

Diabetes 2005

From the 41st Annual Meeting of the European Association
for the Study of Diabetes ■ Athens, Greece

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Statins for All?



Important data on diabetes presented at the 41st Annual Meeting of the European Association for the Study of Diabetes comes 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 (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing fee to the Yale Office of Continuing Education, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

Diabetes 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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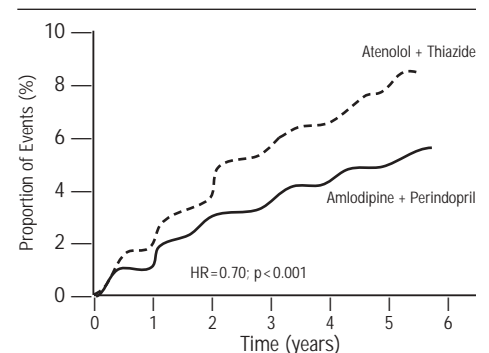
This week's lipid symposium began with a presentation by Dr. Sever from the UK on the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) diabetes subgroup analysis. ASCOT was a primary prevention trial of over 19,000 high-risk individuals (no previous MI, but three or more risk factors and hypertension) begun in 1995. This trial has yielded some interesting information, especially with regard to the effects of anti-hypertensive therapies in Type 2 diabetes.

Patients in this large multi-center trial were first randomized into two blood pressure intervention groups (amlodipine + perindopril vs. atenolol + thiazide) and then patients with a total cholesterol >250 mg/dl were further randomized to receive either atorvastatin or placebo. About one-quarter of the patients recruited had diabetes. ASCOT had previously shown a 36% reduction in fatal and non-fatal MI with lipid-lowering in all subgroups including those with diabetes (*Lancet* 2003). This benefit was seen as early as 90 days after initiation of therapy, and persisted throughout the trial. There was no apparent threshold for the effect as patients benefited from therapy regardless of their baseline LDL-cholesterol (LDL-C) value, a finding consistent with almost all previous lipid-lowering trials.

The blood pressure intervention portion of the trial was stopped prematurely by the data monitoring board. Dr. Sever discussed the results indicating that, for almost all outcome measures, the amlodipine + perindopril combination was better than the atenolol + thiazide combination despite near-identical effects on blood pressure (*Lancet* 2005). ASCOT reported a 11% reduction in all-cause mortality, a 10% reduction in non-fatal and fatal MI, a 23% decrease in stroke (HR 0.84, 95% CI 0.74-0.90), and, most intriguingly, a 30% reduction (HR 0.70, 95% CI 0.63-0.78; $p < 0.001$) in the development of new-onset diabetes over the 5.5 years of the trial with the amlodipine + perindopril combination (Figure 1). The diabetes subgroup enjoyed the same benefits as the non-diabetic patients with regard to all outcome measures.

Dr. Sever summarized by saying that the combination of a statin, amlodipine, and perindopril

Figure 1. Kaplan-Meier Curves of Cumulative Incidence of New-Onset Diabetes



pril reduced the risk of fatal or non-fatal MI by 40%, and of stroke by 44% during the course of the trial. Whether the reduction in new-onset diabetes was due to a positive effect of the amlodipine + perindopril combination or a negative effect of the thiazide + atenolol combination (or both) cannot be known, but the outcomes provide a rationale for changing current hypertension therapy guidelines.

In the second session Dr. La Rosa reminded the audience of the benefits of aggressive lipid-lowering by reviewing the results of the Treatment to New Targets (TNT) Trial, presented in a previous issue of *Diabetes 2005* (Volume 11, Issue 1). This multi-center, randomized trial compared atorvastatin 10 mg with 80 mg once daily in the treatment of non-diabetic and diabetic individuals with stable coronary disease and an LDL-C <130 mg/dl at entry. Higher-dose atorvastatin, which was generally well tolerated, had shown a relative risk reduction of 22% in the primary end-point (HR 0.78, 95% CI 0.69-0.89) in comparison to low-dose atorvastatin, an effect that was also seen in the diabetic subgroup (HR 0.75, 95% CI 0.58-0.97). Interestingly, atorvastatin had a negligible effect on HDL-cholesterol (HDL-C), with no change from baseline seen for either dose.

This set the stage for a discussion by Dr. Barter of Australia on alternative lipid lowering therapy. Dr. Barter first reviewed the fibrate literature. The fibrates are PPAR- α agonists that reduce

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plasma triglycerides (TG), increase HDL-C levels, and, as a result, reverse cholesterol transport. They may also have anti-inflammatory actions. The major intervention trials for fibrates include the Helsinki Heart Study, VA-HIT, BIP, and FIELD. The first three showed benefit on their primary cardiovascular endpoints from fibrates; the latter will be reported later this year at the annual Scientific Sessions of the American Heart Association.

Dr. Barter then presented recent subgroup analyses showing that fibrates may be of particular benefit to individuals with evidence of insulin resistance. For instance, in the Helsinki Heart Study with gemfibrozil, there was a 34% reduction in coronary heart disease (CHD) events in all subjects, but a 48% reduction in those with a BMI >26 kg/m² (vs. 23% reduction in those with a BMI <26 kg/m²). Similarly, dichotomizing the study subjects by HDL-C (<40 vs. >40 mg/dl) showed 44% and 23% respective reductions in CHD risk. Segmenting them by triglycerides (<200 vs. >200 mg/dl) revealed 20% vs. 56% endpoint reductions in CHD risk. Moreover, the subgroup with BMI >26 kg/m², TG >200 mg/dl, and HDL-C <40 mg/dl showed an impressive 78% decrease in CHD risk with gemfibrozil. Similarly, a subgroup analysis from the BIP trial demonstrated greater benefit for those patients meeting criteria for the metabolic syndrome. In the VA-HIT, there was increasing benefit from fibrates with increasing

fasting insulin levels.

Taken together, these findings suggest that fibrates may be of particular value in insulin-resistant subjects, although it is important to remember that these are all post-hoc subgroup analyses. As a result, they should be interpreted with caution. We await with interest the results of the FIELD study (fenofibrate), to be presented in November (and covered by *Diabetes 2005*), which will address many of these issues.

Finally, in a much anticipated discussion, Dr. Haffner from the US, was posed the question: "Should all people with diabetes be on a statin?" Dr Haffner's cautious response was, "Of course not but *almost* all should." Dr. Haffner pointed out that there were obvious groups in whom one should never start a statin, such as pregnant or nursing women. He also thought that severe hypertriglyceridemia would be better treated with a fibrate and noted the recent 4D study showing no benefit of statins in patients on dialysis for end-stage kidney disease. However, Dr. Haffner reminded the audience that those with diabetes were at an equivalent CHD risk as non-diabetics who had already suffered an index myocardial infarction (East-West Study, *NEJM* 1998). He also noted that almost all trials have shown no lower threshold for lipid-lowering therapy benefit in either diabetic or non-diabetic patients. He pointed out, though, that while we have the means to estimate patients' short-term risk over 5-10 years, the same is not true for their long-term

risk, and risk engines such as the Framingham score do not offer confidence intervals for estimating such risk. He wondered whether it was appropriate to treat a younger individual with a 5% long-term CHD risk—there is currently no data available to address this specific question. When pressed at the end of the discussion, he proposed that one could delay statin therapy in a diabetic patient with no cardiovascular risk factors until the age of 40, especially for individuals with Type 1 diabetes. He qualified this by stating that all diabetic individuals who smoke should be on statin therapy, as perhaps should those with any other metabolic risk factor.

We agree that there is a paucity of good data on the benefits of statins or any lipid-lowering therapy in those under the age of 40. These trials are needed, particularly in view of the recent explosion of new cases of diabetes in younger adults, and even children. Indeed, before initiating any therapy that will be required for many years, we need to have good evidence of its efficacy, safety, and long-term benefit in any new group of patients.

Despite these concerns, instead of trying to determine who *should* get a statin, perhaps the simpler obligation of physicians caring for diabetic patients is to identify those who are at sufficiently *low* risk in whom these drugs are *not* necessary. Importantly, when statins are used, they should be prescribed at a dose to lower the LDL-C to <100 mg/dl or by at least 30% from baseline, whichever is lower.



What Does Lizard Spit Have to Do with Diabetes?



As part of the "enteroinsular axis," incretins are peptides of intestinal origin that modulate pancreatic islet secretion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two incretins known to affect glucose metabolism. Of these, GLP-1 is the best studied. For unclear reason, its secretion is impaired in patients with Type 2 diabetes, yet normal in Type 1. This is associated with blunted first phase insulin secretion, excess post-prandial glucagon production, and elevated post-prandial glucose concentrations. GLP-1 replacement therapy, in short-term studies, has been shown to enhance pancreatic β -cell insulin output (both first and second phases) and blunt glucagon secretion by the pancreatic alpha cells. This results in improved glucose levels in a glucose-dependent fashion, especially in the post-prandial state. That is, the glucose lowering effect of GLP-1 is abolished in the setting of normoglycemia—clearly an attractive

aspect of their effect. However, GLP-1 is rapidly cleared from the circulation through the action of the enzyme dipeptidyl peptidase IV (DPP IV). GLP-1 analogues which resist proteolytic degradation are under development.

A novel peptide, exendin-4, initially discovered in the saliva of the Gila Monster (*Heloderma suspectum*), was found to have potent GLP-1 receptor agonist activity. Its synthetic version, exenatide, shares all the effects of GLP-1. In addition, it has the advantage of requiring only twice daily subcutaneous injections, as its amino acid sequence resists DPP IV degradation. In addition to its effects on islet cell function, exenatide also delays gastric emptying, increases satiety, and is associated with weight loss, as opposed to weight gain seen with most other antihyperglycemic therapies. Animal and *in vitro* data additionally suggest that this agent may promote β -cell growth, which could conceivably delay or even prevent the need for

insulin as the disease state progresses. Human trials to date suggest effectiveness on HbA1c extending out to 82 weeks.

Exenatide was approved by the US FDA in April 2005 for use in combination therapy in Type 2 diabetes patients uncontrolled by sulfonylureas, metformin, or the combination thereof. The development of this drug has been closely tracked by us in previous editions of this newsletter. Several presentations at this year's ADA meeting were recently highlighted [see *Diabetes 2005*, Volume 11, Issue 4]. In general, exenatide reduces HbA1c by approximately 1%, and is associated with modest weight loss. Side effects include dose-related nausea, which typically abates with continued use. It can be associated with hypoglycemia when used with insulin secretagogues, in which case the dose of the latter should be reduced.

Continued interest in the incretins was obvious at this week's meeting in Athens. In a

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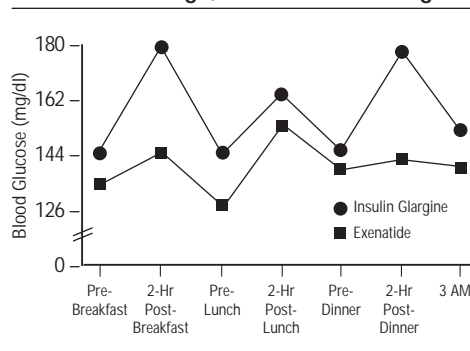
What Does Lizard Spit ...?

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multicenter (82 outpatient sites), international (13 countries), 26-week study of 549 patients with Type 2 diabetes not at glycemic targets on oral agents, Heine and colleagues found that the addition of fixed-dose exenatide reduced post-prandial glucose excursions while titrated insulin glargine did not (abstract 1). While both treatments caused reductions in fasting glucose, glargine did so to a significantly greater extent (exenatide: -22 ± 4 mg/dl; glargine: -52 ± 4 mg/dl, $p < 0.0001$). The rates of symptomatic hypoglycemia were similar between the treatments; however, nocturnal hypoglycemia was lower among those treated with exenatide (0.9 ± 0.4 vs. 2.4 ± 0.4 events per patient-year, $p < 0.0001$). Body weight changes were -2.3 ± 0.2 kg for exenatide vs. $+1.8 \pm 0.2$ kg for glargine ($p < 0.0001$).

Exenatide therapy is associated with a reduction in post-prandial glucose excursions, resulting in a smoother daily blood glucose profile. In a post-hoc analysis of a 30-week study, Trescoli-Serrano and Spanish associates (abstract 2) found that exenatide 10 μ g twice daily ($n = 29$), as compared to glargine ($n = 26$), produced a flatter seven-point blood glucose curve (Figure 2), greater weight reduction (-1.1 kg vs. $+1.0$ kg), and an increased percentage of patients with HbA1c $\leq 7\%$ (42% vs. 36%) and HbA1c $\leq 6.5\%$ (25% vs. 19%), in Type 2 diabetic patients uncontrolled on a sulfonylurea and metformin. Similar results were reported in a larger ($n = 549$) study by McCall and US colleagues (abstract 794) using exenatide (5 μ g twice daily for four weeks then 10 μ g twice daily for 22 weeks) as adjunctive therapy in patients receiving metformin plus a sulfonylurea. Exenatide produced significantly smaller changes in blood glucose from pre-meal to two hours post-meal compared to glargine at breakfast (17 ± 29 mg/dl vs. 45 ± 32 mg/dl, respectively; $p < 0.001$) and at dinnertime (2 ± 31 mg/dl vs. 36 ± 31 mg/dl, respectively; $p < 0.001$). Hypoglycemic risk was low in both treatment groups, but was approximately 50% lower in

Figure 2. Blood Glucose Seven-Point Findings, Exenatide vs. Glargine



those treated with exenatide. Taken together, these data suggest that exenatide may play a role in Type 2 diabetic patients after failure of oral agents and prior to the initiation of insulin.

The exenatide pivotal trials have already been published (DeFronzo *et al.*, Kendall *et al.*, Buse *et al.*, *Diabetes Care* 2005) demonstrating its effectiveness in patients treated with metformin, sulfonylureas, or both drugs. Long-term data from open-label extensions of these trials were presented this week. In an 82-week study (abstract 707), 393 patients with poorly controlled Type 2 diabetes using metformin and/or a sulfonylurea were randomized to one of three 30-week, double-blind treatment arms (placebo, exenatide 5 μ g, or exenatide 10 μ g) and then to 52 weeks of open-label exenatide 5 μ g twice daily for four weeks followed by 10 μ g twice daily. Patients continued their regimen of metformin, sulfonylurea, or both. At week 82, the effects of exenatide on mean HbA1c reduction appeared consistent and durable with an HbA1c reduction of 1.2% in those given placebo until week 30 and a sustained 1.1% reduction from baseline in those on 10 μ g twice daily during the first 30 weeks. In a shorter (34-week) study of 87 patients with Type 2 diabetes under reasonably good control (mean HbA1c $7.5 \pm 0.7\%$) using metformin ($n = 68$) or diet ($n = 19$), Wintle and US colleagues noted similar results (abstract 793). Patients were randomized to receive placebo or

exenatide 2.5, 5, 7.5, or 10 μ g twice daily for four weeks in the blinded phase of the study and then to open-label exenatide 5 μ g twice daily for four weeks followed by 10 μ g twice daily for the remaining 26 weeks. Overall, at week 34 the addition of exenatide to the regimen of metformin or diet reduced HbA1c by 0.9% and 1.0%, and body weight by 3.7 kg and 4.3 kg, respectively.

Another possible therapeutic avenue involving incretin physiology is to inhibit the DPP IV enzyme that inactivates endogenous GLP-1. MK-0431 is a selective DPP-IV inhibitor that offers an advantage to exenatide in that it is administered orally. Following an initial diet/exercise phase and a drug washout period (if needed), Hanefeld of Germany (abstract 791) randomized 552 patients with Type 2 diabetes to one of five treatments: placebo, MK-0431 25 mg, 50 mg, or 100 mg once daily, or MK-0431 50 mg twice daily, each for 12 weeks. At baseline, mean HbA1c levels ranged from 7.6% to 7.8% across the treatment groups. At the study conclusion, all doses of MK-0431 were associated with significant reductions in HbA1c compared to baseline, with the largest reductions observed in those treated with 100 mg once daily as well as in those with higher baseline HbA1c values. Across the MK-0431 groups, the differences in placebo-subtracted HbA1c ranged from -0.4% (25 mg) to -0.6% (100 mg) in the last observation carried forward analysis. No mean change in body weight was noted, however.

The incretin mimetics and related compounds will have a place in the management of patients with Type 2 diabetes. If beneficial effects on β -cell function are confirmed, a role for these drugs in pre-diabetic patients would also seem logical. The effects on satiety and body weight with exenatide are particularly encouraging, although the oral nature of the DPP-IV inhibitors is particularly attractive. The precise role of these agents will evolve with our increasing clinical experience, particularly with regard to efficacy and tolerability in patients outside of clinical trials.

ππαρ — (That's PPAR... But its all Greek to us!)

Numerous presentations were made this week at the EASD Scientific Sessions on the thiazolidinediones (TZDs) and other PPAR activators. While the most interesting new data came from the PROactive study group (reported in Issue 1), other investigators shared information that adds to our understanding of this class' effects in patients with Type 2 diabetes.

Type 2 Diabetes in Kids

The potential role for TZDs in the growing population of children with Type 2 diabetes is under investigation. The results of one such study were presented by Saenger *et al.* from the US (abstract 133). A total of 195 children with Type 2 diabetes (8-17 years, mean BMI 33.6

kg/m²) were randomized to rosiglitazone 2-4 mg twice daily or metformin 500-1,000 mg twice daily for 24 weeks. Statistically significant median reductions in HbA1c were observed in both treatment groups from screening to week 24 (-0.5% for each group). Mean weight gain over the treatment period was 3 kg with the TZD and none with metformin. Larger and longer-term studies are

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clearly needed before these agents are considered standard therapy in this group. At the present time, metformin remains the only antidiabetic oral agent approved for use in children.

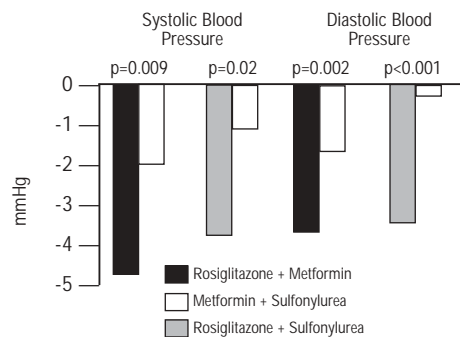
Vascular Effects

Elevations in various inflammatory markers associated with increased coronary artery disease risk have been observed in insulin-resistant subjects. One such marker is CRP, which was measured in several TZD studies presented this week. Also assessed by many investigators was the effect of TZDs on adiponectin, a plasma protein synthesized by fat that is suspected of having anti-inflammatory and anti-atherosclerotic properties. Adiponectin levels are notably decreased in obese persons and those with Type 2 diabetes. Kim *et al.* from Korea randomized 120 Type 2 diabetes patients to glimepiride and either rosiglitazone or metformin for 12 weeks (abstract 677). Patients in the rosiglitazone group, but not the metformin, group, experienced significant decreases in circulating concentrations of CRP (2.5 to 1.5 mg/ml), resistin (3.22 to 1.78 ng/ml), tumor necrosis factor- α (3.47 to 3.05 pg/ml), interleukin (IL)-6 (1.63 to 0.97 pg/ml), and IL-18 (230 to 194 pg/ml), and an increase in adiponectin (5.9 to 11.3 ng/ml), which was significantly correlated with change in a calculated estimation of insulin sensitivity, known as "QUICKI." Axmann and Lubben from Germany documented a 35% decrease in CRP ($p < 0.001$) after pioglitazone 30 mg daily add-on therapy for 24 ± 2 weeks in 552 patients with Type 2 diabetes, the anti-inflammatory effect being independent of glycemic response (abstract 767).

Blood Pressure

Control of blood pressure is as important as control of glycemia in reducing the risk of diabetic complications. TZDs modestly—but more so than other anti-hyperglycemic agents—reduce blood pressure. This effect was confirmed in a sub-study from the RECORD trial, as presented by Beck-Nielsen and international co-investigators (abstract 768). Type 2 diabetes patients inadequately controlled on metformin ($n = 379$) or a sulfonylurea ($n = 380$) were randomized to add-on rosiglitazone vs. a sulfonylurea, or rosiglitazone vs. metformin, respectively. Over 80% of participants were hypertensive at baseline. At 12 months, combination TZD therapy produced sustained reductions in blood pressure as compared to the combination of metformin and a sulfonylurea (Figure 3).

Figure 3. Blood Pressure Effects of Anti-Hyperglycemic Agents After One Year of Treatment



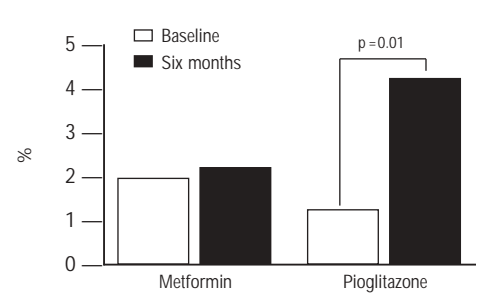
Carotid Intima Media Thickness

Increased carotid intima media thickness (CIMT) by ultrasound is a predictor of cardiovascular and cerebrovascular disease in patients with Type 2 diabetes. Forst *et al.* from Germany randomized 173 Type 2 diabetes patients to pioglitazone 45 mg daily or glimepiride 1 to 6 mg daily (abstract 119). Despite similar improvements in metabolic control at six months, there was a significant treatment group difference favoring the TZD, based on improvement in CIMT. This was related to improvement in HOMA-IR score, a calculated estimate of insulin sensitivity ($r = 0.29$, $p = 0.0003$), but, interestingly, not with HbA1c reduction ($r = 0.03$, $p = 0.68$).

Improvement in Endothelial Function

Insulin resistance has been associated with endothelial dysfunction in patients with Type 2 diabetes. Naka *et al.* from Greece evaluated the effects of adding an insulin sensitizer to established sulfonylurea therapy in 20 Type 2 diabetes patients, who they randomized to metformin 850 mg twice daily or pioglitazone 30 mg once daily (abstract 1168). After six months of study drug, endothelium-dependent flow-mediated dilation (FMD) in the brachial artery (assessed by ultrasound) was observed to increase by three-fold in the TZD-treated patients ($p < 0.01$ vs. baseline), but not in the metformin-treated patients (Figure 4). A change in endothelium-independent, nitroglycerin-mediated dilation was not observed in either treatment group. Investigators from the same university in Greece also evaluated the effect of the two insulin sensitizers on endothelial function in 37 women with polycystic ovary syndrome (PCOS) who were receiving no hormonal or cardiovascular drugs (abstract 1171). Risk factors for cardiovascular disease—insulin resistance,

Figure 3. Flow-Mediated Dilation in Type 2 Diabetes Patients: TZD vs. Metformin



dyslipidemia, obesity, endothelial dysfunction—are common in PCOS. In contrast to the results of their colleagues, Kravariti *et al.* measured a significant increase in FMD with both pioglitazone (5% to 9%) and metformin (4% to 9%) in young women with PCOS.

Adverse Effects

Use of the TZDs is limited by weight gain and edema, the two main side effects of this class. An asymptomatic, mild decrease in hemoglobin concentrations in TZD-treated diabetic patients has been attributed to fluid retention. To further examine the etiology of TZD-induced anemia, Berria and US coworkers randomized 62 Type 2 diabetes patients to 16 weeks of placebo, rosiglitazone (8 mg/day), or pioglitazone (45 mg/day) and an additional 23 Type 2 diabetes patients taking a stable dose of sulfonylurea to either placebo or pioglitazone 45 mg daily (abstract 40). As compared with baseline, hemoglobin and hematocrit both decreased after four months of TZD therapy (from 13.7 gm/dl to 12.8 gm/dl, $p = 0.0003$, and from 39.8% to 37.1%, $p = 0.0004$, respectively), which was *not* correlated with changes in total body water (measured by the $^3\text{H}_2\text{O}$ technique). Total body water remained relatively unchanged over the treatment period (40.7 to 40.9 liters, $p = \text{NS}$). The statistically significant increase in BMI (from 28.9 to 30.2 kg/m 2 , $p < 0.0001$) in TZD patients was therefore attributed solely to fat accretion. A concomitant decrease in WBC count (6.3 to 5.7 $\times 10^3/\text{mm}^3$, $p = 0.002$) and platelets (210 to 191 $\times 10^3/\text{mm}^3$, $p = 0.06$) suggested a mild marrow suppressive effect. The authors proposed that this effect may be mediated through decreases in the circulating concentrations of either testosterone or insulin, both of which have anabolic hematopoietic effects.

In contrast, Karalliedde *et al.* from the UK documented statistically significant increases in total body water and extracellular fluid (by

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bioimpedance) in 381 Type 2 diabetes patients treated with rosiglitazone 4 mg twice daily for 12 weeks (abstract 773). Female gender and baseline hematocrit (but not total body water or extracellular fluid) were the key predictors of TZD-induced hematocrit changes when hematocrit was treated as a binary (<0.5% change vs. ≥0.5% change) or continuous variable. In addition, age was strongly related to continuous hematocrit change; systolic blood pressure and baseline insulin were related to categorical hematocrit change. Further study is necessary before we fully understand the cause of TZD-induced reduction in blood counts.

Up & Coming PPAR-activators

The "glitazars" are a new class of antidiabetic medication that activate both PPAR- α (as do fibrates) and PPAR- γ (as do TZDs). They hold promise for their dual benefits on both glucose and lipid parameters. Muraglitazar was given approval last week by the FDA Advisory

Table 1. Glucose and Lipid Effects* of Tesaglitazar in Type 2 Diabetes

	Tesaglitazar Dose, in mg				
	0.1	0.5	1.0	2.0	3.0
FPG (mg/dl)	-8.9	-30.3	-41.1	-55.0	-60.9
TG (%)	-5.4	-17.2	-32.9	-41.0	-40.9
HDL-C (%)	+1.0	+4.6	+15.0	+13.0	+12.9
LDL-C (%)	-2.9	-4.5	-6.4	-11.1	-17.3

*Placebo-corrected.

Committee, although the approval was limited due to concerns of heart failure risk. Mohideen and international investigators (abstract 759) reported on the lipid effects of muraglitazar in Type 2 diabetes patients having inadequate glycemic control with metformin alone. This double-blind, placebo-controlled, multicenter study included 6,512 patients with baseline HbA1c of 7% to 10% while taking at least 1,500 mg of metformin. Patients were randomized to muraglitazar 2.5 mg or 5 mg or placebo in conjunction

with continued baseline metformin therapy. After 24 weeks, patients on the highest muraglitazar dose experienced a 28.1% reduction in triglycerides and a 14.8% increase in HDL-C, as compared to respective changes of -1.0% and +2.6% with placebo. Earlier in development is tesaglitazar. Goldstein and US collaborators presented results of the GLAD study (abstract 756), a randomized, double-blind, placebo-controlled trial involving this dual agonist in 485 patients with Type 2 diabetes. Doses of tesaglitazar used were 0.1, 0.5, 1.0, 2.0, and 3.0 mg. The mean baseline HbA1c was 7.1 ± 1.0% and BMI 30.7 ± 4.7 kg/m². Placebo-corrected effects on glucose and lipid parameters are seen in Table 1.

Tesaglitazar appears to have potent glucose- and lipid-lowering effects. It is interesting that the glucose-lowering effects are dose related, whereas the TG and HDL effects seem to plateau at lower doses. The LDL-lowering effect, although modest, appears unique among PPAR activators. The precise role of these new compounds, especially in light of safety concerns (e.g., weight gain, edema) that have been raised in clinical trials, remains unclear.



So Many Posters, So Little Time...



Is Diabetes Truly A CVD Risk Equivalent?

It has been widely stated that the risk of cardiovascular events and mortality in primary-prevention patients with diabetes mellitus (DM) is comparable to that of non-diabetic patients with known heart disease. The risk for cardiovascular events is markedly heightened in those with diabetes and coronary artery disease (CAD). Saely and Austrian colleagues (abstract 1124) compared cardiovascular risk between patients with and without Type 2 diabetes, with and without CAD by angiography. After stratification into one of four groups (DM - / CAD -, DM + / CAD -, DM - / CAD +, and DM + / CAD +), the incidence of fatal and non-fatal vascular events was recorded over four years. The incidence of vascular events averaged 20.1% in the 750 patients and was strongly affected by patients' angiographic state, but, interestingly, not their diabetic status. Notably, non-diabetic patients with CAD had a significantly higher vascular event rate than those with diabetes and no CAD (hazard ratios [HR] of 2.2 vs. 1.2, respectively; p=0.034). These data are in conflict with the well-known data from Haffner *et al.* (*N Engl J Med* 1998; 339:229), which led to the consideration of diabetes as a cardiovascular risk equivalent. Diabetic patients with CAD were at substantially higher risk (HR 5.0).

Insulin Pulses

Juhl and Danish associates (abstract 596) compared the effects of pulsatile versus non-pulsatile insulin delivery during an intravenous glucose challenge in 10 healthy young subjects with no family history of diabetes mellitus, studied on two separate occasions. The investigators found that pulsatile insulin delivery played an important role in post-challenge glucose homeostasis. The investigators used the "pancreatic-pituitary clamp" technique where a somatostatin infusion is used to suppress endogenous islet secretion and glucagon and growth hormone are infused at basal levels. Then, on two occasions, insulin was infused for three hours in a pulsatile manner. Thereafter, glucose and insulin were infused by a computer-controlled pump for four hours in a manner to mimic normal post-prandial glucose and insulin profiles. On one study day, insulin infusion was administered in a continuous manner, while on the other study day this profile was converted into a pulsatile profile by the computerized pump. Blood samples were drawn every 15 to 30 minutes for the analysis of glucose, insulin, C-peptide, growth hormone,

glucagon, and free fatty acids. The hypoglycemic effect of insulin was measured as the integrated area under the curve (AUC) for glucose during the four-hour infusion period. The investigators observed near identical (p>0.9) integrated AUC measurements for insulin concentrations. Despite this, the hypoglycemic effect of insulin was significantly greater (by 13%) during pulsatile delivery compared to continuous delivery (p=0.015) and the maximal glucose concentration was significantly lower with pulsatile delivery (p=0.036). We would emphasize that insulin is normally secreted by the pancreas in a pulsatile manner, but, obviously insulin injections provide a more continuous insulin exposure. This is an example of yet another difference between endogenously secreted insulin and exogenously administered insulin that makes glycemic control such a challenge in our insulin-requiring diabetic patients. (The most important difference is that endogenous insulin is secreted into the portal vein, with an immediate and profound effect on hepatic glucose production, whereas subcutaneous insulin injections are ultimately delivered systemically.)

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

Editors, Yale University,
New Haven, Connecticut