patients (treated with 0 to 2 oral agents at enrollment) were randomized to aleglitazar (50, 150, 300, or 600  $\mu$ g), placebo, or to open-label pioglitazone 45mg/day for 16 weeks. A dose-dependent effect on HbA1c was observed with aleglitazar: 0, -0.49%, -0.60%, and -0.99% for the 50, 150, 300, and 600  $\mu$ g groups, respectively (p<0.001 for  $\geq$ 150  $\mu$ g vs. placebo). Favorable effects on lipid parameters were also observed across the dose groups. A ceiling effect on triglycerides (-29.7%) and HDL-cholesterol (+25.1%) were approached with the 150  $\mu$ g dose, as was a 10% reduction of LDL-cholesterol from baseline. The expected PPAR $\gamma$  effects on body weight and fluid retention were also observed with aleglitazar. Body weight change was -0.85, +0.52, and +1.06 kg with placebo, aleglitazar 150  $\mu$ g, and pioglitazone 45 mg/day, respectively. The incidence of edema for the respective treatment groups was 5.5%, 3.6%, and 7.0%. Of some additional concern was a dose-dependent increase in serum creatinine—5% (50  $\mu$ g) to 16% (600  $\mu$ g)—a previously reported effect of PPAR $\alpha$  agonists and at least one dual agonist.

While PPAR $\gamma$  activation leads to improvements in insulin resistance, hyperglycemia, endothelial function, and markers of inflammation, indiscriminate agonism at this nuclear receptor is also associated with several undesirable adipogenic effects, weight gain, fluid retention, and an increased risk of heart failure and bone fractures. Research is underway to determine if specific activities of the PPAR $\gamma$  receptor can be selectively modulated, such that its insulin-sensitizing effects

**Figure 4. Fracture Risk in Diabetes Patients Treated with TZD vs. Control Antihyperglycemic Agent**



can be separated from its adverse effects. In this regard, there is early evidence from animal studies and initial phase 1 human clinical studies that favorable metabolic effects may be achieved with INT131, a non-TZD selective PPAR $\gamma$  modulator or “SPPARM,” with potentially less adipogenic side effects.

DePaoli *et al.* from the US presented results of a 4-week Phase 2 study in which 69 patients with Type 2 diabetes received either placebo or INT131 (abstract 117-OR). Change from baseline in fasting glucose, the primary efficacy parameter, was -53.8 mg/dl with a 10 mg dose, as compared to placebo. Mean change in body weight was +1.4 kg, and mean change in hematocrit (as a marker of fluid retention) was -1.7%, as compared to placebo, at 4 weeks. The authors suggested that these changes were smaller than would have been anticipated with conventional TZD therapy. We are not convinced, given the short duration of the study. Longer-term studies will be needed before the SPPARM concept is confirmed. Whether selective modulation of PPAR $\gamma$  can shift the balance towards greater benefit and less risk remains a theoretical construct.



## So Many Posters, So Little Time....



Segal *et al.* from Boston evaluated the impact of “polypharmacy” on glycemia, cognition, affect, and nutritional status in older diabetes patients over a 1-year period (abstract 562-P). In their study cohort of 139 patients, 54 (39%) were taking  $\geq$ 10 medications/day (“high treatment burden”, mean=12.2/day) and 35 (25%) were taking fewer than 6 medications/day (“low treatment burden”,

mean=3.8/day). The two groups were comparable based on age (77.7 vs. 78.6 years), gender (67% vs. 62% female), diabetes duration (19 vs. 17 years), HbA1c (7.5 vs. 7.6%), and number of oral hypoglycemic agents (1.1 vs. 0.8). The group with high treatment burden was administering more insulin injections/day (1.5 vs. 0.6, p=0.008). Hypoglycemia (69% vs. 44%, p=0.02), cognitive

dysfunction (53% vs. 25%, p=0.02), depression (53% vs. 31%, p<0.05), and under nutrition (63% vs. 7% p=0.026)—factors known to impede self-care in older patients—were significantly more common among those with high treatment burden. One might speculate about the directionality of this association.

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