

Diabetes 2006

From the 66th Annual Scientific Sessions of the
American Diabetes Association ■ Washington, DC

2002 2003 2004 2005 2006 2007 2008

Sponsored by Yale University School of Medicine,
Department of Internal Medicine, Section of Endocrinology

Volume 13 ■ June 13, 2006 ■ Issue 5



The Rational Use of Insulin



Important data on diabetes presented at the 66th Annual Scientific Sessions of the American Diabetes Association come 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 (ACC and ADA 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. Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Supported through an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc.

Despite strong evidence for earlier and better glycemic control in diabetes, there is "clinical inertia" on the part of physicians as well as patients to begin insulin at the appropriate juncture in the disease process. Rubino (324-OR) from the UK performed a retrospective analysis of the electronic records of 31,289 Type 2 diabetes patients to measure the time to insulin initiation in patients failing at least two oral agents. 2,501 patients (54% males) met the entry criteria of HbA1c >8.0%. After adjusting for patients lost-to-follow-up, only 25% and 50% had initiated insulin by 1.8 years and 4.9 years, respectively. The presence or absence of neuropathy or retinopathy did not have any effect on the time to insulin initiation. Most patients began insulin with a mixed basal/prandial regimen. Using HbA1c thresholds of 7.0% or 9.0%, time to insulin initiation for 50% of patients was estimated to be 6.3 and 4.2 years, respectively. So, it appears that about half of patients delay insulin initiation for at least four to six years despite inadequate glycemic control, irrespective of the presence of microvascular complications.

Another related problem is inadequate dosing once insulin is actually started to optimize control. Gough *et al.* from the UK and Germany, showed that the institution of insulin monotherapy failed to maintain HbA1c <7.0% in more than 75% of 3,658 patients with Type 2 diabetes prescribed insulin and not on any oral agents (OAs) in the previous three months (477-P). Overall mean and median HbA1c was 8.4% and 8.1%, respectively. About a third of patients had a HbA1c >9.0%, with one in five having a HbA1c >10%. Starting insulin is not good enough—the regimen must be advanced, as tolerated, to get patients to their glucose and HbA1c targets.

Clearly, insulin treatment is not a simple undertaking. One major question that comes up at the time of therapy initiation, is whether a basal insulin vs. a pre-mix insulin is best. Sun *et al.* conducted a retrospective analysis of electronic medical records of 2.4 million US patients (427-P). Of these, 8,166 patients with Type 2 diabetes were sorted into three groups based on

which insulin regimen they received: once daily basal insulin (n=3,624), twice daily pre-mix human insulin (n=3,647), or twice daily pre-mix analog insulin (n=895). In each of four post-baseline analytical time intervals, patients using a pre-mix analogue (lispro 75/25) had 0.48-0.65% greater drop in HbA1c as compared to those on basal-only (glargine) (all p<0.005). Change in HbA1c in patients using twice daily pre-mix human insulin was not distinguishable from those on basal only. We would caution that such analyses, based predominately on administrative data, may yield misleading results, since the nuances of clinical care are not able to be captured. We'd also point out that there was no mention of hypoglycemia rates during the observation period—a feature of pre-mix that has been shown to be more of a problem than with basal only.

Indeed, several studies this week showed superiority of basal insulin over pre-mix (455-P, 481-P). Hammer from Germany, presented results of an observational study of 5,045 patients with Type 2 diabetes (HbA1c 8.3 ± 1.2%), who were switched from pre-mix insulin (1, 2, or 3 times daily) ± OAs (42%, 16%, 11%, and 3% of patients taking metformin, glimepiride, glibenclamide, or other OAs, respectively) to once daily insulin glargine therapy plus OAs (481-P). Mean pre-mix insulin dose was 35 ± 15 units. After three months of treatment, with a mean glargine dose of 27 ± 12 units, significant reductions in HbA1c (-1.1 ± 1.0%), fasting blood glucose (-55 ± 45 mg/dl), and body weight (-1.6 ± 3.2 kg, p ≤ 0.001) were observed.

Recently the FDA approved a lispro 50/50 mix. Robbins *et al.* presented a study comparing thrice daily Lispro 50/50 before meals + metformin (n = 157) vs. basal glargine insulin at bedtime + metformin (n = 158) in a 24-week open-label trial (554-P). Insulins were titrated to achieve a fasting glucose of <120 mg/dl; 50/50 was also adjusted to target a 2-h post-prandial glucose of <144 mg/dl. The 50/50 + metformin group had a lower HbA1c, and greater reduction in HbA1c both at 12 weeks and at the study's conclusion than the glargine + metformin group (-0.7 ± 0.9% vs. -0.4 ± 0.9%; p < 0.0001), but at the expense of more

Continued on page 2

The Rational Use of Insulin

Continued from page 1

hypoglycemia (0.7 ± 1.7 vs. 0.3 ± 0.8 events/patient/month; $p=0.02$), the majority being mild in nature.

Bretzel (326-OR) from Germany presented the results of a 44-week parallel, open, randomized study comparing OAs + glargine ($n=174$) vs. meal-time lispro ($n=174$) in Type 2 diabetes patients failing OAs. As shown in Table 1, HbA1c dropped significantly in both the groups, with glargine providing better control of fasting glucose ($p<0.0001$) and nocturnal glucose ($p=0.0017$), with no difference in total insulin dose between groups. The numbers of hypoglycemic events were significantly lower with glargine vs. lispro (5.4 vs. 24.4 events/patient-year).

Carbohydrate counting may be the best way to adjust pre-meal insulin doses, but it is somewhat complex to implement in many patients. Bergenstal and US investigators showed that using a simple algorithm to adjust mealtime glulisine (a newer rapid-acting insulin analogue) in Type 2 diabetic patients ($n=136$) based on the pre-prandial glucose value was as effective as using carbohydrate counting ($n=137$) in a 24-week study (baseline HbA1c 8.2%) (441-P). Glargine was used as the basal insulin. There was no difference in HbA1c change (-1.46% vs. -1.59%), proportion of patients achieving HbA1c $<7.0\%$ (73% vs. 69%), or weight gain (3.7 vs. 2.4 kg) between the two groups. Algorithm patients received higher doses of glulisine (110.2 vs. 94.3 units, $p=0.04$) and glargine (103.4 vs. 87 units, $p<0.0001$) and had less symptomatic hypoglycemia <50 mg/dl (4.9 vs. 8.0 events/patient-year, $p=0.02$). Thus using a mealtime rapid acting analogue adjusted by a simple algorithm may be as safe as using carbohydrate counting—and certainly easier to implement in most patients.

Table 1. Comparison (Mean \pm SD) of Once Daily Glargine to Lispro Insulin Three Times Daily

Endpoint	Glargine ($n = 174$)		Lispro ($n = 174$)	
	Baseline	Endpoint	Baseline	Endpoint
HbA1c (%)	8.71 ± 0.95	6.96 ± 0.67	8.64 ± 0.95	6.77 ± 0.83
Fasting blood glucose (mg/dl)	186 ± 36	$111 \pm 27^\dagger$	179 ± 41	145 ± 34
Nocturnal blood glucose (mg/dl)	177 ± 44	$118 \pm 39^\dagger$	177 ± 53	129 ± 33

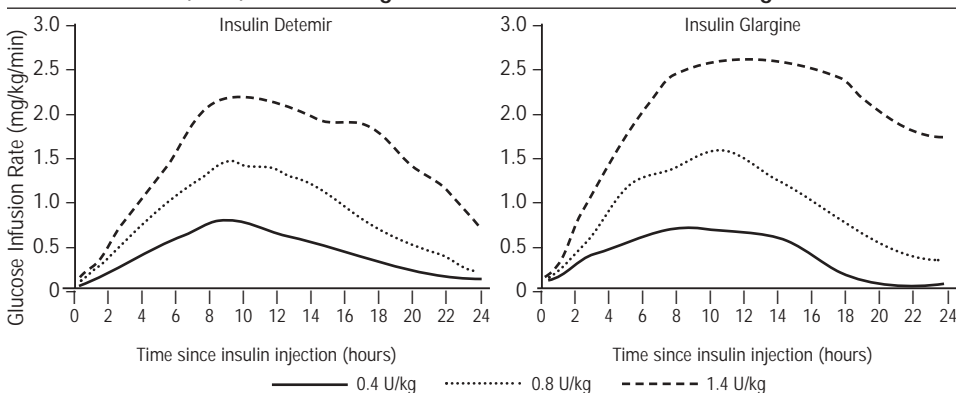
$^\dagger p < 0.0001$ $^\ddagger p = 0.0017$.

Detemir insulin is another long acting basal insulin more recently available in the US. Klein *et al.* from Germany and Denmark compared the pharmacodynamic and pharmacokinetic properties of detemir and glargine in 27 patients with Type 2 diabetes (HbA1c $7.6 \pm 1.1\%$), in a randomized, double-blind, parallel trial (325-OR). Insulin was given at doses of 0.4, 0.8, and 1.4 units/kg under 24-hour glucose clamp conditions (target blood glucose = 90 mg/dl). As shown in Figure 1, mean glucose infusion rates and the dose response relationship were similar with both insulins. Within patient variability, however, was lower for detemir than glargine ($p < 0.0001$). The insulin effect lasted for >24 hrs with the highest dose for both types of insulin. Jungmann from Germany, however, presented data that suggested a superiority of glargine over detemir as a once daily basal insulin in 70 patients (age 61 ± 2 yrs, BMI 32.6 ± 1.1 kg/m²) (496-P). Appropriate basal insulin dose was assessed by basal supplement test with patients fasting from 10 pm to 4 pm the next afternoon. Patients injected their basal insulin either once (glargine, $n=31$; detemir, $n=25$) or twice daily (detemir, $n=14$.) The mean blood glucose was 127 ± 5 mg/dl with glargine vs. 143 ± 4 mg with once daily detemir ($p < 0.05$). In patients requiring more than 16 units of detemir, the mean blood glucose was 154 ± 6 mg/dl in comparison to

134 ± 4 mg/dl in those using less than 16 units/day ($p < 0.05$). The daily dose of glargine was 22 ± 2 U vs. 19 ± 2 U with insulin detemir. The investigators concluded that detemir should be injected twice daily in patients requiring more than 16 units of basal insulin per day, while glargine only required once daily administration.

Dornhorst reported the safety and efficacy of initiating detemir insulin in 1,321 OA-treated, insulin-naive Type 2 diabetic patients (mean age 62 years; diabetes duration 7 years; HbA1c 8.5%; BMI 29.5 kg/m²) (462-P). After three months of detemir therapy (mean dose, 0.23 units/kg), HbA1c was reduced by 1.3% and fasting glucose by 58 mg/dl. This was achieved in conjunction with a weight loss of 0.9 kg and reduction in hypoglycemic episodes. These findings were confirmed in another study in which Type 2 patients were switched to detemir from NPH ($n=251$, BMI 31 kg/m², HbA1c 7.8%) or from glargine insulin ($n=260$, BMI 30 kg/m², HbA1c 7.8%) (614-P). After three months of detemir therapy, there were reductions in hypoglycemic events, HbA1c by 0.6%, and fasting blood glucose by 26 mg/dl, and weight loss of 0.85 kg in both groups. The explanation for the lack of weight gain with detemir is not fully understood. Some have proposed differential effects from detemir on insulin signaling in the hypothalamus, whereas others feel that there may be a greater degree of hepatic vs. peripheral insulin "exposure" with this basal insulin analogue.

Figure 1. Mean GIR-Profiles (Smoothed with a Local Regression Technique) for 0.4, 0.8, and 1.4 U/kg Insulin Detemir and Insulin Glargine



Alternatives to Injection

Inhaled insulin (Exubera[®]) was recently approved by the FDA and its commercial availability should be imminent. There was a noteworthy paucity of abstracts at this year's meeting, in contrast to prior years.

Leung *et al.* compared the effects of an oral, long-acting regular insulin known as "Intesulin-1" given at a dose of 0.33 mg/kg in gel capsule to four fasted Type 2 diabetic patients vs. aspart insulin (0.1 U/kg dose) administered by injection (418-P). Insulin levels peak by 30 minutes with the oral formulation vs. 60 minutes

Continued on page 3

The Rational Use of Insulin

Continued from page 2

with aspart. The biopotency of intesulin was 65% that of aspart and had no adverse effects (hypoglycemia, gastrointestinal complaints).

Insulin remains underutilized in patients with Type 2 diabetes. Admittedly, there are many

obstacles to properly implementing and then optimizing insulin therapy in clinical practice. While there appear to be benefits to both the basal and prandial approaches, which patients do best on which regimen is a complex issue – perhaps not easily addressed by standard clinical trials. Ideally, most patients do best with both basal and prandial components to their therapy,

but adherence and compliance issues are significant. An individualized approach is always best, balancing the convenience of basal-only or premix regimens with the control achievable by more complex regimens. The insulin abstracts presented this week give us further insights into the most effective strategies for our patients.



PPAR Agonists, Diabetes, and CVD



Available for almost 10 years, the thiazolidinediones (TZDs) have become a standard member of the Type 2 diabetes pharmacopeia in the US. The first foray of this drug class into the world of cardiovascular event trials proved a challenge, with mixed results from the PROactive trial (see Volume 12). Interest in these insulin sensitizers continues to be strong, however, as we learn more about their mechanism of action, metabolic effects, safety profiles, and precise role in clinical practice.

Focus on the β -Cell

Failure over time with oral agent monotherapy is a significant concern in the outpatient management of Type 2 diabetes. Riedel *et al.* used claims data from a large geographically diverse US health plan to compare the failure rates with metformin vs. a sulfonylurea vs. a TZD (P-553). New users of the identified drug who filled at least one prescription and who also had at least one baseline HbA1c before and after the index prescription were included and followed for a maximum of 48 months. Drug “failure” was defined as a Hb1c >7% after initial achievement of \leq 7%. Multivariate regression analysis was used to compare drugs. Of the 9,416 patients identified, 38.8% initially achieved target HbA1c values and then subsequently failed at an average of 1.5 years. When compared with a sulfonylurea, metformin had a significantly lower rate of failure (OR [for no failure] 1.23, 95% CI 1.03-1.46). Metformin failure rates were comparable to that seen with thiazolidinediones (OR 0.82, 95% CI 0.65-1.03).

The frequency with which Type 2 diabetes patients fail monotherapy leads to the need for combination therapy. Loebner and German associates reported on a study they conducted of the fixed-dose combination of rosiglitazone and metformin, which was given to 784 Type 2 diabetes patients poorly controlled on metformin alone (518-P). Patients who had taken metformin 1000 mg/day were switched to 4 mg/1000 mg and up-titrated as necessary based on HbA1c >7% at

eight weeks to 8 mg/1000 mg; those on metformin 2,000 mg/day were switched to 4 mg/2000 mg and up-titrated as necessary to 8 mg/2000 mg. Up-titration was required in ~60% of patients. At study endpoint, HbA1c decreased by -0.9%, and fasting plasma glucose, by 40 mg/dl.

Spanheimer *et al.* from the US conducted a three-year, multicenter, double-blind study into which 2,120 diabetes patients were randomized to pioglitazone or glyburide (320-OR). Those previously treated with metformin were allowed to continue taking it during the study, with the dose maximized (up to 850 mg bid), or the agent could be added in metformin-naive subjects, at the investigator's discretion. The addition of insulin was also permitted after three months in patients with poor glycemic control (HbA1c >7.5%). Mean HbA1c level at baseline was -9.5% in both groups. A continuous decrease in HbA1c was observed in the pioglitazone group over the three-year study, significantly greater than that with sulfonylurea at week 72 and thereafter, suggesting more durable effects on glucose control, presumably due to better effects on β -cell function and peripheral insulin sensitivity.

Lashing Out at NASH

Ivanazib *et al.* randomized 51 Type 2 diabetes patients (mean age 48 years, BMI 33.2 kg/m², HbA1c 10.7%) to six months of insulin, with or without pioglitazone (75-OR). In contrast to insulin alone, therapy with the TZD plus insulin significantly reduced (-55%, $p = 0.01$) hepatic triglyceride content and increased plasma leptin levels (from 16.6 μ g/ml to 18.5 mg/ml, $p = 0.01$). These results suggest a favorable effect of TZDs on hepatic steatosis, a common complication of Type 2 diabetes and obesity, which is associated with insulin resistance. The benefits of rosiglitazone in nonalcoholic steatohepatitis (NASH) were described by Ratziu and French coworkers in a “late-breaker” abstract (8-LB). A total of 63 patients (20 with diabetes) with biopsy-proven NASH were randomized to rosigli-

tazone 8 mg/day or placebo for one year. At study end, there was a statistically significant treatment effect based on histological response, defined as >30% improvement in steatosis, (47% and 16% for TZD and placebo, respectively; $p < 0.004$) and biochemical response, defined as normalization of ALT (38% vs. 7%, respectively; $p = 0.005$). Notably, in the TZD group, histological, but not biochemical, response was greater in patients *without* diabetes (61% vs. 11% in diabetics, $p < 0.01$). No hepatotoxicity (as assessed by ALT levels) was observed. A large, NIH-sponsored study of TZDs in NASH is currently underway. It will be important to look at long-term outcomes in these patients who are at risk for developing cirrhosis.

Flack about Plaque

The effects of TZDs on atherosclerosis were assessed in the Pioglitazone in Prevention of Diabetes (PIPOD) study, an open-label, observational study into which Hispanic women with prior gestational diabetes who had completed the Troglitazone in Prevention of Diabetes (TRIPOD) study were enrolled (172-OR). A total of 61 women from the TRIPOD study who did not develop diabetes over a mean 3.8-year period had carotid intimal media thickness (CIMT) measured over a median three-year period. The CIMT progression rate was significantly lower during pioglitazone treatment in PIPOD than it had been during placebo treatment in TRIPOD (0.0031 vs. 0.0100 mm/year; $p = 0.007$), and was slightly, but not statistically significantly, lower in those formerly treated with troglitazone (0.0038 vs. 0.0060 mm/year; $p = 0.32$). The changes were unaffected after adjustment for differences in baseline characteristics and potential during-study mediators of CIMT progression. The implication is that TZD therapy may slow the progression of preclinical atherosclerosis in persons at increased risk for Type 2 diabetes. The reproducibility of this finding, and its implication on actual clinical events is not known. We'd also

Continued on page 4

PPAR Agonists, Diabetes...

Continued from page 3

point out that the PIPOD cohort was pre-selected as "TZD responders", since these women had already proven themselves as diabetes non-progressors with treatment.

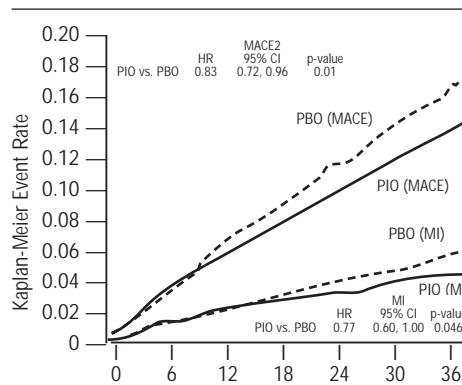
PPARs + CVD

Along the same lines, an entire symposium this week was devoted to cardiovascular disease and the peroxisome proliferators-activated receptor (PPAR) agonists, of which the TZDs are member. Charles Burant, MD, PhD of the University of Michigan began the session with the presentation, "PROactive Study: Why So Controversial?" He proceeded to dissect the PROactive (PROspective pioglitAZone Clinical Trial In macroVascular Events) trial (*Lancet* 2005; 366:1279) and the controversy relating to its less than robust results. The primary endpoint, a broad composite of cardiovascular outcomes (all-cause mortality, non-fatal MI, acute coronary syndrome, major amputation, coronary or leg revascularization) was not significantly different between the study drug, pioglitazone, a PPAR-γ agonist, and placebo. However, the principal secondary endpoint (death, MI or stroke) was reduced in the pioglitazone group (relative risk reduction 16%; absolute risk reduction, 2.1%) compared to placebo (p=0.027).

Other related findings from the PROactive study were presented this week during an oral presentation by Wilcox and Kupfer from the UK (317-OR). Over a mean follow-up period of 35 months, there was a 23% reduction in fatal/non-fatal MI, excluding silent MI (HR 0.77, 95% CI 0.60-1.00; p=0.046), an 18% reduction in the composite of major adverse cardiovascular events (MACE-1) of CV death, nonfatal MI excluding silent MI, or nonfatal stroke (HR=0.82, 95% CI 0.70-0.97; p=0.02), and a 17% reduction in the composite MACE-2 endpoint of all-cause mortality, nonfatal MI excluding silent MI, nonfatal stroke, or acute coronary syndrome (HR = 0.83, 95% CI 0.72-0.96; p=0.01) (Figure 2). When non-CV deaths were excluded from the MACE-2 endpoint, a 20% reduction was observed (p=0.005). We remind the reader that secondary endpoints from large clinical trials are interesting but should be interpreted cautiously. Strict clinical trialists generally frown upon any conclusive statements concerning anything but the primary endpoint.

Dr. Burant concluded his comments by identifying several aspects of the study that, with slight modification, might have provided more promising results, such as elimination of leg

Figure 2. Time to MI and Major Adverse Cardiovascular Events*



* All-cause mortality, nonfatal MI (excluding silent MI), nonfatal stroke, or acute coronary syndrome.

revascularization from the composite primary endpoint (as done by Wilcox [317-OR]) and longer treatment exposure (the "event curves" were beginning to diverge further by study close). He also suggested that PROactive indirectly demonstrated several important points: TZDs are relatively safe at high doses, despite an increase in heart failure diagnosis in the trial (see below); TZDs do appear to slow β-cell failure and decrease the need for insulin therapy; and TZDs are effective in combination therapy at getting patients to target (patients in the pioglitazone group had a 0.5% decrease in HbA1c versus placebo, p<0.001) even in the face of decreased insulin use. He pointed out that presently metformin and, possibly acarbose, are the only diabetes medications that decrease the risk of cardiovascular events. Burant then summarized "what we don't know": do TZDs decrease cardiovascular events beyond glucose and lipid changes?; would the results of PROactive have been different if all patients were on statin therapy?; and are the results applicable to PPAR-γ agonists as a class? Currently, four studies (DREAM,

RECORD, IRIS, and BARI 2D) are under way to clarify some of these issues.

The next speaker, Dr. Fred Masoudi, a cardiologist from the University of Colorado entitled his presentation, "Edema and Heart Failure with TZDs: Is This for Real?" Masoudi began by reviewing the epidemiology of heart failure in patients with diabetes. Greater than 25% of patients in heart failure trials have diabetes and, in the community setting, the prevalence of diabetes in heart failure series is as high as 40%. Heart failure correlates with glycemic control and the risk increases incrementally with increasing HbA1c. The proposed mechanisms linking diabetes to both systolic and diastolic ventricular dysfunction were reviewed. He then listed several ways by which TZDs might lead to fluid accumulation, including altered distal nephron sodium handling. Observational studies suggest that while the diagnosis of heart failure appears to be increased in diabetic patients treated with TZDs, not all fluid overload in these patients is true heart failure. Instead, dependent edema may simply be a sign of excess extracellular fluid. In fact, longitudinal studies show no detrimental effect of the TZDs on ventricular function itself. Clearly, however, in a patient with borderline compensated subclinical ventricular dysfunction, even the small accumulation of fluid can precipitate clinical heart failure.

Masoudi next reviewed the PROactive data, revealing that the pioglitazone group had increased edema and more hospitalizations for heart failure, yet, notably, there was not a higher risk of heart failure death. Finally, he shared data from a retrospective study of Medicare patients with diabetes and principal discharge diagnosis of heart failure. This study identified a borderline higher incidence of hospital admissions due to heart failure in patients receiving TZDs, however, patients in this group actually had a 13% lower risk of death over one year (*Circ* 2005; 111:583).

Table 2. Dual PPAR-Agonists Under Investigation

Drug	Study Phase	Clinical Issues	Pre-Clinical Issues	Status
Ragaglitazar	II	Weight gain, edema, anemia, ↓ hemoglobin	Urothelial cancer*	Stopped
MK-0767	II	?	Hemangiosarcoma in rodents*	
Muraglitazar	III	Edema, weight gain, heart failure, ↑ risk of CVD*	No	Stopped
Tesaglitazar	III	↑ creatinine, ↓ GFR*	No	stopped

*impetus to stop/hold further research and investigation

PPAR Agonists, Diabetes...

Continued from page 4

Randomized clinical trials in this high-risk group of patients to further assess these observations would appear indicated.

The last lecture of the afternoon was presented by Bart Staels, PhD, of the Pasteur Institute in Lille, France, "Dual PPAR Agonists: Dead or Alive?" He reviewed the pharmacology of the PPAR- α , - δ , and - γ agonists providing rationale for combining their properties. Each mediates the inflammatory process with receptors predominately in different target organs: PPAR- α in the liver, - δ in muscle, and γ in the

adipocyte. All three work by modulating gene transcription activity and influencing the inflammatory response. The so-called dual agonists (α/γ), should be complementary in activity, with the α -component targeting hepatic fatty acid oxidation to reduce triglycerides and increase HDL, while the γ component modulates adipocyte biology, improving insulin resistance in peripheral tissues, thereby lowering glucose concentrations. Staels then focused on safety issues associated with the dual agonists. In preclinical trials, carcinogenicity and cardiac effects have been of concern. In clinical studies, safety concerns have focused on edema, weight gain, myopathy, and hepatic and renal dysfunction. He then provided

information on the dual agonists also known as the glitazars: muraglitazar, ragaglitazar, tesaglitazar, and MK-0767 (Table 2). The proposed complementary pharmacologic actions of these agents has been confirmed, as they decrease HbA1c, fasting glucose, fasting insulin, free fatty acids, triglycerides and increase HDL. However, research on each has been stopped or is on hold. Each of these agents has undesirable properties, yet there is no "common denominator" relating the negative aspects associated with each drug. Thus, there may be off-target idiosyncratic effects associated with each dual agonist. Also, he suggested that each of these likely offer a unique α/γ balance that may influence their effects.



Late Breakers



During the final 24 hours of this week's ADA Scientific Sessions the following "hot-off-the-presses", late-breaking clinical studies were presented:

Falciglia *et al.* from the University of Cincinnati reported results from a massive retrospective analysis involving more than 200,000 critically ill veterans, their in-hospital glucose control, and clinical outcomes. Given the demonstrated benefit of intensive glucose control in certain groups of critically ill patients (post-AMI, post-cardiac surgery, surgical ICU), a question that frequently surfaces is "Are these findings generalizable across all patient types?" The collaborators analyzed 216,775 ICU admissions from 73 VA medical centers to determine whether hyperglycemia affects mortality risk in all disease groups. Using a previously validated severity of illness model (*Crit Care Med* 2003; 31:1638) and incremental glycemic quintiles, the researchers confirmed that, overall, hyperglycemia is independently associated with risk-adjusted mortality. Paradoxically, but also consistent with findings by other groups, mortality risk is greatest in patients *without* diabetes. Importantly, however, the magnitude of risk varies with disease. Conditions with a significant association between glucose and mortality included unstable angina, arrhythmias, heart failure, stroke, pneumonia, gastrointestinal hemorrhage, respiratory failure, and sepsis. In contrast, no significant association was determined between hyperglycemia and mortality in several

other conditions, including COPD and hepatic failure. These data suggest that not all medical conditions would necessarily respond equally to tight in-hospital glucose control, a theme that resonates since the recent report of mixed results from intensive insulin therapy in the medical ICU by van den Berghe *et al.* (*N Engl J Med* 2006;354:449).

Jacobson and the DCCT investigators reported the effects of intensive vs. conventional treatment on cognitive function 12 years after completion of that landmark study. Jacobson shared the concern that intensive insulin therapy with its potential for severe hypoglycemia may result in cortical brain injury and cognitive dysfunction. For this reason, periodic cognitive assessments were incorporated into the DCCT and its follow-up study, known as EDIC. Eight cognitive domains were tested allowing for a true longitudinal comparison between the original intensive and conventional groups. The domains included: problem solving, learning, immediate memory, delayed recall, spatial inferences, attention, psychomotor efficiency, and motor speed. Of the 1,136 patients evaluated in the 12-year follow-up, there was no effect of treatment group assignment on any eight of the domains. Even in the known cases of severe hypoglycemia, there were no effects on any of the domains. Instead, there were modest effects of HbA1c values on psychomotor efficiency and motor speed; patients with higher HbA1c values experienced deterioration in these domains. The overall

conclusion is that intensive insulin therapy does not impair cognitive function in Type 1 diabetes.

Stein *et al.* from the US presented head-to-head data from a clinical trial involving a DPP-4 inhibitor (see Issue 2) and a sulfonylurea. The study was comprised of 1,172 patients with HbA1c between 6.5% and 10% after a metformin monotherapy run-in period. Patients were randomized to sitagliptin 100 mg qd vs. glipizide (5 mg qd and increased to 10 mg bid, with titration held if glucose <110 mg/dl or if hypoglycemia occurred) for 52 weeks. The mean HbA1c was 7.5% at baseline. At 52 weeks, a HbA1c reduction of -0.67% was seen in both groups. Not unexpectedly, much larger reductions occurred in more severely hyperglycemic patients (e.g., HbA1c reductions of ~1.7% in patients with HbA1c >9%). The incidence of hypoglycemia was 32% in the glipizide group, and 5% in the sitagliptin group (657 events vs. 50 events). A 2.5 kg weight difference between groups was also measured (1.3 kg weight loss with sitagliptin and 1.2 kg weight gain with glipizide). Summary measures of other adverse events were similar between groups. As discussed in Issue 2, in light of this abstract and the comparison involving vildagliptin and rosiglitazone, the DPP-4 inhibitors may be considered as potent as most conventional anti-hyperglycemic agents, with perhaps an extra margin of safety—at least as compared to the sulfonylureas.

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University,
New Haven, Connecticut