

# Diabetes 2009

From the 69th Annual Scientific Sessions of the American Diabetes Association ■ New Orleans, LA

2005 2006 2007 2008 **2009** 2010 2011

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

Volume **19** ■ June 8, 2009 ■ Issue **4**



## Incretins: Science & Practice



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

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

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

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians.

Yale University School of Medicine designates this continuing medical education activity for a maximum of 11 AMA PRA Category 1 Credits™ (5.5 credit hours per test). Physicians should only claim credit commensurate with the extent of their participation in the activity.

Supported in part through educational grants from Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Amylin Pharmaceuticals, Inc./Eli Lilly and Company, and Boehringer Ingelheim Pharmaceuticals Inc. It is understood that supporters will in no way control the content of this program.

As might be anticipated, the incretin-based therapies were the subject of numerous presentations at the 69th Scientific Sessions including various symposia, oral, and poster presentations. Juris Meier, MD, of Ruhr University, Bochum, Germany moderated the symposium, *Clinical Use of Incretins*, introducing four internationally recognized speakers. The content of the symposium focused on clinical uses of and differences between the various compounds representing the two classes of incretin-based drugs: glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. Additionally, a potentially expanded clinical utility of these agents was addressed.

John Buse, MD, PhD, University of North Carolina, focused his talk on the injectable GLP-1 analogs, presenting recent data and discussing whether there are meaningful differences between the various commercially available agents and those under investigation (Table 1).

He began with a review of these agents' physiologic actions (Figure 1): (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 (through effects on insulin and glucagon); and, (6) promotion of glucose disappearance (through

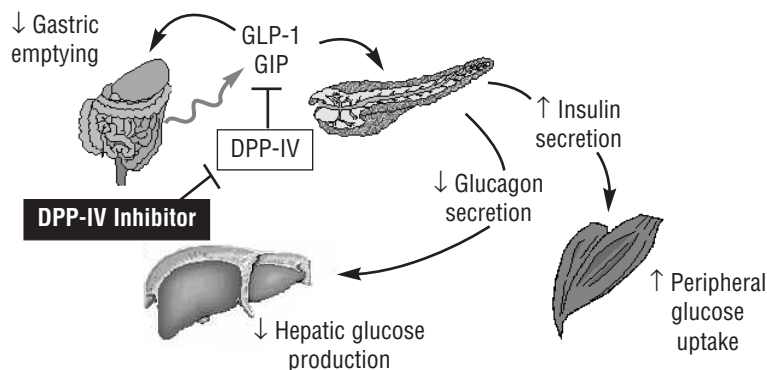
**Table 1. GLP-1 Analogs and Their Development Status in the US**

GLP-1 Agonist	Status
Exenatide—twice daily dosed formulation	Commercially available
Exenatide – weekly formulation	FDA review
Liraglutide	FDA review
Taspoglutide	Phase III
Albiglutide	Phase III

effects on insulin). Clinical trials with exenatide (twice daily formulation) have demonstrated both short-term (6 months) and sustained (3 years) action, resulting in decreased HbA1c and weight loss. Improvement in certain cardiovascular (CV) risk factors (in association with weight loss) has also been observed, including triglycerides (TG), total cholesterol, LDL-cholesterol, HDL-cholesterol, diastolic blood pressure (BP), systolic BP, ALT (as a marker of steatosis), and C-reactive protein (CRP). Common adverse events include nausea, and to a lesser extent vomiting. Antibodies develop in some patients; however, their clinical relevance remains unclear.

The DURATION-1 trial compared twice daily dosed exenatide with a long-acting weekly formulation over a 30-week period. The latter resulted in a greater decrease in HbA1c (1.9% decrease

**Figure 1. Physiology of The Incretin System: Key Regulator of Post-Prandial Glucose Metabolism**



Continued on page 2

## Incretins: Science & Practice

Continued from page 1

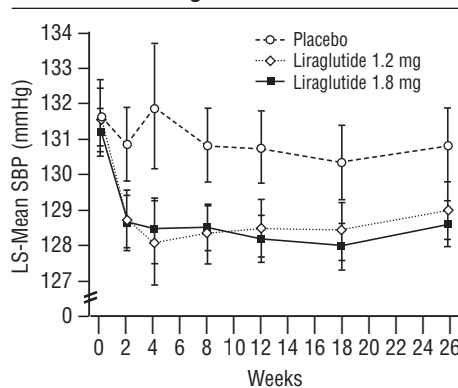
versus -1.5%). This difference was magnified in patients with higher baseline HbA1c values. Weight loss was comparable between groups. The weekly formulation was associated with a greater decrease in fasting plasma glucose (FPG) and increased fasting insulin as well as greater decreases in total and LDL-cholesterol. The weekly compound had a lesser effect on gastric emptying, thus a lower incidence of nausea and, interestingly, less of an impact on postprandial glucose. Weekly exenatide was also associated with a new adverse drug reaction, injection site pruritus, and higher antibody titers.

Similar comparative results were demonstrated in the LEAD trials, which examined liraglutide, dosed daily, compared with the twice daily-dosed exenatide. Although data were not specifically explored with albiglutide and taspoglutide, which are being developed as weekly compounds, Dr. Buse remarked that given their longer duration of activity, these agents will likely mirror the effects of long-acting exenatide and liraglutide.

In summary, the differences between the GLP-1 agonists seem to be favoring the longer-acting agents (ie, impact on HbA1c, FPG, CV risk factors, and improved patient tolerability). One benefit of the twice-daily dosed exenatide, however, may be its greater effect on postprandial glucose. However, Dr. Buse commented that the other benefits of the long-acting agents would likely override that difference.

Several oral and poster presentations during the 2009 ADA Scientific Sessions confirmed this synopsis of the GLP-1 agonists. LEAD-6 was a 26-week randomized trial in which liraglutide was compared to exenatide twice daily in patients on metformin and/or sulfonylurea. Buse and colleagues reported on a 14-week extension study in which exenatide (10 µg twice daily) therapy was converted to liraglutide 1.8 mg daily (abstract 591-P). Patients subsequently experienced a small, but possibly clinically significant, reduction in HbA1c ( $0.32 \pm 0.57$  vs.  $0.06 \pm 0.57$ ,  $p < 0.0001$ ), and those remaining on liraglutide sustained their initial improvement. Significant ( $p < 0.001$ ) improvements also occurred in FPG, weight, and systolic BP. The blood pressure effect was confirmed by Fonseca *et al.*, who completed a meta-analysis of six phase 3 studies involving liraglutide therapy (1.8 mg,  $n=1,363$ ; 1.2 mg,  $n=896$ ; placebo,  $n=524$ ) (abstract 545-P). Using an ANCOVA model, the reduction in systolic BP was 2.6 mm Hg for the 1.8 mg dose ( $p=0.0008$ ) and 2.5 mm Hg for the 1.2 mg dose ( $p=0.0030$ ) (Figure 2).

**Figure 2. Systolic Blood Pressure Effects of Liraglutide vs. Placebo**



Bergental and colleagues from Minnesota and California evaluated whether the improvement in cardiometabolic risk factors is sustainable with long-acting GLP-1 agonists (abstract 165-OR). In an open-label 52-week extension study, once weekly exenatide was assessed for its impact on a number of cardiometabolic risk factors such as BP, LDL-cholesterol, TG, total cholesterol, and ALT. All markers were improved, with the difference from baseline statistically significant ( $p < 0.05$ ) for all except LDL. In patients with abnormal baseline values, all markers improved ( $p < 0.05$ ). Weight loss was mild-moderately correlated ( $r \leq 0.31$ ,  $p < 0.05$ ) with improvements in diastolic BP, LDL, total cholesterol, and ALT, but did not correlate with improvements in systolic BP and triglycerides.

The second speaker of the symposium, Dr. Richard Pratley of the University of Vermont, addressed the oral DPP-4 inhibitors also known as 'incretin enhancers.' These agents prevent the inactivation of endogenous GLP-1 (and GIP [glucose-dependent insulinotropic peptide], the second major incretin). As a result, they also promote glucose-dependent increases in insulin secretion and suppression of glucagon. Only one DPP-4 inhibitor, sitagliptin, is commercially available in the US. The remaining three—alogliptin, saxagliptin and vildagliptin—are in late stages of clinical development. Dr. Pratley first discussed the difference between the DPP-4 inhibitors, then addressed their utility in comparison with the GLP-1 analogs (Table 2).

The four compounds can be categorized by their binding to DPP-4: sitagliptin and alogliptin are non-covalently bound and saxagliptin and vildagliptin, covalently bound. Their comparative pharmacology relates to this property. Sitagliptin and alogliptin have longer half-lives, are eliminated renally, and have greater specificity for DPP-4, whereas saxagliptin and vildagliptin have shorter

half-lives, are eliminated predominantly via hepatic metabolism, and are less specific for DPP-4. As a class, however, the clinical differences between the compounds appear to be minimal. All demonstrate similar efficacy with respect to HbA1c lowering, are generally weight neutral and well tolerated, and have a low risk for both hypoglycemia as well as drug-drug interactions.

When comparing GLP-1 agonists to DPP-4 inhibitors as monotherapy, Dr. Pratley felt that exenatide twice daily and sitagliptin may have comparable efficacy. However, the newer long-acting forms of GLP-1 agonists may provide slightly greater reductions in HbA1c. Although there are limited comparative trials between the two classes, some generalizations can be made: GLP-1 agonists (at least those dosed weekly) appear to have slightly greater glycemic impact, are associated with weight loss, delay gastric emptying, and are only available by injection. The DPP-4 inhibitors have a more favorable tolerability profile, act on both GLP-1 and GIP, are weight neutral and available orally.

In related abstracts this week, Yoon and international co-investigators compared initial combination therapy with a DPP-4 inhibitor plus a thiazolidinedione (TZD) versus TZD monotherapy in drug naïve Type 2 diabetes patients (abstract 522-P). Patients were randomized to sitagliptin 100 mg daily with pioglitazone 30 mg daily versus pioglitazone 30 mg daily for 24 weeks. Not surprisingly, glycemic control parameters were superior in the combination treatment group as compared with TZD alone. Absolute differences between baseline and 24-week values of HbA1c were -2.4% in the combination group versus -1.5% with monotherapy ( $p < 0.001$ ). A greater proportion of patients achieved HbA1c  $< 7\%$  in the combination therapy group (60% vs. 28%,  $p < 0.001$ ). Other parameters such as FPG, insulinogenic index,

**Table 2. Comparison of Incretin-Based Therapies**

	GLP-1 Analogues	DPP-4 Inhibitors
Administration route	Injection	Oral
↑ GLP-1 'levels'	Sustained	Meal-related
HbA1c effect	-1.0%	-0.6 to -0.8%
Effects on body weight	Weight loss	Weight neutral
Side effects	Nausea, vomiting	? urticaria ? pancreatitis
β-cell preservation	?	?

Continued on page 3

## Incretins: Science & Practice

Continued from page 2

and postprandial proinsulin/insulin ratio favored combination therapy.

Vilsboll and co-investigators evaluated sitagliptin as add-on therapy to insulin, with or without metformin, in patients with Type 2 diabetes (abstract 588-P). (We note that this is not currently an FDA-labeled indication.) This 24-week study randomized patients to receive sitagliptin 100 mg daily versus placebo in combination with insulin ± metformin. Patients in the sitagliptin group had a 0.6% decrease in HbA1c compared with no change with placebo ( $p < 0.001$ ) and a greater proportion of patients in the sitagliptin group achieved HbA1c values  $< 7\%$  (although only 12.8% vs. 5.1%,  $p < 0.001$ ). There was an increased incidence of hypoglycemia in the sitagliptin group and no change in body weight with either treatment.

The third presentation in the symposium, delivered by Rodolfo Alejandro, MD, University of Miami, addressed the potential role of exenatide in islet cell transplantation. It was theorized that exenatide might correct ultimate beta-cell failure associated with this procedure. The physiologic

actions of exenatide may result in improved existing islet cell function, the prevention of further loss of islet cell mass, and, perhaps, even the stimulation of islet regeneration. For these reasons, exenatide was administered to 16 recipients of islet cell transplants with allograft dysfunction requiring exogenous insulin. Four of 16 discontinued due to side effects, however, 12 continued with therapy. At the 6-month mark, stable glycemic control was achieved while reducing exogenous insulin requirements. All patients developed nausea and most (15/16) experienced hypoglycemia, primarily postprandial. A total of 7 patients continue to receive exenatide long term (~4 years) and have good islet function. Based on these preliminary (and, we would add, uncontrolled) data, Dr. Alejandro stated that exenatide in combination with immunosuppressant agents may have contributed to long-term islet cell function in his patient population. Clearly, randomized trials are urgently needed in this area.

The final symposium speaker, Dana Andersen, MD, Johns Hopkins University, discussed the CV and metabolic effects associated with the incretin mimetics. He identified unique properties of the incretins, in particular GLP-1 and its active

metabolite, 9-36. GLP-1 may have a potential role in cardiac patients. In patients with acute myocardial infarction, exogenous GLP-1 improved left ventricular ejection fraction and improved wall motion scores when compared to controls (Lazaros *et al*, *Circulation* 2004). In mouse hearts, GLP-1 was administered prior to coronary artery bypass graft surgery and 3 days post-surgery. GLP-1 improved glycemic control and decreased inotrope use (Ban *et al*, *Circulation* 2008). Numerous trials are under way evaluating the role of GLP-1 in surgical and ICU patients, the goal being to maintain euglycemia without increasing the risk of hypoglycemia, given the glucose-dependent nature of these agents' effects.

The incretin-based therapies are now firmly established in the Type 2 diabetes pharmacopeia. More convenient, and perhaps more effective, GLP-1 receptor analogues are in late stages of clinical development. Additional DPP-4 inhibitors are also likely to soon be available. Their precise role in diabetes treatment remains debatable, especially given their high cost and lingering uncertainties regarding long-term effects with any newer drug class.



## The Scoop on 'Closing the Loop'



With continuous glucose monitoring (CGM) now widely available, there is ongoing interest in the clinical impact of this high-tech intervention in patients with diabetes. Current devices typically use a replaceable, subcutaneous filamentous sensor that measures interstitial glucose concentrations every several minutes. These data are communicated to a remote display (or insulin pump), which is typically worn on the belt. There are several obvious advantages to this technology, including real-time information about both hypo- and hyperglycemic excursions, which may be preemptively addressed by the patient. Disadvantages include some degree of imprecision, particularly at the lower ranges of glucose (where greater precision is actually needed!), as well as the devices' semi-invasive nature and high cost. Several presentations were devoted this week to this and related topics.

An entire symposium at this week's sessions covered emerging applications of CGM. Howard Wolpert, MD of the Joslin Diabetes Center delivered the first presentation entitled, *Advances in Technology of CGM*. Dr. Wolpert suggested that glucose monitoring technology is an important driver of diabetes care. As this care has evolved, a major concern identified as far back as 1993 with publication of the landmark Diabetes Control and Complications

Trial (DCCT) results, is that as HbA1c decreases, the risk of hypoglycemia increases. CGM may address this very concern. The results of the Juvenile Diabetes Research Foundation (JDRF) randomized clinical trial to assess the efficacy of real-time CGM validated its clinical utility. However, one rate-limiting step identified in this study is sustaining the use of these devices over time (Figure 3). Simply speaking, "they only work if you wear them!"

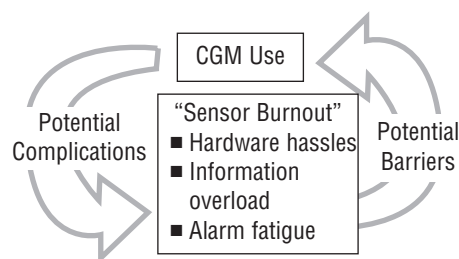
Subsequent analyses from the JDRF and other studies have demonstrated that optimal use of CGM is influenced by cognitive traits and personality style. Executive function is described as capacity to problem solve. This and a coping style of greater self-control and less emotional reactivity favors more positive results with CGM use. Improvements in CGM technology have also been

associated with better adherence. In the first CGM clinical trial (Hirsch *et al*, *Diabetes Technol Therap*, 2008), which utilized a first-generation Medtronic device, only 25% of subjects (age=12-72 years) used the sensor  $> 6$  days/week, whereas 83% of adult subjects in JDRF study, which utilized a second-generation device, consistently used the device with this frequency.

In terms of comparative accuracy between units, studies are conflicting. Koravetch *et al*. (*Diabetes Care*, 2008) compared four devices, reporting that the Dexcom®, Guardian®, Navigator®, and Glucoday® are equally accurate in euglycemia, whereas accuracy in the hypoglycemic range appeared to be greater with the latter two devices. In contrast, Dexcom® was found to have improved accuracy as compared to Navigator® in a subsequent study (Garg *et al*, *Diabetes Technol Therap*, 2009). Dr. Wolpert identified flaws with each study, noting that numerous variables in a CGM study make developing standardized methodology quite difficult.

Another important and recent improvement in CGM technology relates to enhanced alarm functionality. Patients are now able to set different alarm thresholds based on time of day as well as activate an alarm 'snooze' function. Technology to facilitate adoption in clinical care, involving intricate patient education programs, has also evolved.

Figure 3. Challenge in Sustaining CGM Use



Continued on page 4

## The Scoop on 'Closing the Loop'

Continued from page 3

Dr. Wolpert shared the Joslin's patient education website, which is a portal for patients to learn about CGM on-line with very descriptive graphs along with quizzes for patients and live classes.

Irl Hirsch, MD, University of Washington, followed with an update on recent clinical trials. Despite the disappointing results (no difference in HbA1c values) of the first randomized controlled trial assessing outcomes of CGM (Hirsch *et al.*, *Diabetes Technol Therap*, 2008), important lessons were learned. Primarily, and as mentioned above, CGM compliance significantly impacts HbA1c outcomes. Better selection of candidates is critical for CGM to be successful. Results from the JDRF study revealed that there is a significant decrease in HbA1c in patients aged 25 years and older, whereas, improvements in HbA1c were not significant in the 8-14 and 15-24 year old groups. Predictors of success includes baseline HbA1c >7% and compliance of at least 6 days per week. Dr. Hirsch concluded his lecture by proposing that further research is needed on optimizing CGM use, especially as it relates to behavioral issues.

The third lecturer, William Polonsky, PhD, CDE, University of California, San Diego, identified the psychosocial aspects influencing CGM. Behavioral issues clearly impact success: How frequently is the sensor worn? When it is worn? What do patients do with the data? Lack of consistent use may be due to cost, aggravation, and the need for a "diabetes vacation."

There are several perceived benefits of CGM from the patient's perspective. For some patients, CGM provides peace of mind given the decreased fear of hypoglycemia and increased confidence during the day, especially during social events or at work. Patients may simply feel more in control of their diabetes.

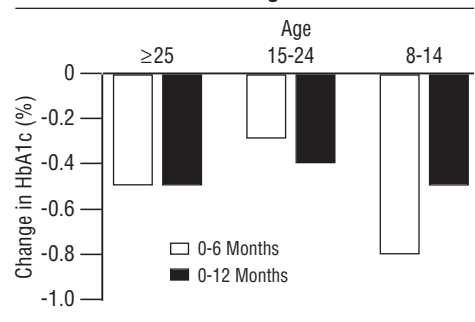
There are also several perceived disadvantages. For example, patients often cite the following reasons for discontinuing use of CGM: (1) cost; (2) adhesive problems; (3) bulkiness of the device; and (4) 'alarm fatigue.' Optimal patient selection is key. Favorable characteristics include patients with: appropriate expectations (it is not a cure and perfect blood glucose is not possible);

an engineering or scientific background (those with high level numeracy skills and problem-solving ability); and somewhat obsessive nature. Unfavorable characteristics include: teenage years, especially those without effective support; innumeracy; and 'hyperglycemia fear syndrome.' Dr. Polonsky concluded his presentation describing the most critical psychosocial issues to be: confidence, perceived treatment efficacy, and trust/mistrust of the device.

In a separate oral abstract presentation, Bode and US colleagues provided the results of a 12-month analysis on the impact of CGM on HbA1c values in patients with Type 1 diabetes whose baseline HbA1c values were  $\geq 7.0\%$  (abstract 204-OR). This group of researchers had previously demonstrated a mean fall in HbA1c of  $\geq 0.5\%$  in 3 different age groups in subjects using CGM for 6 months. The investigation was continued for an additional 6 months to determine if the impact on HbA1c is sustainable. At the end of one year, the change in HbA1c from baseline remained statistically significant ( $p < 0.05$ ), regardless of age group (Figure 4). The researchers concluded that CGM may have long-term beneficial effects on glycemic control.

In a multicenter, controlled, 132 patient trial, Raccach and French investigators randomized patients with HbA1c values  $\geq 8\%$  previously receiving multiple insulin injections to insulin pump therapy with glucose monitored via self-monitored blood glucose (SMBG) or by CGM (Paradigm REAL Time System) (abstract 205-OR). Change in HbA1c was the primary outcome studied, with secondary endpoints of hypo- and hyperglycemic measures. When analyzing the entire population, each group achieved a statistically significant decline in HbA1c (CGM:  $-0.81\%$ ; SMBG:  $-0.57\%$ ,  $p = 0.087$ ), with no difference between groups. However, when evaluating the per-protocol participants (those wearing sensors >70% of time), there was a significant difference in HbA1c reduction in the CGM group ( $-0.96\%$  vs.  $-0.55\%$ ,  $p = 0.004$ ). Additionally, the decrease in hyperglycemia parameters was proportional to the HbA1c reduction in the CGM group, without an increase in hypoglycemia. Based on this analysis, it would appear that pump patients using CGM consistently experience a greater impact on HbA1c than with routine monitoring.

Figure 4. HbA1c by Age in Type 1 Patients Using CGM



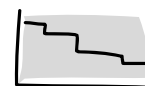
In a very preliminary investigation, Hovorka and international colleagues evaluated 17 pediatric patients with Type 1 diabetes utilizing 33 nights with a 'closed loop' delivery system and 21 nights of CSII (abstract 206-OR). 'Closed loop' here refers to active communication between a CGM device and an insulin pump, with automated and ongoing adjustments to the insulin infusion guided by the sensor output. Three separate studies were conducted: (1) closed loop vs. CSII in the setting of self-selected meals and prandial insulin; (2) closed loop after large slowly and rapidly absorbed meals and prandial insulin; and (3) closed loop vs. CSII following exercise. In general, patients in the closed loop groups versus CSII demonstrated an increased time in target glucose range (77% vs. 40%,  $p = 0.007$ ) and decreased risk of hypoglycemia (6.1% vs. 28%,  $p = 0.002$ ).

In a related study, equally preliminary, Castle and co-investigators from Oregon examined the utility of providing automated glucagon delivery in response to glucose decline during closed loop glycemic control in Type 1 patients as a method to minimize hypoglycemia (abstract 207-OR). Their findings suggested some benefit from this dual infusion on preventing hypoglycemia in the late postprandial period.

These are all encouraging findings. The benefits of CGM in selected patients are being clarified. Optimizing CGM use, however, remains an ongoing challenge. The closed loop devices will clearly need much further study before they will be ready for clinical implementation.



## Hypoglycemia: Clinical Impact & Prevention



Last year, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was ended prematurely when routine safety monitoring detected an excess of sudden deaths (257 vs. 203) in the intensively treated group, HbA1c goal of <6.0%,

relative to the standard group whose HbA1c goal was 7.0 to 7.9%. In this study of over 10,000 subjects with Type 2 diabetes, 20% of subjects in the intensively treated group had episodes of severe hypoglycemia. In comparison, the intensively treated

group in the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) trial, which had less aggressive treatment targets, had fewer severe hypoglycemic episodes, and did not demonstrate any difference in cardiac

Continued on page 5

## **Hypoglycemia: Clinical Impact & Prevention** *Continued from page 4*

deaths relative to the standard treatment groups. In this context, a symposium conducted this week was dedicated to addressing the clinical impact of hypoglycemia and its relationship to mortality.

**Phil Cryer**, MD of Washington University emphasized that iatrogenic hypoglycemia remains the limiting factor in achieving tight glycemic control. Hypoglycemia is relatively infrequent in the early course of Type 2 diabetes, even when managed with insulin. However, as endogenous insulin secretion decreases over the natural history of Type 2 diabetes, the frequency of hypoglycemia increases, approaching the rates of hypoglycemia found in individuals with Type 1 disease. He added that 6 to 10% of sudden death in Type 1 diabetes is probably due to hypoglycemia, and he feels that hypoglycemia was most likely the cause of excess mortality in the intensively treated Type 2 group in ACCORD.

**Simon Heller**, MD from Sheffield, UK addressed whether diabetic autonomic neuropathy (DAN) contributes to the morbidity and mortality of hypoglycemia. Multiple studies have shown an increased risk of sudden death related to hypoglycemia in patients with Type 1 diabetes. However, in most of these investigations, there was no attempt to separate the presence of DAN from the effects of glycemic control, duration of diabetes, and antecedent hypoglycemia on mortality. DAN is associated with decreased counter-regulatory responses to hypoglycemia. It may also be associated with abnormal cardiac repolarization and increased mortality. For instance, QT intervals are longer in those with Type 1 vs. Type 2 diabetes, as compared to non-diabetic peers. Although prolonged QT interval is a predictor of sudden death in the general population, in the setting of experimental hypoglycemia, DAN does not appear to cause additional QT prolongation. The risk of increased

mortality in hypoglycemia may be attributed to other factors such as age and duration of diabetes.

**Rory Freeman**, MD, a neurologist from Boston, expanded on the potential mechanisms of hypoglycemia-related arrhythmias in diabetes. He re-iterated the association of autonomic neuropathy with increased cardiac mortality, quoting the Steno Study. In this trial, heart rate variability was an independent risk factor predicting CV morbidity and mortality in Type 1 patients with nephropathy. He also proposed alterations to the familiar concept of hypoglycemia associated autonomic failure. Since hypoglycemia is a profound stress, it induces a multi-faceted response to restore homeostasis. In the time period following an episode of hypoglycemia multiple changes occur, including attenuation of CV autonomic function with impairment of cardiac vagal baroreflex sensitivity. The baroreflex serves to maintain blood pressure within an optimal range.

In a related poster presentation, **Rana *et al.*** from Dorset, Great Britain investigated a potential mechanism for how hypoglycemia may contribute to CV mortality, namely hypoglycemia-induced reduction in cardiac blood flow reserve (abstract 634-P). They measured myocardial blood flow (MBF) in 19 healthy, non-diabetic volunteers at baseline, during a hyperinsulinemic euglycemic clamp, and during a hyperinsulinemic hypoglycemic clamp. MBF was measured using myocardial contrast echocardiography at rest and after induced stress from dipyridamole administration. They demonstrated that hypoglycemia caused a higher resting blood flow but lower stress blood flow than at baseline. This indicates that the myocardium requires more blood in the setting of hypoglycemia but may be less capable of coping with any additional imposed stress. In the setting of underlying coronary artery disease, any reduction in blood flow may lead to significant ischemia and, potentially, arrhythmia and myocardial damage.

The final symposium speaker, **Carmine Fanelli**, MD, PhD of the University of Perugia, Italy described approaches for preventing hypoglycemia in diabetes. He noted the importance of individualized glycemic targets, with less stringent HbA1c goals for patients with a history of severe hypoglycemia. Routine glucose monitoring is necessary to identify the frequency of hypoglycemia. For instance, CGM has been useful in revealing the frequency and duration of nocturnal hypoglycemia. In a study using CGM, it was demonstrated that 33% of patients with insulin-treated diabetes had nocturnal hypoglycemia, occurring for a mean of 78 minutes.

Another preventative measure to consider is the use of rapid-acting insulin analogues to avoid hypoglycemia between meals, since they better mimic physiological insulin secretion with a shorter onset and duration of action. Dr. Fanelli also recommended vigilance in adjusting insulin and sulfonylurea dosing as renal function declines. The use of sulfonylureas also requires specific caution in the elderly or when individuals have reduced caloric intake. He suggested that DPP-4 inhibitors may be a good substitute for traditional insulin secretagogues, since they have a reasonably similar glucose-lowering potential but without the risk of hypoglycemia.

In conclusion, he mentioned novel approaches to improve defenses to hypoglycemia, including improved counter-regulation and reduction of hypoglycemia unawareness. For instance, terbutaline has been used to prevent nocturnal hypoglycemia. However, further studies are needed to establish efficacy and safety of this and other similar agents in this setting, particularly given the CV impact of beta-adrenergic agonists.

The link between hypoglycemia and cardiac mortality in ACCORD remains theoretical. The data discussed at this week's ADA Scientific Sessions, however, lend greater importance to the deleterious effects of hypoglycemia on the CV system.



## **Putting the "D" in Diabetes**



**Vitamin D** seems to have become the most recent hit sensation in medicine, with a pervasive media presence, similar to vitamin C many years ago. The role of vitamin D has evolved from just a means to prevent rickets to a potential player in many disease processes, including multiple sclerosis, cancer, and diabetes. It is distinguished by its impact on many cellular activities as the agonist for an important nuclear receptor, with links to phenomena that are still not entirely understood.

**Stella Volpe**, PhD, RD from the University of Pennsylvania opened a symposium on vitamin

D and diabetes with an introduction to vitamin D structure, function, and therapeutic dosing. A fat-soluble vitamin, 25-vitamin D is now considered a prohormone since it is converted to its active hormone state, 1,25-vitamin D (Figure 5). 1,25 vitamin D binds to the vitamin D receptor (VDR) located in the cell nuclei of most organs, transforming it into a transcription factor that modulates expression of many genes.

**Anastassios Pittas**, MD of Tufts University examined the evidence for any potential link between vitamin D and Type 2 diabetes. He stated there

are plausible mechanisms for how vitamin D may affect both pancreatic beta cell function as well as insulin sensitivity in peripheral cells. He reviewed the observational studies that may suggest a role in diabetes prevention, namely, in the NHANES database, 25-vitamin D levels were inversely associated with the metabolic syndrome. In another sub-analysis within the Nurses Health Study, a 20% risk reduction of Type 2 diabetes was shown in those women who self-reported vitamin D supplementation. However, this risk reduction was not statistically significant when

*Continued on page 6*

## Putting the "D" in Diabetes Continued from page 5

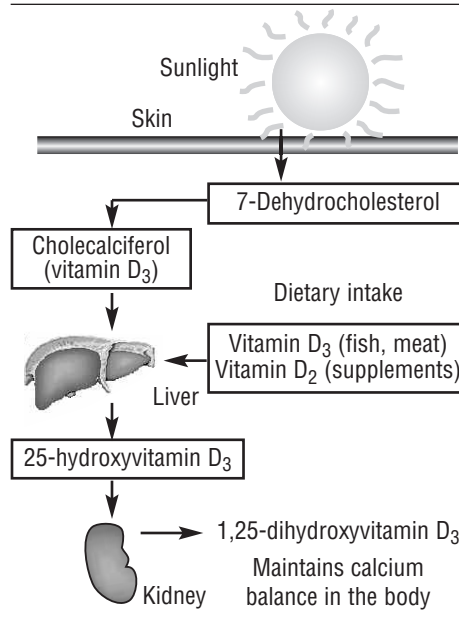
corrected for calcium intake. Also, there was no difference between vitamin D<sub>3</sub> supplementation and placebo on diabetes incidence in a post-hoc analysis of the Women's Health Initiative Trial.

Dr. Pittas admitted the difficulty of confounders in observational or case cohort studies, and stated the need for randomized, controlled trials to test the hypothesis raised by these studies. Since many factors affect vitamin D, including age and sunlight exposure, it is challenging to prove that vitamin D is not just a marker of general health status. The Vitamin D and Omega-3 (VITAL) trial is proposed to include 20,000 healthy older men and women randomized to either vitamin D<sub>3</sub> or placebo, with evaluation of diabetes and CV outcomes as endpoints.

For Type 1 diabetes, the evidence for a link with vitamin D is somewhat stronger. Elina Hyponnen, PhD, from the UK is an epidemiologist who spoke about the animal experiments, human case control studies, and genetic analysis that to date have suggested causation. Vitamin D is known to have immunomodulatory properties, which may play a protective role in the autoimmune dysregulation that occurs in Type 1 diabetes. It is well known that the incidence of Type 1 diabetes is lowest in countries closer to the equator where there is a high exposure to sunlight.

Various studies in the non-obese diabetic (NOD) mouse suggest that vitamin D supplementation offers protection from the development of Type 1 diabetes. However, this protection occurred at very high doses of vitamin D—in a range sure to cause hypercalcemia in humans. Nevertheless, Dr. Hyponnen quoted four different human case

**Figure 5. Overview of Vitamin D Metabolism**



control studies that suggested a protective effect in man. The most recent of these was EURODIAB Substudy 2, published in 1999, which showed vitamin D supplementation in infancy was associated with a 30% reduction (95% CI, 14-47%) in Type 1 diabetes. Even adjustment for possible confounders did not alter the significance of this finding.

The largest of the studies was the Northern Finland Birth Cohort of 1966, which enrolled all pregnant mothers (n=12,058) in the two most northern provinces of Finland with an expected delivery date in 1966. The study was designed to

look at the incidence of rickets in the offspring of women given nutritional information on vitamin D supplementation to their infants. Data was collected in the first year of life about frequency and dose of vitamin D. The incidence of Type 1 diabetes was then determined through 1997, representing 30 years from birth. Of the 10,366 babies receiving follow-up, 81 were diagnosed with Type 1 diabetes. Vitamin D supplementation in infancy was associated with a decreased incidence of diabetes, and this association was strongest when the dosing of vitamin D was taken into account. The analysis was adjusted for neonatal, anthropometric, and social characteristics. Children who regularly took the recommended dose of vitamin D (2,000 IU daily) had a relative risk (RR) for diabetes of 0.22 (95% CI 0.05-0.89) (ie, 78% reduced risk) compared with those who received less than the recommended amount. Moreover, children suspected of having rickets in the first year of life had a 3-fold higher risk (RR of 3.0, 95% CI 1.0-9.0) compared to the remainder of the cohort.

Finally, Dr. Hyponnen discussed two genes, CYP2R1 and CYP27B1, that play a role in vitamin D metabolism. Variants of both these genes were found at increased rates in separate cohorts with vitamin D deficiency or Type 1 diabetes. This may provide a genetic basis for the proposed link between vitamin D deficiency and Type 1 diabetes.

While these data are of significant interest, particularly in light of the veritable epidemic of vitamin D deficiency reported in multiple recent surveys, we need to await the results of randomized clinical trials. Until these data are available, it makes sense to ensure adequate vitamin D levels in our patients with diabetes.

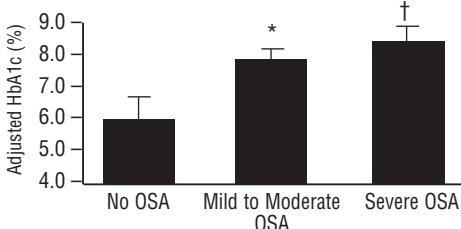


## So Many Posters, So Little Time....



Aronsohn *et al.* from Chicago assessed the prevalence of obstructive sleep apnea (OSA)

**Figure 6. Impact of Obstructive Sleep Apnea on Glycemic Control in Type 2 Diabetes Patients**



\*p=0.017, mild to moderate OSA compared to no OSA.  
†p=0.004, severe OSA compared to no OSA.  
OSA=obstructive sleep apnea.

and its impact on glycemic control in 54 patients with Type 2 diabetes (mean age=58 years, 46% male, BMI=33.7 kg/m<sup>2</sup>, mean total sleep time=6.6 hours) (abstract 684-P). Overnight polysomnography was used to assess OSA (defined as apnea-hypopnea index [AHI]≥5, ie, ≥5 obstructive respiratory events per hour of sleep) and its severity (mild:5≤AHI<15; moderate:15≤AHI<30; severe:AHI≥30). The majority (47, 87%) of study patients had OSA (mild 24%, moderate 35%, severe 28%). Notably, increasing severity of OSA was associated with poorer glucose control, after controlling for potential confounding factors

(ie, age, gender, race, BMI, insulin use, years of diabetes, and sleep time) (Figure 6). HbA1c was independently associated with markers of OSA severity, including number of obstructive events (p=0.013) and oxygen desaturations (p=0.014) during rapid eye movement (REM) sleep. These findings suggest that treatment of OSA may improve glucose control. The investigators estimated that the effect size of such an intervention would be comparable to that of commonly used oral anti-hyperglycemic agents. We would caution that randomized trials will be needed before we can speculate to this degree.

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

Editors, Yale University,  
New Haven, Connecticut