

Diabetes 2008

From the 44th Annual Meeting of the European Association for the Study of Diabetes ■ Rome, Italy

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Important data on diabetes presented at the 44th Annual Meeting of the European Association for the Study of Diabetes comes 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 (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 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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DIRECT to the Point



Duration of diabetes is a major risk indicator for the development of retinopathy, a progressive condition with potentially devastating consequences. After 20 years of disease, nearly all Type 1 patients and over 60 percent of those with Type 2 diabetes will have developed some degree of retinopathy. There are currently three approaches with long-term, favorable effects on its progression—glycemic control, anti-hypertensive therapy, and laser photocoagulation. There is some evidence that inhibition of the renin-angiotensin system (RAS) may have benefits on diabetic eye disease above that fully accounted for by effects on blood pressure.

The Diabetic Retinopathy Candesartan Trials (DIRECT) Program consisted of three randomized, double-blind, placebo-controlled, multicenter studies. These were designed to assess if RAS blockade with candesartan, an angiotensin receptor blocker (ARB), will halt the progression of retinopathy in Type 1 and Type 2 diabetes patients (DIRECT Protect), and even possibly prevent the development of retinopathy in those with Type 1 diabetes (DIRECT Prevent). (The third analysis, DIRECT Renal, determined the impact of candesartan on the development of microalbuminuria.) Patients enrolled in these studies were normotensive or had their blood pressure (BP) controlled with anti-hypertensive therapy. Retinal involvement was graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) 7-step scale based on 7-field stereophotographs performed annually. After baseline studies, patients were randomized to treatment with 16 mg candesartan or matching placebo; the dose was increased to 32 mg after one month.

Any other anti-hypertensive agents were not changed.

Members of the DIRECT Steering Committee, Drs. Chaturverdi (UK), Sjolie (Denmark), and Bilous (UK), presented the DIRECT results on the final day of the EASD meeting. A total of 5,231 patients were randomized in 30 countries. Type 1 diabetes patients in DIRECT Protect had baseline HbA1c of 8.5%, with 49% having mild proliferative retinopathy (PDR) and 9% having moderate-to-moderately severe PDR. Type 2 diabetes patients in DIRECT Protect were similar, with a baseline HbA1c of 8.2%; 17% had moderate-to-moderately severe PDR.

In DIRECT Protect, there was no significant change in the progression of retinopathy in Type 1 patients (Table 1). However, Type 2 diabetes patients in DIRECT Protect did enjoy a significantly increased (~34%) likelihood of retinopathy regression. DIRECT Prevent demonstrated 18% and 35% decreases in the incidence of retinopathy as per 2-step or 3-step changes on the ETDRS scale, respectively. There was no significant difference between groups relative to the incidence of microalbuminuria, but the overall rate was exceedingly low (~10% of that observed in the DCCT). Of note, however, mean BP in the active-therapy groups in the DIRECT trials was 2 to 4 mmHg lower than placebo. When the investigators adjusted for BP, the hazard ratios (HR) did not change appreciably—suggesting that any benefit on retinopathy may be a direct effect of the drug. So, the ARB candesartan appears to reduce the incidence of retinopathy in patients with Type 1 diabetes and retinopathy progression in those with Type 2 diabetes. These results may be viewed at: www.direct-results.org.

Table 1. Retinopathy Results in DIRECT

		Hazard Ratio	95% CI	p value
DIRECT Prevent: Incident Retinopathy				
Type 1 Diabetes				
2-Step ETDRS change		0.82	0.67-1.00	0.051
3-Step ETDRS change		0.65	0.48-0.87	0.003
DIRECT Protect: Retinopathy				
Type 1 Diabetes	Progression	1.02	0.80-1.31	0.8
	Regression	*	*	0.9
Type 2 Diabetes	Progression	0.87	0.70-1.08	0.2
	Regression	1.34	1.08-1.68	0.009

*Data not presented.



Under Investigation



The past decade has seen a significant increase in the number of oral and injectable glucose-lowering agents available for treating patients with diabetes. Each of these carry with them certain risks and benefits and each may not be appropriate for or tolerated by an individual patient. Accordingly, although not as acute as in the past, there remains a considerable need for more agents with different mechanisms of action and, hopefully, better side effect profiles. International diabetes meetings are often the site for the unveiling of new compounds in early stages of clinical development, spanning the spectrum from safety/tolerability phase 1 investigations, to proof-of-concept and dose-finding phase 2 studies, all the way through larger, multi-center phase 3 trials used for FDA registration. Data regarding several interesting novel compounds were presented in Rome this week.

Despite the recent woes of inhaled insulin, investigators remain interested in non-injectable ways to deliver this important hormone in both Type 1 and Type 2 diabetic patients. Broke-Smith and UK colleagues tested the glucose-lowering effects of an oral insulin formulation (Capsulin™) in 16 patients with Type 2 diabetes under suboptimal glycemic control with oral agents for at least 3 months (abstract 4). The mean age at baseline was 60.2 ± 5.5 years, BMI 28.3 ± 3.4 kg/m², and HbA1c $7.5 \pm 1.3\%$. During the study, all oral agents except metformin were withdrawn. The insulin was administered at a dose of 150 units one hour prior to breakfast and dinner for 10 consecutive days. Fingerstick glucose samples were obtained 5 times per day—before and 2 hours after these meals and at bedtime. By day 10, the 2-hour post-prandial glucose (PPG) value was within the ADA target range (<180 mg/dl) in nearly 36% of participants, whereas this figure was only 10% before oral insulin therapy. Of note, the glucose-lowering effect was more pronounced following the evening meal. No hypoglycemia was reported. The investigators concluded that Capsulin™ appeared to be effective in lowering PPG levels safely, perhaps a reflection of delivery via the hepatic portal system, which is, after all, the pathway through which insulin is normally secreted. Caution is advised in over-interpreting this short-term, non-randomized and unblinded study.

A new approach with an old drug was proposed by Cincotta and American colleagues (abstract 39). This is a quick-release form of the dopamine agonist, bromocriptine, which is usually used to lower prolactin levels in patients with hyperprolactinemia. Prior studies have suggested

that reduced dopaminergic tone in the hypothalamus is associated with obesity and insulin resistance. In this study, 3,070 patients were randomized in a 2:1 fashion to bromocriptine or placebo on top of their usual anti-hyperglycemic therapy. All patients had a baseline HbA1c between 7.5 and 10% (mean 8.3%) on one or two oral agents. Mean age was 58 years, with 63% of participants being male; the mean BMI was 33 kg/m². In the entire group, active therapy was associated with a 0.6% reduction in HbA1c ($p < 0.0001$). More patients on bromocriptine achieved the HbA1c ADA target of $\leq 7\%$ (32 vs. 10% on placebo; $p = 0.0001$). In the subgroup of patients on either metformin or a sulfonylurea, the mean HbA1c reduction with active therapy was 0.7%, whereas it was slightly greater in those on a thiazolidinedione (TZD) (0.9%). This centrally-acting agent therefore appears to be modestly effective, with HbA1c reductions on the order of that observed with dipeptidyl peptidase (DPP)-4 inhibitors.

Glucokinase (GK) is an enzyme expressed within pancreatic β -cells that acts as the first rate-limiting step in the metabolism of glucose. Within pancreatic β -cells GK acts as a sensor of blood glucose. Increased GK activity is associated with increased insulin secretion and reduced hepatic glucose production. Pharmacological GK activators, an investigational drug class, appear to reduce glucose through these two mechanisms. Zhi and colleagues from the US and Switzerland reported results from a small, double-blind, randomized, placebo-controlled study involving the GK activator R04389620 in 59 patients with Type 2 diabetes (abstract 42). Patients were either treatment naïve or previously treated with oral anti-hyperglycemic agents. The schedule was a single dose on day 1, multiple doses up to 200 mg twice daily on days 3 to 8, and then 200 mg once daily for an additional 6 days. Fasting glucose and PPG were measured. Plasma exposure to R04389620 was dose proportional over the tested range, with no appreciable drug accumulation or effect from concurrent food intake. There was a dose-dependent decrease in fasting glucose of up to 33% by day 6. A relative increase in insulin secretion was observed at the higher doses. The drug was well tolerated, with the most common adverse effect being headache. No significant laboratory or ECG abnormalities were noted during therapy. These results are promising in the short term, but need to be confirmed in randomized, double-blind studies. In addition, long-term safety data, especially with regard to hypoglycemia, will be needed.

Another group of investigational anti-hyperglycemic agents with a unique mechanism of action is the sodium glucose transporter-2 (SGLT-2) inhibitors, which enhance renal glucose excretion by decreasing renal tubular glucose reabsorption. These drugs produce a modest reduction in plasma glucose levels. One such drug, dapagliflozin, is currently in phase 3 trials. Woo *et al.* from the US and Mexico presented the results of a 12-week randomized, double-blind, parallel-group study involving 389 treatment naïve Type 2 diabetes patients with inadequate glucose control and low mean glycosuria at baseline (abstract 796). They were randomized to several doses of dapagliflozin or metformin. The former was associated with a sustained increase in urinary glucose excretion, with mean glycosuria values climbing to 52 to 85 g/day by week 12, as compared with values of 6 to 11 g/day at baseline. With this, mean urinary volumes were increased by 107 ml/day at the lowest dose and by 470 ml/day at the highest dose. Despite this, only 1.4% of patients reported polyuria as an adverse event and there were no reports of nocturia. Of particular interest, the decrease in urinary glucose excretion caused a significant reduction in body weight (2.5 to 3.4 kg) and BMI (0.8 to 1.1 kg/m²). However, given the mode of action of these agents we would like to see extensive renal safety data, especially in the elderly, those with chronic kidney disease, on diuretics, or with a history of urinary tract infections before using them clinically.

To date, the pharmacological management of obesity has been disappointing, with drugs not resulting in enough weight loss, associated with serious side effects, or both. One new approach is combination therapy with pramlintide, an amylinomimetic, and human recombinant leptin (metreleptin). Pramlintide is currently available for use in both Type 1 and insulin-treated Type 2 diabetes patients. This injectable is an analogue of amylin, an islet-cell product co-secreted with insulin, that serves to reduce glucagon secretion, delay gastric emptying, and enhance satiety. Its cardinal metabolic effect is to reduce post-prandial glycemic excursions. Although leptin, an adipocyte signal to central appetite centers, also serves to enhance satiety, early therapeutic studies in obese patients were disappointing. It was subsequently learned that obese patients are leptin resistant and enthusiasm for developing leptin analogues waned. Koda and US collaborators, however, have now studied this hormone in combination with pramlintide in 177 obese or overweight

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Under Investigation

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subjects over 24 weeks, using a randomized, active-controlled, double-blind design (abstract 83). The mean age was 39 ± 8 years, 63% female, BMI 32.0 ± 2.1 kg/m², and weight 93.3 ± 13.2 kg. During a 4-week run-in period, all patients were treated with pramlintide alone (180 mcg twice daily for 2 weeks, then 360 mcg twice daily) and diet (40% calorie deficit). Those that lost 2 to 8% of body weight during this time ($n=139$) were then randomized to pramlintide+metreleptin (5 mg twice daily), pramlintide alone, metreleptin alone, or placebo. Combination therapy patients lost more weight (mean \pm SE, $-12.7 \pm 0.9\%$) than did those on pramlintide alone ($-8.4 \pm 0.9\%$; $p < 0.001$) or metreleptin alone ($-8.2 \pm 1.3\%$; $p < 0.01$). The proportion of patients achieving at least a 10% reduction in weight was 56% with combination

therapy vs. 35% with pramlintide and 21% with metreleptin. The most common side effects were injection site reactions and nausea/vomiting. The investigators correctly suggested that further research is warranted on this integrated neurohormonal approach to weight loss.

Advances are also being made in the realm of glucose monitoring—one of the more unpleasant aspects of diabetes management for our patients. An Israeli group, led by Karasik (abstract 1061), reported their initial experience with a non-invasive glucose monitoring device that employs a red/near-infrared sensor at the base of the finger. The device temporarily occludes blood flow, resulting in an enhanced, time-dependent optical signal that enables the calculation of glucose concentration. The sensor was tested in 15 patients for 24 hours each, resulting in 1,068 paired glucose values. The investigators analyzed a Clark Error Grid, a standard

way to assess the accuracy of sensors, using subcutaneous continuous glucose monitors (CGM) as the comparator. More than 95% of readings were deemed to be ‘clinically acceptable’ (Clarke Error Grid Zone A [similar results] = 66.7% and Zone B [different results that would result in the same therapeutic decision] = 28.4%). The device was well tolerated and appeared to be safe. The researchers concluded that their results are comparable to those from subcutaneous CGM. Larger studies will be needed, but these data are very encouraging.

From novel monitoring strategies to new therapeutic approaches, the management of diabetes will likely continue to evolve significantly in the foreseeable future. Of note, however, the FDA will probably soon require more extensive safety data for any new drug applications in diabetes. We suspect that this will likely delay the appearance of any new compounds to the market.



An Ounce of Prevention...



It is increasingly recognized that physiological abnormalities in glucose homeostasis can be identified well before the development of Type 2 diabetes. In this light, the diabetes research community is currently addressing two major questions: What are the benefits to the individual and to the population of identifying pre-diabetes (Table 2) at its earliest stage, and what is the best and simplest means of detecting such mild hyperglycemia?

A number of presentations at the EASD this week addressed this issue. Faerch *et al.* from Denmark looked at insulin sensitivity and secretion in 3,145 pre-diabetic individuals taking part in a Danish prospective, non-pharmacological intervention study (Inter99) (abstract 192). They reported that, 5 years prior to their pre-diabetes diagnosis, individuals who later developed isolated impaired fasting glucose (i-IFG—i.e., IFG but normal glucose tolerance) exhibited defective absolute insulin secretion which was followed by insulin resistance. In contrast, insulin resistance with secondary β -cell failure characterized the transition to i-IGT (IGT but normal fasting glucose). These pre-diabetic states may therefore have different etiological origins. This has clear implications for future prevention and treatment of pre-diabetes and overt Type 2 diabetes.

If clinicians wish to seriously tackle pre-diabetes, we will likely require better means of diagnosing this early stage in the development of diabetes. Current standards such as fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT) have limitations. Phillips and US colleagues hypothesized that simple screening could be accomplished with a 2-step ‘glucose challenge

Table 2. Definitions of Diabetes and Pre-diabetes States

Pre-diabetes/Diabetes State	Fasting Plasma Glucose	2-h Plasma Glucose by Oral Glucose Tolerance Test	Random Glucose
Impaired Fasting Glucose (IFG)	100-125 mg/dl		
Impaired Glucose Tolerance (IGT)		140-199 mg/dl	
Diabetes	≥ 126 mg/dl	≥ 200 mg/dl	≥ 200 mg/dl*

* In conjunction with typical hyperglycemia symptoms.

test’ (GCT) strategy—similar to that used in the screening for gestational diabetes (abstract 347). This entails a 50g oral GCT at any time of day, regardless of meal status, with a single 1-hour sample. If the GCT exceeds a cutoff, patients would then proceed to a 75g OGTT following an overnight fast. 1,419 adult volunteers (mean age 48 yr, BMI 30.2 kg/m², 60% female, 56% black, 5% with diabetes, 21% with diabetes or IGT, and 24% with diabetes, IGT, or IFG) had a random plasma and capillary glucose measurement, followed by the 50g GCT with 1-hour samples for plasma and capillary glucose. All subjects then underwent an OGTT at a second visit, following an overnight fast. The investigators reported that GCT plasma glucose provided areas under the receiver operator characteristics (ROC) curve of 0.89, 0.82, and 0.81 for detection of diabetes, diabetes/IGT, and diabetes/IGT/IFG, respectively, each higher than for GCT capillary glucose (AROC 0.85, 0.77, and 0.76; $p < 0.05$). To detect diabetes or IGT, GCT plasma glucose was better than random plasma glucose and GCT capillary glucose was better than random capillary glucose, both $p < 0.001$. Multivariate analysis showed that the c-

statistic (equivalent to AROC) of GCT plasma glucose for the detection of diabetes or IGT was highly significant and independent of age, sex, race, BMI, waist circumference, HDL-cholesterol, systolic BP, and family history ($p < 0.001$). The investigators estimated that the cost of GCT capillary glucose screening should be $< \$5$ per person. This is an interesting approach, but early identification should only be considered with an eye toward effective diabetes prevention strategies.

Hanefeld *et al.* from Germany and Canada, in a multi-center trial, looked at the interaction between different components of the metabolic syndrome, as defined by the National Cholesterol Education Program (NCEP)—Adult Treatment Panel (ATP) III, and the development of Type 2 diabetes (abstract 223). Subjects ($n=1,368$) were taking part in a double-blind, placebo-controlled trial of acarbose in the prevention of Type 2 diabetes (STOP-NIDDM). Acarbose is an α -glucosidase inhibitor that retards proximal small bowel carbohydrate absorption, thereby lowering PPG levels. Overall in STOP-NIDDM, acarbose therapy resulted in a 25% risk reduction for diabetes progression in patients with IGT. In this

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An Ounce of Prevention

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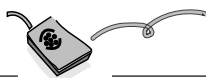
secondary analysis, the investigators found that IFG, hypertriglyceridemia, low HDL-cholesterol, and hypertension, as single traits, significantly increased the risk for diabetes with HR of 1.5, 1.4, 1.3, and 1.2, respectively; overall, a diagnosis of metabolic syndrome resulted in a HR of 1.6 ($p < 0.0001$). The annual incidence for diabetes in the placebo group with metabolic syndrome was 18.7% vs. 11.2% without metabolic syndrome. Acarbose reduced the incidence to 13.5% and 9.4%, respectively, meaning that the number needed to treat for patients without metabolic syndrome was 16.5 and with metabolic syndrome was 5.8. The investigators concluded that acarbose reduces the incidence of diabetes in people with as well as without metabolic syndrome. However, those with metabolic syndrome appear to enjoy a distinctly greater benefit.

In a related trial, Tripathy *et al.* of the US examined the impact of pioglitazone on progression from the pre-diabetic state (abstract 224). ACT-NOW was a randomized, double-blind, placebo-controlled study to examine whether treatment of IGT with pioglitazone can prevent and/or delay the devel-

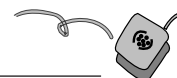
opment of Type 2 diabetes. A total of 602 IGT subjects (age 52.3 years, BMI 34.3 kg/m², 42% male, FPG 105±0.3 mg/dl, 2-hr PPG [OGTT] 168±1 mg/dl, HbA1c 5.5±0.01%) were randomized to the TZD (45 mg/day) or placebo and returned every 3 months for FPG/HbA1c and annually for OGTT for 2 years or until the development of diabetes. Overall, 45 placebo-treated subjects developed diabetes vs. 10 in the pioglitazone group (6.8% vs. 1.5% per year; $p < 0.000001$). In addition, 42% of individuals on pioglitazone vs. 28% on placebo reverted to normal glucose tolerance at study end ($p < 0.0005$). Insulin sensitivity (Matsuda Index, 4.3±0.4 to 7.1±0.6, $p < 0.0005$) and insulin secretion/insulin resistance index (3.1±0.2 to 5.1±0.4, $p < 0.0005$) both improved with the TZD and were unchanged with placebo. Adverse events such as weight gain (3.9 vs. 0.8 kg) and edema (22 vs. 15%) were more frequent with pioglitazone. There were 2 cases of heart failure (1 in each group) and 13 bone fractures occurred (8 in the pioglitazone group and 5 in the placebo group), all related to trauma. The investigators concluded that pioglitazone significantly reduced

the conversion of IGT to Type 2 diabetes in association with improved β -cell function and reduced insulin resistance.

Very clearly, there is growing interest in identifying patients at risk and ultimately preventing the progression from pre-diabetes to Type 2 diabetes. However, there are many important questions that remain: Would early identification of diabetes risk necessarily result in the implementation of effective preventative strategies? Although lifestyle change and pharmacotherapy are clearly effective over a period of 2 to 3 years in the context of a clinical trial, what would be the overall effectiveness of such strategies in the 'real world' setting? For how long can diabetes be prevented or delayed? In which patients and at what juncture should insulin-sensitizing medications be considered? Finally, what are the cost implications of such interventions? More studies will be required before we know the answers to some of these questions. Until then, the reader is referred to the comprehensive consensus statement from the ADA and the EASD, published last year (Nathan DM *et al. Diabetes Care* 2007;30:753).



Come to Your Sensors!



Continuous glucose monitoring (CGM) currently requires the insertion of a "glucose sensor" into subcutaneous tissue such that the glucose concentration within interstitial fluid can be measured continuously over an extended period of time, typically 3 to 7 days at a time (Table 3). While limited by poor accuracy and precision when introduced some 3 decades ago, CGM technology has advanced appreciably since then. Three proprietary devices are now available, although their applicability to clinical practice remains unclear and limited to some extent by their significant cost. To date, in small studies, use of these CGM devices has been shown to modestly improve HbA1c and time within the normoglycemic range as well as to decrease hypoglycemic and hyperglycemic excursions. Results from several CGM studies were presented at this week's meeting.

Voelmler *et al.* from the US evaluated the role of CGM for the optimization of glucose control in pregnant women with Type 1 diabetes (abstract 1066). Glycemic control in 19 patients (mean ± SE age 30.5±4.2 years and duration of diabetes 15.3±5.9 years) who used self-monitored blood glucose and also initiated CGM at 0 to 24 weeks gestation was compared to that in a control group of 19 patients (matched for age, diabetes duration, ethnicity, and normal albumin excretion rates [< 20 μ g/min]) using only self-monitored blood glucose.

Table 3. FDA-Approved Real-Time Continuous Glucose Monitoring Devices

Device	Locations Sensor Can be Worn	Initial Calibration Time (hr)	Calibrations		
			per 72 Hour Lifespan of Sensor	Frequency of Glucose Readings (min)	Hypo- and Hyperglycemia Alarms
Guardian® Real-time	Abdomen, arm, buttock, thigh	2	7	Every 5	Yes
Seven STS®	Abdomen	2	5	Every 5	Yes
Freestyle Navigator®	Posterior arm, abdomen, buttocks	10	4	Every 1	Yes

Baseline HbA1c values were 6.8±0.89% and 7.1±0.96% in the sensor and control groups, respectively ($p > 0.05$). Reductions from baseline in mean HbA1c values were seen at all timepoints in the sensor group ($p < 0.001$; Figure 1), importantly without any increase in the percentage of time in the hypoglycemic range. The favorable findings from this pilot study are encouraging given the difficulty in managing glucose control safely in pregnant women with diabetes. Larger studies are clearly needed to evaluate the clinical implications of CGM in this setting, specifically on gestational and fetal outcomes.

CGM is becoming an important clinical research tool, given its ability to generate a large amount of glycemic data so that underlying conditions

or medications affecting glucose control can be assessed or compared.

Pallayova *et al.* from Slovakia utilized CGM to determine the glycemic consequences of sleep apnea in patients with Type 2 diabetes. In 30 patients (19 men; age 55.5±7.8 years, BMI 34.7±7.4 kg/m², duration of diabetes 3.0±1.7 years, HbA1c 7.1±0.8%), the investigators measured mean nocturnal glucose values and various indices of nocturnal glucose variability (standard deviation, coefficient of variance, etc.) in relationship to objectively assessed quality of breathing during sleep (abstract 18). The patients with moderate to severe sleep apnea accompanied by severe oxygen desaturation had significantly

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increased nocturnal glucose variability ($p < 0.008$) and worse overnight glucose control as compared to those without sleep-disordered breathing, despite no significant difference in HbA1c between subgroups. There were strong positive correlations between apnea-hypopnea index (AHI) and parameters of nocturnal glucose variability ($p < 0.005$) and a strong positive correlation between AHI and mean nocturnal glucose values ($r = 0.6$; $p < 0.001$). The investigators observed negative correlations between mean nocturnal glucose values and both mean oxygen saturation level ($r = -0.59$; $p < 0.001$) and minimum oxygen saturation level ($r = -0.54$; $p < 0.001$). These findings have important implications on patient management in light of the rapidly increasing incidence of

Figure 1. HbA1c Over Time in Pregnant Women with Diabetes

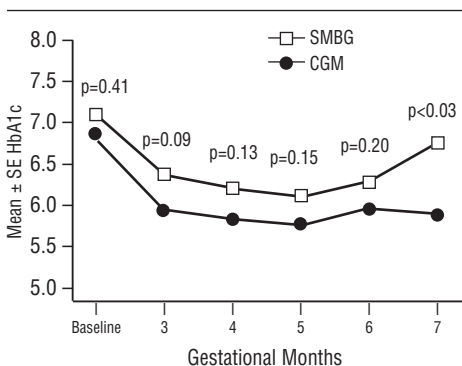


Table 4. Glycemic Control at Study End Following 4 Weeks Treatment With an Insulin Secretagogue

Measure of Glycemia	Repaglinide	Glimepiride	Gliclazide	p-value*
Mean ± SD glucose (mg/dl)	118 ± 21	128 ± 32	121 ± 23	0.463
MAGE ± SD (mg/dl)	77 ± 18	100 ± 28	107 ± 43	0.011
Mean ± SD maximal glucose (mg/dl)	211 ± 28	249 ± 53	244 ± 54	0.028
Mean ± SD minimal glucose (mg/dl)	59 ± 19	64 ± 18	62 ± 13	0.658
Median (min-max) % of time BG:				
<70 mg/dl	2.0 (0-44)	0.0 (0-58)	1.0 (0-35)	0.699
>140 mg/dl	18.0 (1-52)	27.0 (2-91)	18.5 (2-95)	0.749
>200 mg/dl	1.0 (1-11)	3.0 (0-40)	2.5 (0-35)	0.168

*Across the 3 treatment groups.

BG=blood glucose, MAGE= Mean amplitude of glycemic excursions during 72 hours based on CGMS.

coexisting diabetes and sleep apnea and their impact on cardiovascular morbidity and mortality.

In a multicenter, open-label study, Li *et al.* from China randomized 60 newly diagnosed Type 2 diabetes patients to receive the rapid-acting insulin secretagogue, repaglinide 1 mg three times daily, or one of the longer-acting sulfonylureas, glimepiride 1 mg once daily or gliclazide 30 mg once daily, each being titrated to a fasting blood glucose (FBG) target of ≤ 126 mg/dl (abstract 17). Glucose concentration was monitored by a CGM system for 72 hours at the end of a 4-week treatment period. The treatment groups were comparable at baseline based on patients' age, BMI, FBG, and HbA1c. After 4 weeks of treatment, mean glucose values during 72 hours were similar in the 3 groups (Table 4). However, mean ampli-

tude of glycemic excursions (MAGE) was significantly lower in repaglinide as compared with glimepiride and gliclazide ($p = 0.006$ and 0.007 , respectively); no difference was found between glimepiride and gliclazide ($p = 0.581$). The same trend was observed in the mean maximal glycemic values ($p = 0.016$, 0.016 , and 0.948 , respectively). Mean minimal glycemic values were similar for the 3 groups, as were the percentages of time during which patients experienced hypoglycemia (<70 mg/dl) and hyperglycemia (>140 and >200 mg/dl). These results suggest that glycemic excursion profiles can vary with different insulin secretagogues despite similar glucose control—differences that can be assessed with CGM. The implications on clinical outcomes from such differences remain unclear.



So Many Posters, So Little Time....



Pandya and US researchers compared glycemic control (i.e., achievement of HbA1c $<7\%$) in patients with Type 2 diabetes who were treated with metformin and pioglitazone, either in combination or sequentially, first with metformin, later augmented with the TZD (abstract 921). A total of 561 adult study patients were identified from the Integrated Healthcare Information Services claims database (01/01/00 to 03/31/07); 213 and 348 were treated with the combination and augmentation approaches, respectively. A significantly higher proportion of patients in the combination therapy group achieved goal HbA1c at all evaluation timepoints between 6 and 24 months (each $p < 0.0001$). According to logistic regression, controlling for age, gender, baseline HbA1c, comor-

bidities, prior resource utilization, and prior medication use, the clinical advantage of combination therapy was greater among patients with baseline HbA1c $>9\%$ (odds ratio [OR] 0.13-0.15; all $p < 0.001$) than among those with baseline HbA1c between 7 and 9% (OR 0.36-0.43; all $p < 0.0025$). These data suggest that the early use of combination oral antihyperglycemic agents may actually result in a long-term clinical benefit over the more traditional sequential, augmentation therapy—especially among patients with higher baseline HbA1c levels. It would be interesting to see if these results could be confirmed by other groups and using other types of combinations.

Spruce *et al.* from the United Kingdom (abstract 1252) carefully measured the force applied

during Semmes-Weinstein 10g monofilament testing, purportedly a reliable method to assess for the presence of peripheral neuropathy. Prior studies, however, had been conducted using automated equipment. Peak force applied by 20 trained individuals was assessed using a research grade strain gauge. Significant differences in both mean and median peak force were found between all subjects ($p = 0.021$). In addition, a highly significant difference was observed between subjects for the total range of peak force ($p = 0.001$). This small study demonstrates that the total range of peak force applied from a monofilament varies significantly between subjects. The clinical reliability of the 10g monofilament may be more unstable than previously thought, once the human variable is factored in.

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