

Diabetes 2008

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

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After Metformin, What?



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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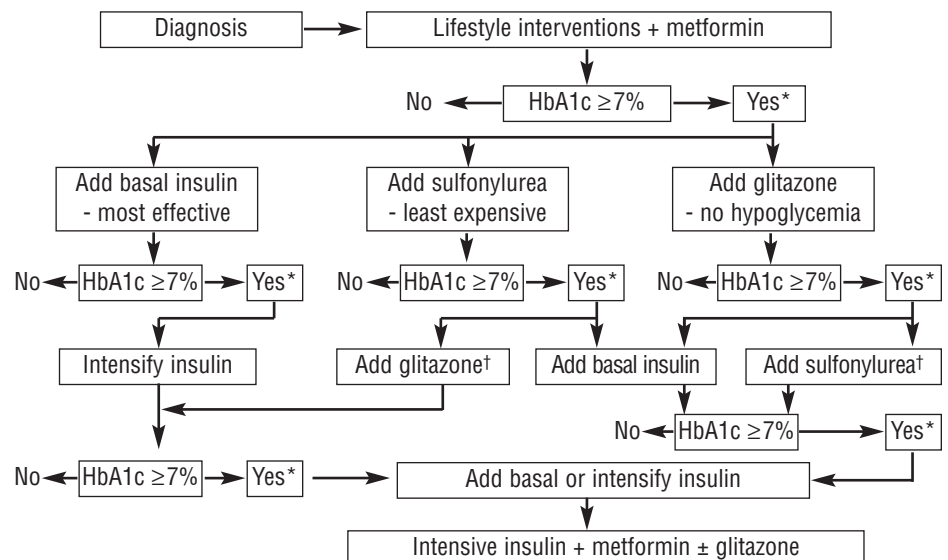
In 2006, the ADA and EASD proposed a general hyperglycemia treatment algorithm for patients with Type 2 diabetes (Figure 1). The two most important recommendations of this consensus statement were: (1) initial therapy with both lifestyle interventions and metformin for newly diagnosed patients, and (2) a relatively rapid progression to combination therapy, including the early use of insulin if glycemic targets are not reached. The ‘second line’ agents in this algorithm are sulfonylureas (SUs), thiazolidinediones (TZDs), and insulin. In the last two years, there has been a surge of new information and controversy regarding some of these medications. While much of the attention has focused on side effects of TZDs, several recent large clinical trials—ACCORD, ADVANCE, and VADT—have raised questions as to the risks and benefits of all agents, especially when used in combination to achieve aggressive targets. In a symposium moderated by Drs. Rury Holt (UK) & Michael Stumvoll (Germany), the pros and cons of each option were addressed within the context

of the important “after metformin, what?” question. Position statements were heard from four speakers, each defending one of the following: SUs (and glinides), TZDs, insulin, and incretin-based drugs.

Insulin Secretagogues

Dr. Leif Groop from Sweden initiated the symposium by recommending SUs (or glinides) as the optimal second-line agents. The use and safety profile of these drugs have been well documented since 1948. He noted that the SUs have shown effectiveness, durability, and a predictable side effect profile. Their mode of action directly addresses the decline of β -cell function, which is a critical aspect to the natural history of Type 2 diabetes. In addition, SUs remain up to 10 times cheaper than other second-line agents. With regard to side effects, Dr. Groop observed that the combination of metformin and SUs entails considerably less weight gain than combination with insulin. Although hypoglycemia does occur, it's usually mild; episodes of severe hypoglycemia occur less frequently than

Figure 1. ADA / EASD Treatment Algorithm for the Management of Type 2 Diabetes



* Check HbA1c every 3 months until < 7% and then at least every 6 months.

† Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

Adapted from: Nathan DM et al. *Diabetes Care* 2006;29:1963.

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After Metformin, What?

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with insulin as well. In endorsing an SU to be added to metformin as second-line therapy, Dr. Groop advised the audience to take the most cost-effective approach.

TZDs

In his support of TZDs, Dr. Richard Nesto from the US noted that this drug class has been shown to change the natural history of diabetes, since these insulin sensitizers improve pancreatic β -cell function over time. In terms of cardiovascular (CV) protection, he noted that TZDs are the only anti-hyperglycemic drug class that raises HDL-cholesterol. Specifically, pioglitazone's effects on overall lipid composition may be underestimated, and may actually be more important to improving CV outcomes (as suggested by the PROactive trial) than its effect of lowering glucose. Effects on direct measures of atherosclerosis have also been demonstrated, and Dr. Nesto will soon be presenting data on rosiglitazone's effect on the progression of coronary atherosclerosis by intravascular ultrasound from the APPROACH trial. While he acknowledged the recent controversy surrounding TZDs, particularly with rosiglitazone, he soundly criticized the 2007 meta-analysis by Nissen & Wolski (*N Engl J Med* 2007;356:2457) which suggested a deleterious effect on CV events from this drug. It was emphasized that several large, randomized trials—which specifically focused on CV outcomes—have failed to show any negative effect from rosiglitazone on CV mortality: RECORD, ADOPT, DREAM, VADT, ACCORD, & VICTORY. However, while the TZDs probably do not negatively effect CV mortality, neither do they positively effect CV mortality.

Dr. Nesto also acknowledged that TZDs do increase the risk of heart failure (HF), although not HF mortality. He noted that the majority of trials showing an increased risk of HF used forced titration of the TZD, usually into a high-dose range. However, at low or moderate doses of TZDs, the risk of edema is cut in half, and the risk of HF is low. In patients without a history of CV disease, the annual incidence of HF is only 1 per 300 to 600 patients treated—much less than the incidence of hypoglycemia with insulin.

Dr. Nesto also pointed out that the effects of TZDs on body weight can be attenuated in combination with metformin. This pairing may have enhanced cardioprotective effects. He reminded the audience that the combination of metformin plus a SU was actually associated with increased mortality rate in the UKPDS. Importantly, TZDs not only have the most durable effect on glycemic control over time, but are also not associated with hypoglycemia and are generally well tolerated by patients—important issues when increasingly complex medical regimens are being used.

Insulin

Dr. Hannele Yki-Jarvinen from Finland next assessed the advantages and disadvantages of insulin as a second-line therapy following metformin. In comparison to oral agents, insulin has the benefit of no upper limit to dosing, and it is, in the end, the most effective agent to reduce HbA1c. For these reasons, most treat-to-target trials include insulin as a therapeutic component. The mean insulin dose involved in these studies is ~60 units when used in combination with oral agents; its effectiveness is in part based on how aggressively the dose is actually titrated. Also, multiple trials have shown a decreased incidence or less progression of both microvascular and macrovascular complications when insulin is used in Type 2 diabetes. Intensive therapy with SUs or insulin in the UKPDS, for example, showed clear benefits on renal and retinal outcomes, and a 16% decrease in myocardial infarction (MI), although this effect only trended toward significance ($p=0.053$). In the DIGAMI study, CV mortality was decreased by 29% in post-acute MI patients assigned to intensive insulin therapy.

Dr. Yki-Jarvinen did share her concern over recent trials involving insulin. For example, in the ACCORD trial, there was a mean 2.1 kg weight gain, a 3-fold increased risk of hypoglycemia, and a 22% increased risk of CV death ($p=0.04$) in those patients assigned to the intensively treated group, the majority of whom did receive insulin. In reviewing the benefits and side effects of basal versus prandial insulin, she noted that the use of multiple injections of insulin is associated with overall better control,

but also more weight gain and hypoglycemia. In her conclusion, while endorsing insulin as the best second-line agent, Dr. Yki-Jarvinen emphasized that we need better solutions for Type 2 diabetes patients, especially in targeting lifestyle changes.

Incretin-Based Therapy

Finally, Dr. Michael Nauck of Germany discussed how incretin-based therapy, including glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, might emerge as optimal second-line drugs. Among the many effects of incretins (see article below), there is evidence that GLP-1 agonists promote β -cell neogenesis from islet cell precursors as well as replication from mature β -cells. This effect, while not yet confirmed in humans, might alter the progression of Type 2 diabetes. GLP-1 agonists decrease HbA1c by up to 1.0%, and consistently result in decreased body weight of approximately 3 kg during long-term therapy. Nausea and vomiting is the most common side effects, although Dr. Nauck observed that very few people discontinue therapy for this reason. Other side effects, such as hypoglycemia, are uncommon. He noted that DPP-4 inhibitors, generally regarded as weaker anti-hyperglycemic agents, appear in some studies to be as potent in decreasing HbA1c as SUs, but with no weight gain or hypoglycemia. With regard to the recent FDA reports of a small number of cases of hemorrhagic pancreatitis in patients taking exenatide, Dr. Nauck commented that there is no clear excess of incident pancreatitis in this group, as compared with the general obese, diabetic population. Clearly, ongoing analysis of this potential side effect will be needed.

Each of the speakers recognized that none of the therapeutic options beyond metformin is perfect. The challenge is to tailor an optimal therapy for a specific patient. We would add that the pharmacological reduction in HbA1c for our patients with Type 2 diabetes should always be undertaken gradually, while attempting to minimize side effects and maximize safety. The ADA and EASD are currently revising their treatment algorithm, in light of more extensive experience with newer agents as well as the results of recent clinical trials.



Enhancing Incretins



The DPP-4 inhibitors, also known as 'incretin enhancers', are relatively new anti-hyperglycemic agents for Type 2 diabetes. They prevent the normal inactivation of the endogenous incretin hormones, GLP-1 and glucose-dependent insulinotropic peptide

(GIP). These peptides, released in response to meals, maintain glucose homeostasis through a number of mechanisms including the stimulation of insulin synthesis and release from pancreatic β -cells. GLP-1 (but not GIP) also decreases glucagon secretion,

slows gastric emptying, and enhances satiety, thereby limiting food intake. Numerous presentations were devoted to DPP-4 inhibitors this week, both those currently available and those still under investigation.

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Enhancing Incretins

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Qi and US colleagues reported 2-year data with sitagliptin (available in the US since 2006), as monotherapy and in combination with metformin (abstract 73). Of 1,091 patients receiving active therapy in an initial 54-week trial, 511 extended their participation for an additional 54 weeks, 402 of which were eligible for analysis (meaning at least 1 measurement in the extension period). Measures of glycemic control including mean HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) remained durable over the 2-year mark across all treatment categories (Table 1). Based on the results of this investigation, this prototypical DPP-4 inhibitor appears to maintain a durable glycemic response over at least 2 years both as monotherapy or when added to metformin. Whether such durability will extend further is not yet known, although preclinical experiments do suggest, at least in animal models, a possible beneficial effect on β -cell mass and function.

Saxagliptin, still investigational, was evaluated in combination with a number of oral therapies. Chen and international researchers investigated initial therapy in combination with metformin in drug naïve Type 2 diabetes patients (abstract 78). A total of 1,306 patients were randomized to 1 of 4 treatments in this 24-week, double-blind study: (1) saxagliptin 5 mg + metformin; (2) saxagliptin 10 mg + metformin; (3) saxagliptin 10 mg, and (4) metformin. Metformin was titrated in 500 mg increments based on FPG to a maximum dose of 2,000 mg daily. Statistically significant reductions in HbA1c, FPG, and PPG from baseline were observed in the combination treatment groups when compared with either monotherapy. The percentage of patients achieving HbA1c <7.0% was 60.3% in the saxagliptin 5 mg + metformin group ($p < 0.0001$ vs. each monotherapy), 59.7% in the saxagliptin 10 mg + metformin group

Table 2. Saxagliptin versus Placebo in Combination with a TZD for 24 weeks

	Saxagliptin 2.5 mg + TZD* (n=193)	Saxagliptin 5 mg + TZD* (n=185)	Placebo + TZD* (n=181)
Mean change in HbA1c from baseline (%)	-0.66, $p=0.0007^\dagger$	-0.94, $p < 0.0001^\dagger$	-0.30
Mean change in FPG from baseline (mg/dl)	-14.3, $p=0.0053^\dagger$	-17.3, $p=0.0005^\dagger$	-2.8
Patients achieving target HbA1c < 7%	42.2%, $p=0.001^\dagger$	41.8%, $p=0.0013^\dagger$	25.6%

*pioglitazone 30-45 mg or rosiglitazone 4-8 mg daily.

† versus placebo.

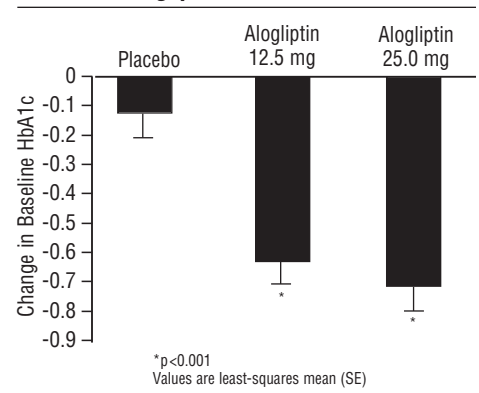
FPG=fasting plasma glucose, TZD=thiazolidinedione.

($p < 0.0001$) versus 32.2% and 41.1% in the saxagliptin and metformin monotherapy groups, respectively. Rates of adverse events were similar over all treatment assignments.

Similar results were reported in other combination therapy trials with saxagliptin. Ravichandran *et al.* from the US, Brazil, and Philippines added the DPP-4 inhibitor to 7.5 mg/day of glyburide (abstract 858). Allen and co-investigators from the US added saxagliptin to varying doses of a TZD (see Table 2) (abstract 859). In both studies, the combination appeared to be well tolerated and did not increase the risk of hypoglycemia.

Lastly, the efficacy and safety of the investigational alogliptin was studied in a number of trials both as monotherapy and in combination with other diabetes therapies. Mekki *et al.* from the US assessed 12.5 and 25 mg doses in a 26-week, placebo-controlled trial in 329 patients with Type 2 diabetes inadequately controlled on diet and exercise (abstract 862). Mean changes in HbA1c and FPG from baseline were significantly greater (all $p < 0.001$) in the alogliptin groups when compared with placebo. Similarly, the percent of patients achieving goal HbA1c (47%, $p=0.001$ [12.5 mg dose] and 44%, $p=0.008$ [25 mg dose]) were greater at week 26 when compared

Figure 2. Mean Change from Baseline HbA1c at Week 26 with Placebo or Alogliptin in Insulin-Treated Patients



with placebo (23%). The incidence of hypoglycemia was similar across all groups and overall, quite low (1.5 to 3.0%).

Rendall and American colleagues shared results of a 26-week study evaluating the addition of alogliptin to insulin regimens (abstract 77). Patients taking metformin (59%, mean dose=1,733 mg/day) continued the oral agent with no change in dose. As with previous studies, alogliptin 12.5 mg or 25 mg daily improved glycemic control when compared with placebo as measured by mean change in HbA1c from baseline ($p < 0.001$) (Figure 2). These results were achieved independent of age, BMI, ethnicity, and presence/absence of background therapy with metformin. The incidence of severe hypoglycemia was very low and similar across all groups (0 to 1.6%).

Similar results were reported by Fleck *et al.* (abstract 76) and Ellis *et al.* (abstract 861) with alogliptin added to glyburide and metformin, respectively.

In addition to the currently available sitagliptin, there may soon be 2 to 3 additional DPP-4 inhibitors on the market. Each of these agents appears to be modestly effective in lowering HbA1c as monotherapy as well as in combination

Table 1. Long-Term (2-Year) Glycemic Response of Sitagliptin

	Sitagliptin 100 mg + metformin 2,000 mg (n=105)	Sitagliptin 100 mg + metformin 1,000 mg (n=96)	Metformin 2,000 mg (n=87)	Metformin 1,000 mg (n=64)	Sitagliptin 100 mg (n=50)
Mean change in HbA1c from baseline (%)	-1.7	-1.5	-1.7	-1.4	-1.4
% of patients with HbA1c <7%	60	45	45	28	32
Mean change in FPG from baseline (mg/dl)	-57.6	-50.4	-43.2	-41.4	-27.0
Mean change in 2-h PPG from baseline (mg/dl)	-109.8	-95.4	-86.4	-72.0	-73.8

FPG=fasting plasma glucose, 2-h PPG=2h post-prandial glucose.

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Enhancing Incretins

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with other anti-hyperglycemic agents. To date, however, no DPP-4 inhibitor appears to be strikingly

different on the basis of efficacy parameters. Importantly, while these drugs appear to be safe in the short-term, there are still no long-term

safety data available. As a result, their specific role in an increasingly varied Type 2 diabetes therapeutic armamentarium remains unclear.



Hyperglycemia in the Hospital



There has been much attention of late on the control of blood glucose in the hospital setting. Hyperglycemia is correlated with adverse clinical outcomes in a variety of inpatient settings, from the ICU to the CCU to the general medical-surgical ward. What is less clear is whether aggressive strategies to intensively control blood glucose will improve these outcomes. To date, the data have been somewhat conflicting.

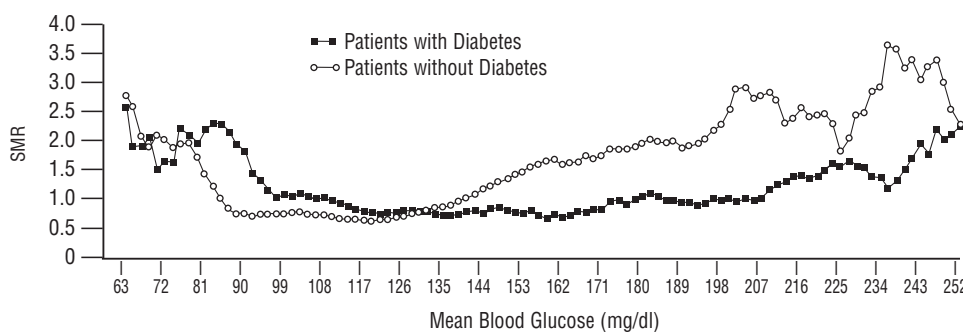
Juneja and American collaborators analyzed data from the Systemic Utilization of Glucose Assessment and Response (SUGAR) program, which was implemented at two academic centers (abstract 1085). This process improvement project focused on tight inpatient glucose control that incorporated computerized insulin ordering and electronic glycemic data collection. The investigators focused on the relationship between mean blood glucose (BG) and in-hospital mortality for patients with and without known diabetes. The primary outcome was a standardized mortality ratio (SMR), calculated with the actual mortality rate divided by the expected mortality rate from an accepted benchmark. More than 36,000 patient encounters (10,988 with and 25,416 without preexisting diabetes) were examined. The results are seen in Figure 3). The investigators concluded that patients without known diabetes appear to derive maximum benefit when their mean BG is between 90 and 130 mg/dl, and there was a pronounced trend toward increased mortality when mean BG was above or below this range. In contrast, diabetic patients appear to derive maximum benefit when mean BG is between 100 and 180 mg/dl. Increased mortality was also noted above or below this range, although hyperglycemia in this group seemed to be better “tolerated” than in the non-diabetic patients. We would add that the steeper relationship of glucose and mortality in the inpatient setting in those without an estab-

lished diabetes history has been observed by several groups. The explanation remains unclear. Whether these are truly diabetic patients and their lack of diagnosis reflects decreased access to quality care, whether their hyperglycemia is a reflection of greater underlying stress, or whether they simply cannot tolerate relatively abrupt elevations in BG is not at all clear. This study confirms those findings and expands upon them to suggest an optimal glycemic range. We'd also caution that since patients were not randomly assigned to more intensive vs. less intensive therapy in SUGAR, it is not possible to know whether the greater mortality with higher BGs is simply a manifestation of sicker patients or whether glucose is actually driving the adverse clinical outcomes.

In an important study, Umpierrez and American colleagues compared two comprehensive strategies to lower glucose in the hospital: the ‘basal-bolus’ approach vs. the more traditional ‘split-mixed’ regimen (abstract 964). A total of 130 non-surgical patients (mean age 58±10 years, BMI 33±10 kg/m²) admitted to the medical service with a BG of 140 to 400 mg/dl and a history of Type 2 diabetes for at least 3 months were randomized

to detemir once daily + aspart three times daily (n=67) or NPH + regular twice daily (n=63). The total daily dose (TDD) was initially calculated as 0.4 units/kg for BG 140 to 200 mg/dl and 0.5 units/kg for BG >200 mg/dl. The mean BG was 238±90 mg/dl and HbA1c was 8.3±2%. The basal-bolus regimen was apportioned as 50% TDD detemir along with 17% aspart before each meal. The NPH/regular program was dosed 60% pre-breakfast (2:1 ratio) and 40% pre-dinner (1:1 ratio). The mean daily doses achieved were 30 U detemir, 27 U aspart, 27 U NPH, and 18 U regular. By the end of the trial, no glycemic differences could be detected between groups. Mean daily BG was 158±72 mg/dl with basal-bolus and 155±72 mg/dl with split-mixed (p=NS). The pre-meal target of <140 mg/dl was reached in 45% and 48% of the two groups, respectively. BG readings <60 mg/dl occurred in 1.7% and 1.3%, respectively. No differences in length of stay or mortality were observed. In this inpatient setting, equivalent glycemic control was achieved with these two insulin regimens. We note that in both groups, the control achieved was reasonably good and the hyperglycemia rates appeared encouragingly low.

Figure 3. Standardized Mortality Ratio (SMR) for Patients with and without Diabetes Correlated with Mean Blood Glucose During Hospitalization



Update on Type 1 Diabetes



Long-term microvascular and macrovascular complications develop in many patients with Type 1 diabetes; however, there is evidence

to suggest that their rates are decreasing, particularly in those receiving intensive therapy. In a presentation made this morning, Dr. Orchard on

behalf of North American colleagues estimated the 30-year cumulative incidence rates of CV disease (CVD), albumin excretion rate (AER) of >300

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Update on Type 1 Diabetes

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mg/24 hours, and proliferative retinopathy (PDR) in 3 patient cohorts. These were: 1) patients enrolled in the Diabetes Control and Complications Trial (DCCT) trial and treated with conventional therapy; 2) a subgroup of patients enrolled in the DCCT/Epidemiology of Diabetes Complications (EDIC) study and provided intensive therapy (defined as 3 or more insulin injections per day and at least 4 self-monitored blood glucose tests per day), and; 3) a cohort of 658 patients with Type 1 diabetes who had received intensive therapy for approximately 25% of their disease duration. The investigators noted that the estimated 30-year cumulative incidence rates of CVD, AER, and PDR were lower in the DCCT intensive therapy population (~9%, ~9%, and ~21%, respectively) as compared to either the DCCT conventional therapy group (~15%, ~25%, and ~49%) as well as compared to the cohort who received occasional intensive therapy (~15%, ~17%, and ~47%). These lower rates of microvascular and macrovascular complications are hypothesized to represent what we can expect to observe with intensive therapy on the clinical course of Type 1 diabetes.

Despite its benefits on vascular complications, insulin therapy is associated with weight gain in both Type 1 and Type 2 diabetes patients. One factor that might contribute to weight gain is the relative peripheral hyperinsulinemia that occurs following insulin injections. In contrast, endogenously produced insulin is secreted in small quantities by the pancreatic islet cells directly into the portal circulation. Hepatocytes are thereby rapidly exposed to high levels, but peripheral exposure is more modest. This difference between subcutaneously delivered insulin and that which is secreted normally is of critical importance, given the integral role played by the liver in glucose regulation. Investigators have therefore been studying the benefits of intraperitoneal insulin delivery for years. This experimental technique attempts to mimic the portal concentrations of insulin that occur in non-diabetic individuals. Logtenberg and colleagues of The Netherlands performed an open-label, randomized, controlled, cross-over trial to assess whether continuous *intraperitoneal* insulin infusion (CIPII) delivered with an implantable pump provides equal or greater glycemic control as compared to the use of intensive subcutaneous (SC) multiple-dose injection (MDI) insulin therapy (abstract

182). Following a 3-month baseline/qualification phase during which insulin therapy was optimized, 24 patients with a HbA1c >7.5% and/or ≥ 5 hypoglycemic events/week were randomized to receive either 6 months of CIPII followed by 6 months of SC or vice versa—with a maximum 4-week washout phase between periods. The investigators found that administration of insulin via CIPII was associated with significant improvements in HbA1c as compared to SC administration at both the 3-month ($p=0.006$) and 6-month ($p=0.025$) evaluation timepoints.

Vitamin D deficiency has been recently linked to increased incidence of both Type 1 and Type 2 diabetes. Piekarski and Polish colleagues explored the potential benefit from the vitamin D analogue, alfacalcidol, in a group of 54 children and adolescents with Type 1 diabetes (abstract 116). Children treated with alfacalcidol for 2 years required lower doses of insulin as compared to those not given vitamin D supplementation. These results are intriguing and need confirmation in larger, controlled, double-blind clinical trials. The concept of slowing Type 1 diabetes progression by vitamin D supplementation, which is a simple and generally safe therapy, is appealing especially in the management of children.



So Many Posters, So Little Time....



The "A1c-Derived Average Glucose (ADAG)" study demonstrated a linear relationship between average glucose (AG) during 3 months and HbA1c at the end of 3 months. In a sub-study analysis of 268 patients with Type 1 and 159 patients with Type 2 diabetes, the ADAG investigators (Kuenen *et al.*) examined the influence of glycemic variability on the relationship between AG and HbA1c levels (abstract 1065). AG was calculated from 7-point self-monitored blood glucose measured during 3 days/week and continuous glucose monitoring (CGM) performed for 2-3 days on 4 occasions during a 12 week-period (~2,700 glucose values per subject). Three measures of glucose variability were calculated from the CGM data: the mean amplitude of glycemic excursions (MAGE), the standard deviation (SD) of all glucose levels, and the continuous overlapping net glycemic action (CONGA), which measures intraday variability. As expected, linear regression analysis showed a high correlation between HbA1c and AG values ($r^2=0.84$, $p<0.0001$). Most tertiles of glucose variability had a statistically significant effect on the HbA1c-AG relationship, but especially in the highest variability group and particularly in those with Type 1 diabetes. The investigators summarized

that although the differences in "interpretation" of HbA1c were influenced by glucose variability, the clinical impact was modest. We would disagree—for Type 1 patients, who often show high variability, differences appear significant and again call into question the rationale of using the term "ADAG" when interpreting HbA1c results. There are many unmeasured variables that may affect glycosylation, including heterogeneity in glucose transport rates into red cells, erythrocyte lifespan, hemoglobin polymorphisms, as well as glucose variability.

Subclinical hearing impairment may need to be added to the list of diabetic complications. Dabrowski and colleagues from Poland compared hearing function in 31 patients under age 45 (mean 29.1 ± 7.1 years) with Type 1 diabetes duration less than 10 years (mean 4.6 ± 2.7 years) and no clinical evidence of hearing impairment to an age-matched control group of 26 healthy volunteers (abstract 1259). The investigators confirmed the existence of subtle but significant hearing impairment among those with diabetes. The hearing threshold in frequencies 3 to 12 kHz

was significantly higher among those with Type 1 diabetes as compared to the controls. Hearing thresholds were correlated with age, but not with either metabolic control or disease duration. The investigators also found that both cochlear micromechanics and central auditory pathway function appear to be altered.

Ozcan *et al.* from Turkey determined the prevalence of and risk factors for glucometer miscoding in a multicenter study of 454 diabetes patients (mean duration of diabetes= 10.5 ± 7.3 years, age= 53 ± 15 years, 50% female) (abstract 1017). Based on subject interviews and evaluation of glucometer and strips coding, it was determined that 18% of subjects miscoded their blood glucose meters. There were more coding errors among those who were older, those with low literacy, lower economic status, Type 2 diabetes, or had not received meter education. Of note, fasting and postprandial blood glucose levels and HbA1c were all higher among the patients who had these errors. The investigators suggested that all patients should have their glucose meters checked periodically for proper coding.

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