

Diabetes 2008

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VADT: Further Insights into Glucose & CVD



Important data on diabetes presented at the 68th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2008**, 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 2008** will be followed by a **Diabetes 2008** 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 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

Diabetes 2008 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

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

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The Veterans Administration Diabetes Trial (VADT) is the second of three major randomized control trials presented at this year's conference addressing the effect of intensive glycemic control on clinical cardiovascular (CV) endpoints in Type 2 diabetes. The study population consisted of 1,742 enrollees over 41 years of age, who had uncontrolled diabetes with an HbA1c $\geq 7.5\%$ already on a maximum dose of at least one oral hypoglycemic agent. They were predominantly male (97%), of mean age of 60.4 years, with a mean BMI of 31.3 kg/m², and with a mean HbA1c of 9.4%. The majority of enrollees had multiple CV risk factors and preexisting diabetic complications: 72% had hypertension at baseline, 40% established macrovascular disease, 62% retinopathy, and 43% some evidence of diabetic neuropathy.

Over a six- to seven-year period, study participants received stepped therapy with glimepiride or metformin plus rosiglitazone and insulin, with a target HbA1c of <6% in the intensive arm or 8-9% in the standard treatment arm. Concomitant therapy for other CV risk factors including hypertension, hyperlipidemia, and cigarette use was managed according to current diabetes guidelines. Table 1 shows the overall effectiveness of both treatment arms. Unlike the ADVANCE (Action in Diabetes and Vascular Disease) trial (see Volume 17, Issue 2, "ADVANCing Our Understanding of the Clinical Impact of Glycemic Control"), the VADT was better able to isolate the effect of intensive glycemic control on macrovas-

cular events because all other risk factors were aggressively treated to goal. The primary endpoint included major cardiovascular disease (CVD) events (CV death, myocardial infarction [MI], stroke, heart failure), amputation, and coronary or peripheral revascularization. Secondary endpoint analysis was not presented at the meeting—these included angina, transient ischemic attack, critical limb ischemia, total mortality, retinopathy, nephropathy, neuropathy, quality of life, cognitive function, and cost effectiveness.

As part of therapy, the majority of participants were on rosiglitazone for some portion of the study period. In light of the recent Nissen-Wolski meta-analysis on the potential increased risk of CVD events with the use of this agent, statistician Thomas Moritz of the VA in Hines, Illinois, presented a specific analysis to ensure the safety of continuing use of rosiglitazone in the trial. Notably, the VADT was not designed to test the effect of any specific anti-diabetic agent on outcomes. However, by using a case control method within the existing clinical trial data set, Mr. Moritz demonstrated that the odds ratio (OR) was consistently <1.0 for measures of rosiglitazone use for the primary and other CV endpoints (including, curiously, heart failure). Accordingly, this analysis appears to indicate that rosiglitazone did *not* pose an increased risk of CVD for VADT participants. The Data Monitoring Committee agreed and allowed the study to proceed.

Dr. Peter Reaven from the Phoenix VA

Table 1. Cardiovascular Risk Factor Profile during VADT

Risk Factor	Baseline		Year 6	
	Intensive	Standard	Intensive	Standard
HbA1c (%)	9.4	9.4	6.9	8.4
Blood pressure (mmHg)	132/76	132/76	126/69	126/68
LDL-cholesterol (mg/dl)	103	104	75	74
HDL-cholesterol (mg/dl)	34	34	39	39
Triglycerides (mg/dl)	160	162	124	124
Anti-platelet agent use (%)	76	76	91	94
Statin use (%)	57	59	83	86

Continued on page 2

VADT: Further Insights...

Continued from page 1

presented data from RACED (Risk Factors, Atherosclerosis, and Clinical Events in Type 2 Diabetes) trial, an ancillary study conducted in a subset of VADT enrollees. RACED was performed to determine the relationship between baseline coronary and aortic calcification and longitudinal CVD events. It employed electron beam computed tomography (EBCT) to measure coronary arterial calcification (CAC) and abdominal aorta calcification (AAC) at baseline and nine months into therapy for 324 participants within the intensive and standard treatment arms.

As in prior studies, CAC was highly correlated to CVD outcomes, with a stepwise progression of event rates as CAC values increased. Four categories of CAC scores in Agaston units were designated: 0-10, 11-100, 101-400, and >400. Of note, an impressive 45% of these veterans had a CAC over 400, and very few were in the lowest CAC category—a distinct finding of VADT as compared to other EBCT studies. As compared to the lowest grouping of CAC scores, 0-10, hazard ratios (HR) of a CV event for the higher categories were 1.7, 4.9, and 7.5 respectively. Importantly, the effect of intensive glycemic control showed a significant beneficial impact on the time to first event in those with a CAC <100. The incidence of a primary CV event with a CAC <100 was dramatically reduced from 17.7 in the standard arm to 1.9 in the intensive arm. In contrast, in those with a CAC >100, intensive glycemic control did not alter the event rate. This suggests that achieving intensive glycemic control early in the course of disease (before extensive atherosclerosis takes hold) may reduce the risk of CVD. These findings and their implications will resonate with the study's main findings.

Dr. William Duckworth, also from the Phoenix VA, presented the primary endpoint data and their

initial interpretation. Despite the significant difference in median HbA1c achieved between the two arms (-1.5%), no statistical difference was seen in CVD outcomes. There were 263 (29.3%) CVD events in the standard arm, and 231 (27.4%) events in the intensive arm. The time to event rate comparisons also did not reach statistical significance (HR = 0.868 [95% CI: 0.718, 1.036]; $p = 0.12$). It is noteworthy that in both arms of this trial there were fewer CVD events than had been predicted—40% for standard arm, 31.6% for intensive arm—calculated based on CVD event rates from prior trials. This effect was likely the result of the investigators' strenuous and ultimately very successful control of other CVD risk factors.

When baseline characteristics were examined for their ability to predict a future CVD endpoint, age and history of prior CVD event were the only statistically significant variables ($p < 0.0001$). Indeed, glucose control had very little effect at all, particularly when controlling for minor baseline differences between the groups. However, when the analysis looked at predictors of primary outcome with treatment, HDL-cholesterol levels and HbA1c became significant ($p < 0.0001$ and $p = 0.0024$, respectively). Of concern, however, was the finding that on-trial severe hypoglycemia—defined as low blood glucose and altered consciousness in the three months prior to an event—was also predictive of CVD outcomes.

The most interesting finding emerged when the duration of diabetes was factored into the analysis. Early in the course of Type 2 diabetes, intensive glycemic control showed clear benefit—a benefit that steadily declines with increasing duration of diabetes until about 12-15 years of disease. At that juncture, intensive management appears to become increasingly detrimental for CVD outcomes. This post-hoc analysis must be interpreted cautiously, but suggests that stringent control of blood glucose is perhaps more effective

at reducing macrovascular events in the more recently diagnosed patients. Such an aggressive strategy may be 'too little, too late'—or actually harmful—in those with well-established disease in whom, presumably, advanced atherosclerosis is entrenched.

Although the time to CVD-related death outcome was not different between the two arms (HR 1.258, [0.771-2.002]; $p = 0.36$), hypoglycemia again became relevant in the discussion of predictors of CVD-related death, with a HR of 4.042 ($p = 0.01$). The total number of CVD deaths in the standard arm was 29, four of which were sudden. Although the numbers are too small to interpret definitively, the intensive arm had a greater number of CVD deaths ($n = 36$). Eleven of these were sudden—almost one in three CVD-related deaths. Although possible variables correlating with the sudden death events were discussed, it remains unclear precisely why there was a higher rate in the intensive arm.

In summary, this important trial demonstrates that the ADA goals for blood pressure, lipids, and glycemic control can be achieved even in a previously difficult-to-control population. On top of the reduction in event rates from blood pressure and lipid control, however, overall, glycemic control appears to add little to CVD risk reduction in this population. The VADT was more successful than the ADVANCE trial in being able to isolate the effect of glycemic control over and above other CVD risk factors. However, the EBCT findings and the analysis incorporating diabetes duration continues to suggest that early, aggressive therapy may have long-term benefits, whereas an overly intensive approach in high-risk, older patients with extensive diabetes histories may hold some risk. Further analysis of secondary outcomes, especially those involving microvascular endpoints, are to be presented at the 2008 EASD meeting in Rome, Italy in September.



Miming and Enhancing: The Incretin Story Evolves



Incretin-based therapies were the subject of countless presentations at the 68th ADA Scientific Sessions, with content ranging from bench research all the way to new clinical outcomes data. These compounds are a source of immense interest, unanswered questions, and, potentially, great promise as further insight is gained regarding their physiological and clinical effects. The symposium, "New Incretin Mimetic Agents," addressed both commercially available and investigational glucagon-like peptide-1 (GLP-1)

receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. The GLP-1 analogs, also referred to as the incretin mimetics, improve glucose homeostasis by several mechanisms later described, whereas the DPP-4 inhibitors (or incretin enhancers) prevent the inactivation of endogenous GLP-1 (and GIP [glucose-dependent insulinotropic peptide]).

Dr. David D'Alessio of the University of Cincinnati, began the symposium with the presentation entitled "New Incretin Mimetic Agents—

Liraglutide and Others." He initially reviewed the breadth of physiologic actions associated with the GLP-1 receptor agonists including: (1) regulation of islet hormone secretion (glucose-dependent stimulation of insulin secretion and suppression of glucagon secretion); (2) regulation of islet gene transcription; (3) slowing of gastrointestinal (GI) motility/gastric emptying; (4) increased satiety/decreased food intake; (5) inhibition of hepatic glucose production; and (6) promotion of glucose disappearance. GLP-1 receptors are expressed in the

Continued on page 3

Miming and Enhancing...

Continued from page 2

heart/vascular endothelium, central and peripheral nervous systems, and the GI tract. Dr. D'Alessio commented that the more we learn about these agents, the more complex they become. A central challenge for drug development of these drugs is their rapid degradation.

Exenatide, the only FDA-approved GLP-1 analog, is dosed twice daily by the subcutaneous route (Table 2). Exenatide long-acting release (LAR), a formulation permitting weekly dosing, has been reported to have enhanced efficacy relative to HbA1c lowering when compared with the twice daily-dosed exenatide (see abstract 107-OR, described later). Liraglutide, a GLP-1 analog currently under investigation and the subject of several abstracts at the Sessions, binds to serum albumin, prolonging its half-life and allowing for once daily injections. Liraglutide appears to have similar activity and comparable clinical efficacy (although, head-to-head trials are lacking) to exenatide. Other GLP-1 receptor agonists are under development (*eg*, albiglutide, R-1583, AVE-0010, CJC 1134-PC); at the present time their activity seems predictable based on the actions of GLP-1.

In summary, Dr. D'Alessio described the GLP-1 receptor agonists as a promising class of drugs with predictable pharmacodynamic actions. Further research on strategies to enhance efficacy by altering the pharmacokinetics of existing and future compounds is needed. Specific issues requiring further investigation include: (1) the value of increasing their duration of action; (2) the potential limit to duration of action; (3) the likelihood of dissociating efficacy from adverse effects (predominately GI); and (4) should they "trump" other more established classes of drugs in diabetes treatment algorithms?

Dr. Carolyn Deacon of the University of Copenhagen, followed with a presentation on the DPP-4 inhibitors. She described clinical data previously establishing these agents as safe and effective. Sitagliptin is the only DPP-4 inhibitor commercially available in the US and several others are in development (Table 3). The comparative efficacy among agents in this class may be a function of DPP-4 inhibitor selectivity, substrate selection, specificity, and toxicities unique to the individual compounds (unrelated to DPP-4 inhibition). Each agent under investigation is selective for DPP-4, however, the degree of selectivity varies to some degree. To date, however, this has not been shown to result in any differential efficacy or safety. Pre-clinical data in rats demonstrated that agents that inhibit other DPPs, such as DPP-8 and -9, may result in alopecia, thrombocytopenia,

Table 2. Properties of Selected GLP-1 Receptor Agonists

	<i>Exenatide</i>	<i>Exenatide Long-Acting Release (LAR)</i>	<i>Liraglutide</i>
FDA approved	Yes	No	No
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
Frequency of administration	Twice daily	Once weekly	Once daily
Half-life	2 to 4 hours	>1 week	12 to 14 hours
Dose per injection	5 to 10 µg	Up to 2 mg	Up to 2 mg
Susceptibility to DPP-4 breakdown	No	No	No

reticulocytopenia, splenomegaly, and histopathological changes in multiple organs. The role of DPP-4 specificity in humans remains unclear, however. A meta-analysis evaluating the adverse events associated with these compounds suggests that, since the vast majority of clinical trials are less than 30 weeks in duration, long-term safety data are needed (Amori RE *et al.*, *JAMA* 2007). As post-marketing data accumulate relative to safety, current advantages for these compounds appear to be their weight neutrality, lack of GI effects and, like the incretin mimetics, low-to-no hypoglycemia. Their efficacy remains somewhat modest, although, in certain comparative studies, on par with sulfonylureas and thiazolidinediones (TZDs).

A substantial portion of the incretin research presented at the Sessions was devoted to optimizing doses and dosing regimens, in particular, with the GLP-1 analogs. Drucker and colleagues reported the results of a 30-week, randomized, open-label trial comparing exenatide LAR 2 mg once weekly with traditional dosing of exenatide 10 µg twice daily (abstract 107-OR). Patients were either drug naïve or receiving one or more oral agents. There were no differences between groups relative to baseline HbA1c, fasting blood glucose, BMI, and duration of diabetes. The weekly exenatide group demonstrated a significantly greater reduction from baseline in HbA1c ($-1.9 \pm 0.1\%$ vs. $-1.5 \pm 0.1\%$, $p = 0.002$) and fasting blood glucose (FBG) (-42 ± 3 mg/dl vs. -25 ± 3 mg/dl, $p < 0.0001$) when compared to the group dosed twice weekly. In addition, a greater percentage of patients on the weekly regimen (77% vs. 61%, respectively; $p = 0.004$) achieved HbA1c values of $\leq 7\%$. Weight loss did not differ between groups. Nausea was generally mild and occurred with a lower frequency in the group dosed weekly.

Complementing this study, Dr. John Buse of the University of North Carolina, in a late-breaking trial update, shared the results of a 52-week study of exenatide administered once weekly. Patients from the aforementioned 30-week trial continued on exenatide an additional 22 weeks in an open-ended study. Those who were originally randomized to weekly exenatide remained on

weekly doses and those previously receiving twice daily converted to weekly doses. Both groups experienced durable glycemic improvement and weight loss at the 52-week mark regardless of the original dosing regimen. It was noted, however, that a temporary decline in glycemic control occurred in patients while converting from twice daily to weekly exenatide, because of the long half-life of the LAR formulation that may require 4 to 6 weeks to achieve steady state. At 52 weeks, HbA1c decreased by 2% and the percentage of patients achieving HbA1c $< 7\%$ and $< 6.5\%$ was 72% and 54%, respectively. The mean HbA1c was 6.6%. On average, patients experienced a 4 kg weight loss. There were no episodes of major hypoglycemia and those patients not receiving a concomitant sulfonylurea had no episodes of minor hypoglycemia. Exenatide LAR was generally well tolerated. The results from these studies raise the question as to whether intermittent versus continuous activation of GLP-1 receptors results in differential effects on glycemic control.

Other approaches to manipulate exenatide administration include changes in the timing (lunch/dinner [L/D] vs. breakfast/dinner [BD]) and an alteration in route. Oliveira and co-investigators evaluated whether administration of exenatide at L/D versus the traditional times of B/D would impact patient outcomes (abstract 442-P). The move to L/D might accommodate patients from cultures where the breakfast meal is traditionally smaller than that consumed at lunchtime. A total of 377 patients were randomized to either regimen in an open-label, 12-week trial. Both groups demonstrated similar reductions in mean HbA1c values from baseline.

Table 3. Regulatory Status of DPP-4 Inhibitors

<i>Agent</i>	<i>Status</i>
Sitagliptin	Available in US, Europe
Vildagliptin	Available in Europe
Alogliptin	NDA Submitted to FDA
Saxagliptin	Phase 3
BI-1356	Phase 3

Continued on page 4

Miming and Enhancing...

Continued from page 3

Blase and San Diego researchers evaluated an intranasal formulation of exenatide in a single-blind, placebo-controlled, dose escalation study in patients with Type 2 diabetes (abstract 195-OR). Pharmacokinetic data were evaluated and it was determined that a dose of 600 µg would be needed to maintain therapeutic plasma concentrations of exenatide for 3 to 5 hours to result in improvements in post-prandial glucose levels. Side effects were dose related (occurred only at doses ≥600 µg) and included nausea, vomiting, and sneezing.

The still investigational GLP-1 receptor agonist, liraglutide, was compared with rosiglitazone, both in combination with a sulfonylurea (abstract 13-OR). Marre and co-investigators conducted a double-blind, placebo-controlled trial over a 26-week period in which increasing doses of liraglutide in combination with glimepiride were compared to monotherapy with glimepiride and the combination of glimepiride and rosiglitazone. The two higher doses of liraglutide (1.2 and 1.8 mg daily) resulted in a significant reduction in HbA1c and fasting plasma glucose when evaluated against all other comparator regimens ($p < 0.0001$). A greater percentage of patients achieved an HbA1c goal of $< 7\%$ in the liraglutide 1.2 and 1.8 mg groups ($p \leq 0.0003$). Nausea was the most frequent side effect and 9.3 to 12.7% of patients treated with liraglutide developed antibody-positivity—something that has been observed with exenatide, but which doesn't appear to alter efficacy. Overall, the side effect profile of liraglutide appeared similar to other GLP-1 receptor agonists.

A recent area of research associated with the incretins is the potential for cardioprotection. Data are extremely limited, but quite provocative. Liraglutide was studied in mice by Noyan-Ashraf and Toronto colleagues for its role in the protection of cardiomyocytes and improved survival and

cardiac output following MI (abstract 190-OR). Liraglutide administered for seven days was associated with the stimulation of genes described as 'cardioprotective' in mice. Treated animals also had improved survival following experimental induction of an MI. Mice-treated with liraglutide demonstrated a significant decrease in infarct size, cardiac rupture, and mortality (20% vs. 60%, $p = 0.0001$). Improvement in parameters of cardiac structure and function continued at 28-days post-MI. The experiments were also repeated in diabetic mice and the investigators continued to see a statistically significant improvement in survival with liraglutide. GLP-1 receptor activation in the heart is thought to be playing a role in these effects. We would emphasize the highly preliminary nature of these data.

As a class, the DPP-4 inhibitors continue to proliferate. Alogliptin is likely the next DPP-4 inhibitor to reach the US market, while research continues with already available sitagliptin. Canadian investigators, Stafford and Meneilly, assessed the safety and efficacy of sitagliptin in elderly Type 2 diabetes patients in a single dose, randomized, crossover study (abstract 550-P). Despite the frequency with which diabetes occurs in the elderly, few studies have focused on the impact of the incretins in this patient population. A single 100 mg dose of sitagliptin was administered followed by initiation of a hyperglycemic clamp. At 60 minutes, a significantly increased insulin response to an oral meal challenge was seen as compared to control. From these preliminary results, it was inferred that the DPP-4 inhibitors may be a reasonable treatment alternative in the elderly, a group that is prone to drug side effects, especially hypoglycemia. It is important to remember that the dose of the drug may need to be reduced in elderly patients with reduced renal function.

Several abstracts evaluated the role of alogliptin monotherapy and in combination with

other agents in the management of Type 2 diabetes. Monotherapy with alogliptin was studied by DeFronzo and colleagues, demonstrating significant ($p < 0.001$) decreases in HbA1c for 12.5 (-0.56%) and 25 mg (-0.59%) doses of alogliptin when compared with placebo over a 26-week period (abstract 446-P). The most common adverse event was nasopharyngitis and each group had similar and low rates of hypoglycemia. The role of alogliptin added to glyburide was assessed by Pratley *et al.* in a randomized, double-blind, placebo-controlled trial over a 26-week period in 500 subjects (abstract 445-P). Similar to the results experienced in alogliptin monotherapy, groups treated with 12.5 and 25 mg doses experienced reductions in HbA1c ($p < 0.001$ for both doses) when compared with placebo. Alogliptin improved glycemic control when added to glyburide without increasing weight or the incidence of hypoglycemia. Alogliptin was also evaluated as add-on therapy to insulin in patients with Type 2 diabetes by Rosenstock and colleagues (abstract 444-P). Similar to the previous studies, HbA1c values significantly improved with both active treatment groups (-0.63% and -0.71%, respectively; $p < 0.001$), but FPG improved in the 25 mg dose group only ($p = 0.030$). No differences in weight, incidence of hypoglycemia, or daily insulin requirements between groups were observed.

At present, the DPP-4 inhibitors each appear comparable in that they are effective in lowering HbA1c both as monotherapy and in combination with other agents and are generally well tolerated with a low incidence of hypoglycemia. How we will distinguish these agents once several have become available is not clear. Whether differential specificity between drugs to DPP-4 is an important feature remains unknown. More research will be required to determine the optimal implementation of these and other incretin-based therapies for our patients with Type 2 diabetes.



Honing in on Bones



A symposium conducted on Friday, June 6th, at the ADA Scientific Sessions addressed one of the hot topics in current diabetes therapy—namely the interaction between diabetes, osteoporosis, and TZD therapy. First off, and setting the stage for the talks that followed, Dr. Peter Vestergaard, Aarhus, Denmark, reviewed the potential mechanisms through which diabetes may affect bone turnover and addressed the question of whether fracture rates are increased in diabetic patients.

Impaired glucose metabolism has a number of detrimental effects on bone metabolism, which

can be divided into mechanisms that decrease bone mineral density (BMD) or weaken bone structure, and those that increase the likelihood of falls and other traumas. BMD is reported to be negatively effected in diabetes by increased urine calcium excretion (linked to hyperglycemia), which leads to a negative calcium balance, functional hyperparathyroidism, alterations in vitamin D metabolism (especially in patients with nephropathy), insulin deficiency (loss of anabolic effect), and alterations in the glycosylation of collagen. In addition to these effects on BMD, the complications

of diabetes may also contribute to fracture risk— notably, renal failure, neuropathy, and microangiopathy (decreasing blood supply to parts of the skeleton). Finally, hypoglycemic events and impaired vision related to retinopathy might contribute to an increased risk of falls, and the increased body mass of many patients with Type 2 diabetes means they will sustain a greater traumatic insult on falling. On the other hand, it is well known that obese patients tend to have increased BMD, due to chronic physical loading of the skeleton.

Continued on page 5

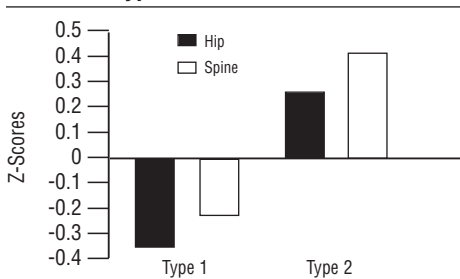
Honing in on Bones

Continued from page 4

In the light of these risk factors associated with diabetes, Dr. Vestergaard revealed the results of a meta-analysis of clinical trials examining fracture rates in individuals with Types 1 and 2 diabetes. This showed an increased fracture risk in patients with both forms of diabetes, although overall risk was much greater for individuals with Type 1 (odds ratio [OR] 6.2 [2.6-15.1]) vs. Type 2 (OR 1.7 [1.3-2.2]). Interestingly, a consistent finding was that BMD, while decreased in Type 1 was increased in patients with Type 2 diabetes (Figure 1). Available studies also pointed to greater fracture risk and lower BMD in patients with complications (retinopathy, neuropathy, nephropathy, macroangiopathy), but this interpretation is limited by the small number of patients and events in these categories. Overall, Dr. Vestergaard stated that evidence from these published trials suggests there is an increased fracture risk linked to diabetes, which is countered by certain factors in Type 2 diabetes leading to a comparatively lower fracture rate when compared with Type 1 diabetes.

Following on from this presentation Dr. Ann Schwartz of the University of California, addressed the issue of fracture risk with TZD therapy, a subject of great interest to clinicians. This issue is a major concern to have emerged from recent intervention

Figure 1. Hip and Spine Z-Scores in Patients with Type 1 or Type 2 Diabetes



So Many Posters, So Little Time...

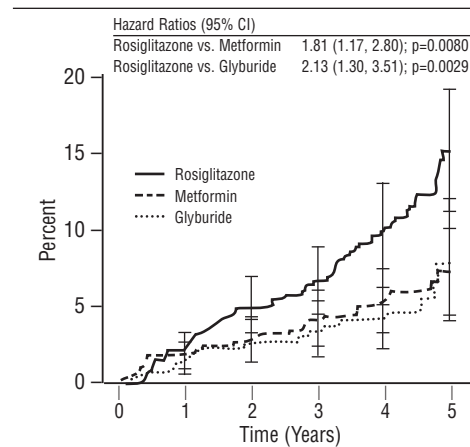


Lucero *et al.* from Atlanta determined the annual number of emergency department visits for adverse drug events (ADEs) due to diabetes medications from cases identified in the National Electronic Injury Surveillance System-Cooperative Adverse Event Surveillance Project, 2004-2005 (a collaboration among the Centers for Disease Control, the Consumer Product Safety Commission, and the Food and Drug Administration) (abstract 929-P). The investigators estimated that there

were 68,510 emergency department visits for ADEs from diabetes medications each year, with 27% resulting in hospital admission, observation, or transfer to another hospital. The most common ADEs were altered mental status (33%) and hypoglycemia with shock (24%); insulin was implicated in the majority of these events (79%). The elderly (>74 years) accounted for 29% of visits and 42% of admissions. Management errors

were primarily due to missed meals/decreased oral intake (46%), wrong insulin dose (24%), and, interestingly, insulin glargine confused with other insulins (13%). These data underscore the role of patient education for prevention of ADEs related to diabetes medications. We should be mindful of the risk of serious ADEs, especially among the elderly and long-term care residents, when individualizing patient care regimens.

Figure 2. Cumulative Incidence of First Fractures in Women



trials and important to review because TZDs are widely prescribed and are becoming advocated for individuals with pre-diabetes. Dr. Schwartz noted that in the recently reported fracture data from ADOPT (A Diabetes Outcome Progression Trial) (Kahn *et al. Diabetes Care*, 2008), in which 1,840 women and 2,511 men were randomized to rosiglitazone, metformin, or glyburide for a median of 4.0 years, a clear increase in fracture rates with rosiglitazone was seen in women (Figure 2), but not in men. She noted in ADOPT that if the data were re-analyzed by menopausal status the increased fracture risk in women remained, and, hormone replacement therapy risk did not change the relative risk. Similarly, in a letter released by the manufacturer of pioglitazone, a similar increase in bone fractures was reported for women, but not for men, in 7,400 patients taking the TZD during clinical trials. Dr. Schwartz then addressed the issue of the gender difference and also the question as to why fractures appeared to be occurring in peripheral bones rather than hip and spine. The observations may reflect the overall increased fracture risk in post-menopausal women and also the age of the patients included

in these trials. Hip and spine fractures more often occur in patients in their 60 to 70's, but the mean age of patients participating in these studies was the mid-50s. Dr. Schwartz noted the recent report of the UK General Practice Research Database, which looked at 66,696 patients with Type 2 diabetes on TZD therapy from 1994-2005 and compared these with a control population. In this older cohort, TZD therapy was associated with an overall increase in the rate of fractures (adjusted OR 2.86), and importantly, in this older population there was indeed an increased rate of femur/hip fractures (adjusted OR 4.5). Men also showed an increase risk of fracture with TZDs (OR 2.5). No increase in fracture risk was seen with other oral hypoglycemic agents such as metformin and sulfonylureas. Overall, Dr. Schwartz concluded that, while the numbers are small, the current data suggest TZDs increase fracture risk in both men and women.

Dr. Andrew Grey, New Zealand, presented the data from animal models that might indicate why we are seeing these problems. In his opinion the animal literature is very consistent and current TZDs show a class effect, negatively impacting bone remodeling. TZDs appear to redirect pluripotential mesenchymal bone marrow cells away from osteoblast formation and towards adipocyte formation. Thus, the bone marrow balance between osteoclast and osteoblast function is tipped toward increased bone resorption.

Because it appears that TZD therapy confers an increased fracture risk, at least in women, and now perhaps in men, the drugs should be used cautiously in those with or at risk for osteoporosis. Proper measures to preserve bone health should be considered in all patients with diabetes, but particularly in those taking these insulin sensitizers. We also need to better understand the mechanisms involved so that preventive measures can be undertaken. Additional trial data are urgently needed to further clarify this issue.

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