

# Diabetes2009

From the 45th Annual Meeting of the European Association  
for the Study of Diabetes ■ Vienna, Austria

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Department of Internal Medicine, Section of Endocrinology

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## Diabetes, Insulin, and Cancer



Important data on diabetes presented at the 45th Annual Meeting of the European Association for the Study of Diabetes comes 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 (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 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.

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This past June, *Diabetologia*, the journal of the European Association for the Study of Diabetes (EASD), sent shock waves through the medical community when it reported on four observational studies\* examining insulin therapy for Type 2 diabetes and the potential risk for cancer. This news comes at a time of heightened awareness of the side effects of all diabetes therapies, creating frustration and perhaps even some cynicism over how to treat this disease effectively and meet goal expectations. A packed house, including hundreds seated on the floor, gathered to hear the symposium on diabetes and cancer, chaired by Dr. Edwin Gale, editor of *Diabetologia*, and Dr. Ulf Smith, president of the EASD.

In his introduction, Dr. Gale remarked that this is one of the most challenging, controversial, and confusing issues facing diabetes caregivers. He emphasized that two separate concepts were under consideration: first, the connection between Type 2 diabetes and an increased rate of malignancy, and second, how exogenous insulin therapy and oral hypoglycemic agents may affect this risk.

Jeffery Johnson, PhD from Canada reviewed the epidemiology alerting a probable connection between malignancy and both Type 2 diabetes and obesity. He stated that there are many complicated and convoluted factors in sorting out the pathogenic role of obesity and Type 2 diabetes in cancer incidence and survival. Between 2005 and 2007, there were six meta-analyses showing an increased risk with several cancers and Type 2 diabetes. One hundred twenty-two original epidemiological studies contributed to the meta-analyses. Overall, the hazard ratio (HR) for breast cancer was found to be significantly increased by 20%, with pancreatic and colorectal cancer increased by ~80%, for those with Type 2 diabetes vs. the reference group of non-diabetic individuals.

Dr. Johnson also reviewed several studies indicating a potential role of oral hypoglycemic agents in further modulating this risk. The sulfonylureas, similar to insulin, may be associated with an increased risk of cancer, but studies involving thiazolidinediones (TZD) have indicated

a possible risk reduction. For instance, in the *Journal of Clinical Oncology* (2007;25:1476-81), Govindarajan *et al.* reported on over 80,000 men with Type 2 diabetes, comparing the use of TZD's versus other therapies. The authors concluded a 33% risk reduction (RR 0.67, 95% CI 0.51-0.87) in lung cancer for users of TZD's versus non-users. Of note, all epidemiological data contain confounding variables, and Dr. Johnson cautioned that to date there are no results of randomized control trials (RCT) appropriately designed to address the issue of malignancy in the setting of Type 2 diabetes therapies. However, 10 trials are currently in progress, specifically examining the potential role of pioglitazone or rosiglitazone in the prevention or treatment of cancer.

Craig Currie, PhD, an epidemiologist from the UK, next addressed the influence of metformin on malignancy. He was the lead author in the retrospective cohort study from a UK general practice database of over 40,000 people with Type 2 diabetes (*Diabetologia* 2009;52:1766-77). Compared to the databases within the other three *Diabetologia* studies, this database had the most detail with regard to type of therapy as well as the dosing of insulin used by each person in the study. The study provided two observations. First, higher dosing of insulin was associated with a higher rate of cancer, particularly in lean people. Second, he concluded that metformin attenuated the cancer risk in all but the highest insulin dose group, with some variability by tumor site. Specifically, metformin was associated with a reduced rate of pancreatic and colon cancers.

Ulf Smith, MD, PhD from Sweden next carefully explained how insulin may be involved in the mechanisms of cancer growth, and how metformin may provide some protection. He emphasized that insulin is *not* an oncogene and does *not* cause cancer. However, it is a growth promoter, predominately through activation of certain non-metabolic intracellular signaling cascades, and may create faster growth in cells that have already undergone neoplastic transformation. Since the 1950's and 60's, it has been known that insulin

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## Diabetes, Insulin, and Cancer

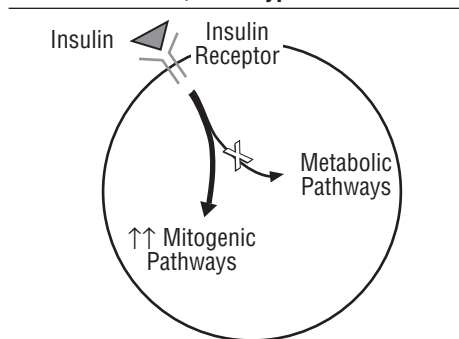
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has mitogenic (growth promoting) properties in non-cancerous cells as well as experimental cancer cell lines. Normally in humans, physiological insulin levels are too low to play a role in significant mitogenesis, but this may not be the case in insulin resistance and exogenous insulin therapy when supra-physiological insulin levels are required to maintain glycemic control. In insulin-resistant states, the insulin-stimulated metabolic pathways are significantly blocked, but the mitogenic pathways (through MAP-kinase signaling) are still active and may actually receive a greater proportion of the signal (Figure 1). An additional concern is that certain cancer cells have increased expression of receptors that transmit this enhanced mitogenic signal, including the insulin receptor type A, IGF-1 (insulin-like growth factor I) receptor, and a hybrid IGF/insulin receptor.

Dr. Smith noted that the potential protection afforded by metformin is “extremely exciting.” Metformin has recently been reported to be a useful adjunct to cancer therapy in breast cancer (*J Clin Oncol* 2009;20:3297-3302) and in the suppression of its stem cells (*Cancer Research* 2009;69:7507-11). Metformin’s mechanism of action is thought to be through stimulation of adenosine mono-phosphate activated protein kinase (AMPK), but there are likely other, yet undiscovered mechanisms.

In each of the four studies published in *Diabetologia*, the widely used long-acting insulin analogue glargine (Lantus®, Sanofi-Aventis) was focused upon because of its increased biological activity at the IGF-1 receptor. In some of these papers, a possible link between this insulin and certain forms of cancer were raised. Jay Skyler, MD from the US was asked by the manufacturer to provide an overview of the safety record of insulin glargine. He reported that no RCT’s to date have indicated a signal of concern for malignancy. He emphasized

**Figure 1. Theoretical Model of Increased Mitogenicity in Insulin-Resistant States, Like Type 2 Diabetes**



Insulin resistance is isolated to post-receptor insulin signaling cascades involving the metabolic pathways (PI3-kinase). In contrast, the mitogenic pathways (MAPK) remain intact. With hyperinsulinemia, there may be a greater activation of the latter.

that in each of the four *Diabetologia* articles, the hazard ratio for the “all cancers” analysis did not demonstrate an increased risk of malignancy with the insulin analogue. He pointed out the need for prospective, randomized trials addressing this issue. The Outcome Reduction with Initial Glargine Intervention (ORIGIN), an ongoing RCT involving glargine and omega 3, needs two more years of data collection before any conclusions can be drawn. With the publication of the *Diabetologia* articles, however, an independent data monitoring committee reviewed available outcome data, and concluded that the trial was safe to continue. In summarizing his review, Dr. Skyler criticized the media for not using the same cautionary language as the authors of the observational studies in describing the results of their studies.

In a following talk, David Russell-Jones from the UK spoke on behalf of Novo Nordisk to report on the safety data for detemir (Levemir®), another long-

acting insulin analogue. In contrast to glargine, pre-clinical data on detemir showed a lower strength of binding to the IGF receptor than human insulin, the inference being that it may have less mitogenic potential. He discussed one RCT comparing detemir to NPH in a population, half of whom had Type 1 and the other half, Type 2 diabetes. Insulin exposure was 24 weeks. There was an overall low malignancy rate. However, the study was not designed to look at cancer as an outcome. Nevertheless, there were fewer malignancies reported in the detemir group than the NPH group (8 vs. 13). The number of people with Type 2 diabetes versus Type 1 diabetes with this outcome was not mentioned.

In summary, there is biological plausibility linking insulin resistance and neoplasia, in addition to clinical trials that may support the association of Type 2 diabetes and cancer incidence. Any potential connection between insulin therapies and cancer growth is highly speculative and under cautious exploration. Clearly, appropriately designed prospective studies are required. In the meantime, the EASD, American Diabetes Association (ADA), and American Association for Clinical Endocrinologists (AACE) have issued statements guarding against over-interpretation of the limited data and recommending continuation of current insulin regimens.

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## Glucose & CVD: Does It Matter?



In a lively debate, David Matthews from the UK and Bruce Psaty from the US weighed the balance of the risks and benefits of intensive glucose control with quite disparate conclusions. Matthews began by reviewing the evidence, starting with his own RCT, the original UKPDS, which showed a 16% reduction in the risk for myocardial infarction (MI) in the intensive glucose control group, albeit not quite reaching statistical significance ( $p=0.052$ ). The subgroup of overweight patients in

the UKPDS who were treated with metformin, however, had a significant 39% reduction in MI risk ( $p=0.01$ ), despite a small number of patients ( $n=342$ ). He further argued that a large prospective observational UKPDS study showed that each 1% reduction in updated mean HbA1c was associated with a 14% risk reduction in MI. Epidemiological and interventional data appear to tell the same story, he explained, thus strengthening the evidence.

Matthews then went on to review the other major RCTs of intensive glucose control, including the recent ADVANCE, ACCORD, and VADT trials (see *Diabetes 2008*, Volume 17, pages 11, 21, and 26). The ACCORD trial actually showed a mortality risk associated with the intensive glucose strategy, but Matthews explained that this is not surprising. The ACCORD study population differed drastically from that of UKPDS in that the average duration of diabetes

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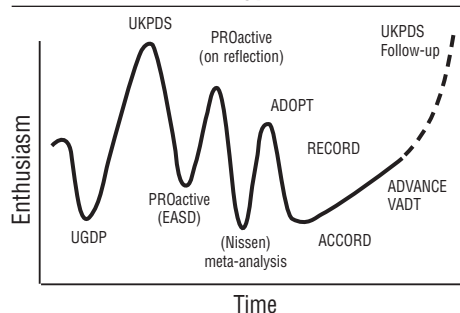
**Glucose & CVD: Does It Matter?***Continued from page 2*

was about 10 years (compared to newly diagnosed in UKPDS) and it included ~35% of individuals with already established cardiovascular disease (CVD) (compared to none in UKPDS). Moreover, Matthews argued, there was a massive and rapid decrement in HbA1c achieved in ACCORD within the first year, a “kitchen sink” approach being used to lower glucose (77% on insulin, 92% on TZDs, 78% on sulfonylureas, 95% on metformin). Increased mortality may, therefore, have resulted from hypoglycemia, even if it was not necessarily clinically detected. ADVANCE and VADT also included individuals at high risk for CVD, but found neither benefit nor harm from intensive glucose control for CVD. The enthusiasm for glycemic control has been fluctuating as a result of these trial data (see Figure 2).

Several meta-analyses have been performed to date in an effort to further clarify the issue of intensive glucose control and CVD. Matthews admitted that the one conducted by Kelly *et al.* (*Ann Int Med* 2009) showed no significant risk reduction from more intensive control of glucose on CVD (relative risk [RR] 0.94, 95% CI 0.86-1.02) using two of the UKPDS trials, ACCORD, ADVANCE, and VADT data, but argued that summary rather than individual patient data were used. (We point out that the Kelly paper did indeed show a benefit when all 5 trials were considered [RR 0.90, 95% CI 0.83-0.98], but that the speaker was referring to the effect size from solely the 3 more recent RCTs.) Ray *et al.* (*Lancet* 2009) conducted a similar meta-analysis but added the PROactive trial (which admittedly was not designed to test glucose intensity but rather a specific anti-hyperglycemic strategy, namely pioglitazone), again using summary data. This analysis revealed a 17% decrease for non-fatal MI (OR 0.83, 95% CI 0.75-0.93). Matthews went on to point out that the recent Turnbull *et al.* meta-analysis (*Diabetologia* 2009) was actually performed correctly by using raw trial data and censoring the UKPDS trial at 5 years to make it more comparable to ACCORD, ADVANCE, and VADT. This showed the same risk reduction for MI (hazard ratio [HR] 0.85, 95% CI 0.76-0.94) as that demonstrated originally in UKPDS, thus proving his point that the data converge.

In concluding remarks, Dr. Matthews added that it's likely that the establishment of atherosclerosis takes a long duration of time and that many trials were simply too short to see a difference in outcomes. To this effect, he pointed out that in the UKPDS follow-up study, when individual treatment was no longer dictated by the trial and HbA1c values in the two groups con-

**Figure 2. Effect of Trial Data on Enthusiasm for Glycemic Control in Type 2 Diabetes**



Adapted from EASD presentation by Dr. Matthews and *Diabetes and Vascular Disease Research*, 2008.

verged, the risk for MI remained stable over time (HR 0.85,  $p=0.014$ ), as long as 10 years later (*NEJM* 2008). He suggested that this “legacy effect” was the result of such a slowly developing pathological process. All in all, he is convinced that the evidence of a 15-16% risk reduction shown in epidemiological studies, RCTs, and meta-analyses is strong and consistent. He remarked that early intensive therapy may be particularly beneficial and that rapid lowering of glucose in those with established CVD may actually be harmful.

Bruce Psaty took the podium next and began by stating that he is not opposed to glucose control *per se*, but has several concerns with regard to the intensive glucose control data: 1) All too often, the data for Type 1 diabetes are extended to apply to those with Type 2 diabetes, despite the fact that the two patient types have totally different pathophysiologies; 2) We commonly rely on surrogate endpoints in our studies, which may be misleading (risk factors may be associated with a disease but may not be causally related, and drugs themselves may have off-target effects, either beneficial or detrimental); and 3) Drug evaluation has been, historically, too often handed over to industry, which has asymmetric interests in the assessment of both efficacy and safety.

Dr. Psaty went over the major differences between Type 1 and Type 2 diabetes. Although both are characterized by hyperglycemia, Type 2 diabetes is associated with insulin resistance and obesity, which are themselves significant additional risk factors for CVD. He argued that therapies that address insulin resistance itself merit special attention, and again pointed out the CVD risk reduction seen with metformin in the obese subgroup of UKPDS. In contrast, in Type 1 diabetes, therapies focused on hyperglycemia itself have proven quite effective—the risk for cardiovascular (CV) events in the DCCT follow-up trial, EDIC, was reduced by 57% (95% CI 12-79), far exceeding that suggested by any

epidemiological data. In contrast, the aforementioned Kelly meta-analysis of intensive glucose control in Type 2 diabetes showed non-significant risk reduction for CVD when only the three modern trials (ACCORD, ADVANCE, VADT) were included.

In his talk, Psaty went on to use rosiglitazone as an example of how beneficial effects on surrogate endpoints may not match the effects on hard clinical outcomes. Even though rosiglitazone reduces HbA1c effectively, it does increase LDL-cholesterol and weight, both of which may contribute to CV risk. He argued that even though the recent RECORD trial (*Diabetes* 2009, Volume 19, page 13) did not show rosiglitazone to be associated with increased mortality, he is still concerned that the event rate in RECORD was exceedingly low (4.5 MI events per 1,000 person-years) and the study may therefore not be conclusive.

The theme of glucose and CVD was carried on in several poster sessions. Yet another meta-analysis of RCTs assessing intensive glycemic control in Type 2 diabetes was conducted by Monami *et al.* from Italy (abstract 1352). The five studies included were ACCORD, ADVANCE, PROactive, VADT, and UKPDS with 17,267 and 15,362 patients in the intensive and conventional groups, respectively. Similarly to Ray *et al.* (*Lancet* 2009), the authors found a significant reduction in incident CV events (OR 0.89, 95% CI 0.83-0.95) and MI (OR 0.86, 95% CI 0.78-0.93), but not in stroke (OR 0.93, 95% CI 0.81-1.07) nor CV mortality (OR 0.98, 95% CI 0.77-1.23). In their meta-regression analysis, higher BMI, longer duration of diabetes, and severe hypoglycemia were all associated with CV death in the intensive treatment group. We would point out the previously mentioned issue regarding the pooling of data from 4 studies (UKPDS, ACCORD, ADVANCE, VADT) that essentially tested a specific glucose target with one that explored the effects of a specific strategy (PROactive). (Admittedly, UKPDS really had both features.)

Although, traditionally, Type 2 diabetes has been considered a coronary heart disease (CHD) risk equivalent, recent advances in evidence-based treatments for CV risk factors have improved outcomes in those with and without diabetes. Whether Type 2 diabetes still confers as high a risk as a prior CHD event remains unclear. Flores *et al.* from Spain compared all-cause mortality, CV mortality, and coronary events between two large cohorts in Catalonia: 2,260 Type 2 diabetes patients recruited between 1993 and 1995 without prior CHD and 2,150 patients selected from a heart registry between 1990 and 2003 with a first episode of MI but without Type 2 diabetes (abstract 1302). Baseline characteristics between

*Continued on page 4*

## Glucose & CVD: Does It Matter?

Continued from page 3

the two groups differed significantly, with the MI cohort being younger and more male, having less baseline dyslipidemia and hypertension but a greater percentage of smokers. In multivariable models adjusted for those characteristics, the diabetic patients had significantly lower all-cause mortality (HR 0.42, 95% CI 0.35-0.50), CV death (HR 0.21 [0.16-0.28]), CHD death (HR 0.12, [0.08-0.18]), and fatal and non-fatal MI (0.35, [0.28-0.44]) than MI patients. Further subgroup analyses stratified by duration of diabetes ( $\leq 8$  vs.  $> 8$  years), baseline HbA1c ( $< 7\%$  vs.  $\geq 7\%$ ), and treatment of diabetes (diet, oral anti-hyperglycemic agents, and insulin) showed consistently lower risk for CV death and CHD in all strata compared to those with prior MI. The investigators did not compare the frequency of statin and anti-thrombotic therapy use between the two groups, however. Flores postulated that regional differences may possibly contribute to these findings, given that persons from southern Europe have a generally lower CVD risk than their northern European counterparts.

Ideally, identification of CHD prior to MI may result in an effective intervention, leading to better outcomes in those individuals at high risk. Reinhard *et al.* from Denmark examined the prevalence of asymptomatic coronary artery disease (CAD) in patients with Type 2 diabetes and albuminuria—a known risk factor for CVD—using coronary calcium scores (CCS) by electron

beam computed tomography (EBCT) and NT-proBNP levels for risk stratification (abstract 1219). Out of 200 patients (74% male, mean age 59, HbA1c 7.9%, diabetes duration 13 years, 62% with retinopathy,  $\geq 90\%$  on statins, aspirin, and RAAS blockers), 133 were categorized as high risk based on  $CCS > 400$  or NT-proBNP levels above the median (43.2 ng/l). They then underwent further testing with myocardial perfusion imaging (SPECT,  $n=108$ ), CT-angiography ( $n=20$ ), and/or coronary angiography ( $n=81$ ). In over half of the patients (70/133), these imaging studies confirmed significant CAD, with 9 patients requiring revascularization. Prevalence of CAD paralleled increasing CCS among the high-risk patients;  $CCS < 100$  had a negative predictive value of 94% for significant stenosis. Eighty-eight percent of the high-risk patients with NT-proBNP levels  $> 100$  ng/l and  $CCS > 800$  ( $n=14$ ) had significant CAD, compared to 53% in those with lower values ( $p=0.013$ ). Whether CCS and/or NT-proBNP will become useful and, importantly, cost-effective tools in clinical practice will need to be determined in future studies, which must include actual clinical outcomes.

Once a coronary event occurs, individuals with Type 2 diabetes appear to suffer from more short- and long-term complications including death, reinfarction, and heart failure. Kamaratos *et al.* from Greece determined the prevalence of various glucose abnormalities in acute coronary syndrome (ACS) patients and correlated them to the incidence of short-term complications (abstract

1324). Out of 520 patients (mean age 66) hospitalized in a coronary care unit for ACS, 152 (29.2%) were previously diagnosed with diabetes, 57 (10.9%) were newly diagnosed with diabetes (2-hr plasma glucose [PG] during an oral glucose tolerance test (OGTT)  $\geq 200$  mg/dl performed one month after discharge), 110 (21.1%) were diagnosed with impaired glucose tolerance (IGT, based on 2-hr PG 140-199 mg/dl), and the remaining 201 (38.8%) had normal glycemic parameters. The incidence of 30-day complications (CV death, MI, and heart failure based on clinical or echocardiographic criteria, and unstable angina) was 10.5% for those with known diabetes, 12.8% for those with new diabetes, 7.3% for those with IGT, and 5% in the normal group ( $p=0.031$ ). After adjustment for age, gender, smoking, waist circumference, HDL, triglycerides, total cholesterol, presence of metabolic syndrome, and hypertension in multivariable models, the HR (risk) for complications was 1.87 (95% CI 1.23-5.23) in known diabetic patients, 2.15 (95% CI 1.11-4.16) in new diabetic patients, and 1.22 (95% CI 0.98-2.99) in IGT patients, when compared to those with normal glycemic measures. Based on this study, those with newly diagnosed diabetes were at highest risk for complications following ACS. Further studies are needed to assess whether earlier diagnosis and intervention in this group will lead to reduction of the risk.

Our understanding of the links between diabetes and CVD continue to evolve with each meeting. We look forward to ongoing investigations in this critically important area.



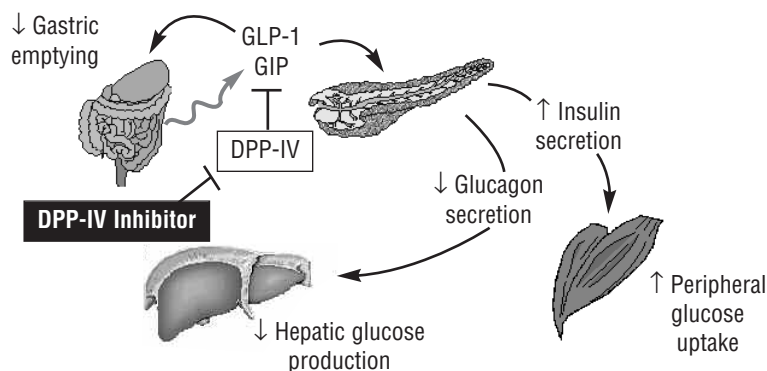
## Update on GLP-1 Therapies



Several oral and poster sessions were devoted to incretin-based therapies this week in Vienna. Dr. B. Gallwitz of Germany chaired the symposium entitled, *Incretins at Work*, introducing three internationally recognized speakers. The session focused on the benefits and risks of glucagon-like peptide-1 (GLP-1) receptor agonists.

The first presentation, *GLP-1 Effects and Side Effects*, delivered by Dr. Bo Ahren of Sweden, provided a comprehensive review of the physiologic, clinical actions, and side effect profiles of GLP-1 and related compounds. He described them as novel therapies that may meet many of the concerns of patients with diabetes: poor glycemic control, risk of hypoglycemia, increased body weight, progressive beta-cell failure, and adverse drug effects. Ahren detailed the physiologic action (Figure 3) of these agents: (1) regulation of islet hormone secretion (glucose-dependent stimulation of insulin secretion and suppression of glucagon secretion); (2)

Figure 3. Physiology of the Incretin System



regulation of islet gene transcription; (3) slowing of gastrointestinal (GI) motility/gastric emptying; (4) increased satiety/decreased food intake; and (5) inhibition of hepatic glucose production

(indirectly through glucagon). He also identified the numerous compounds available/in development (Table 1).

Continued on page 5

## Update on GLP-1 Therapies

Continued from page 4

**Dr. Ahren** summarized the literature describing clinical effects of the incretin-mimetics, particularly decreases in HbA1c. He commented that when used in combination with other anti-diabetic drugs, this effect is quite robust. He also reviewed the safety profiles of these agents, describing them as safe and highly tolerable, with a minimal risk of hypoglycemia (<3%; higher when used in combination with sulfonylureas). While there is the potential for immunogenicity, the antibodies generated are primarily non-neutralizing and have had no impact on clinical effects. Extraprostatic effects are not yet fully elucidated. However, GLP-1 receptors are expressed in multiple organs/tissues: liver, heart, endothelial tissue, lung, kidney, CNS, bone, etc. Data continue to evolve regarding GLP-1 action at these sites. During the question and answer period, concerns regarding pancreatitis and medullary cancer were expressed. The speaker noted that pancreatitis is a concern in all patients with diabetes and, at present, data do not support that the incidence is increased specifically in patients receiving incretin mimetics. He noted that medullary thyroid tumors have been seen in rats with certain GLP-1 based compounds and have been associated with increased calcitonin levels. However, in humans, the tumors have not been observed.

**Dr. Dan Drucker** of Canada next proceeded with *Cardiovascular Effects of GLP-1*. He shared data from multiple animal models demonstrating cardioprotective effects that are independent of glucose. He also reminded the audience of the animal and clinical data that support decreases in CV risk factors that appear to be independent of weight loss, including decreases in triglycerides and systolic blood pressure. Lastly, he shared data regarding the vasodilatory properties of the GLP-1 metabolite, GLP-1 (9-36), that shows some promise with respect to its positive impact on cardiac function. In addition to vasodilation, GLP-1 (9-36) also appears to have beneficial effects on glucose and reactive oxygen species.

The final presentation, *CNS Effects of GLP-1-Like Peptides*, was delivered by Dr. Stephen Bloom of the UK. He emphasized the complexity of GLP-1-mediated satiety and weight control at the level of the hypothalamus, noting that precise mechanisms have not been fully elucidated. He shared data regarding a 37 amino acid gut hormone, oxyntomodulin, which is released in the plasma in proportion to meal size. Interestingly, oxyntomodulin is increased in a number of bowel conditions associated with weight loss (e.g., pancreatic failure, malabsorption syndromes). Early clinical data with

**Table 1. Incretin-Based Agents**

GLP-1 Analogs	Exendin-4 Analogs	DPP-4 Inhibitors
liraglutide*	exenatide*†	sitagliptin*†
semaglutide	lixisenatide	vildagliptin*
albiglutide	exenatide LAR	saxagliptin†
tasoglutide		alogliptin
LY2189265		linagliptin
		dutogliptin
		metogliptin

\*Available in Europe; †available in US.

this gut hormone demonstrate significant weight loss in the short term with little to no nausea. From this morning's symposium, it is clear that the GLP-1 story will continue to be a fruitful area of clinical and basic research for years.

**Many** oral and poster presentations this week were also devoted to research on incretin-based therapies. For example, Kielgast and Danish colleagues compared the effects of endogenous and exogenous GLP-1 on glucagon secretion and glucose excursions in patients with Type 1 diabetes, with (n=8) and without (n=8) residual beta-cell function, to control subjects (n=8) (abstract 128). Each diabetes group received 3 mixed meal tests and GLP-1, a GLP-1 receptor antagonist (exendin 9-39), or saline were infused. The infusions were started within 30 minutes of meals, and the patients injected 50% of their normal prandial insulin dose shortly before the meal. Acetaminophen was added to meals to assess gastric emptying. Measures of post-prandial glucose, glucagon, insulin secretion, and gastric emptying were assessed from incremental area-under-plasma-concentration (AUC) curves (over -30 to 180 minutes). Glucagon concentrations were decreased by GLP-1 infusion in each of the groups when compared with saline (p<0.05), as were glucose excursions (p<0.01). Exendin 9-39 increased glucagon levels when compared with saline for all three groups (p<0.01). Post-prandial glucose following GLP-1

was identical to that of the control subjects in both groups of diabetic patients. Infusion of exendin 9-39 resulted in increased glucose levels in patients with residual beta-cell function (p=0.02), but the increase was not significant in those who were C-peptide negative or in control subjects. Yet, when the diabetes patients were combined, blood glucose was significantly elevated in response to exendin 9-39 when compared with saline (p=0.002). Gastric emptying was decreased by GLP-1 in both diabetes groups (p<0.01), whereas exendin 9-39 enhanced emptying as compared to controls (p<0.05). From these data, the investigators concluded that exogenous GLP-1 controls blood glucose excursions, through mechanisms that are independent of beta-cell function. Most likely, this occurs as a result of decreased gastric emptying and lowering of glucagon levels.

**Given** the notable favorable impact of exenatide on post-prandial glucose, researchers from the US, led by Cusi, studied the impact of replacing prandial insulin with exenatide in patients with Type 2 diabetes managed with basal-bolus insulin regimens (abstract 248). A total of 24 patients, well controlled (HbA1c 7.1±0.9%) on insulins detemir and aspart, were recruited. Detemir was maintained; however, exenatide twice daily was substituted for aspart for six months. No changes in detemir doses were required by study completion. Several measures of glycemic control were measured at baseline and at six months (Table 2). The exenatide/insulin regimen was well tolerated, with no reports of significant hypoglycemia; 3 patients developed nausea, which resolved within 4 weeks. This unconventional approach may pose several advantages, weight loss in particular.

**Trautmann et al.** from the US reported interim results of an open-label exenatide trial in which patients received 30 weeks of the conventional formulation of the GLP-1 agonist twice daily or a new once-weekly depot formulation, followed by 70 weeks of the exenatide depot 2 mg weekly

**Table 2. Metabolic Effects of Substituting Exenatide for Insulin Aspart**

Parameter	Baseline	At 6 months	
	Detemir + Aspart	Detemir + Exenatide	p-value
HbA1c, %	7.1 ± 0.9	6.8 ± 0.7	NS
Body weight, kg	—	-4.6 ± 1.1	<0.001
4-hour mixed meal			
Mean plasma glucose, mg/dl	190 ± 9	138 ± 7	<0.001
Glucose increase above baseline, mg/dl	83 ± 8	32 ± 8	<0.001
Plasma hsCRP levels (mg/l)	3.8 ± 0.9	1.9 ± 0.5	<0.04

Continued on page 6

## Update on GLP-1 Therapies

Continued from page 5

(abstract 730). Of the original 181 patients entered into the trial (52-week data previously reported), 135 (75%) completed the full two years of treatment. It was this open-label cohort for which data were reported. Patients received a variety of background therapies to additionally manage their Type 2 diabetes. At the end of two years, significant improvements in HbA1c ( $-1.8 \pm 0.1\%$  [95% CI  $-2.0$  to  $-1.6\%$ ]), fasting glucose ( $-36.7 \pm 4.0$  mg/dl [ $-44.6$  to  $-28.6$  mg/dl]), and body weight ( $-3.6 \pm 0.6$  kg [ $-4.8$  to  $-2.3$  kg]) were maintained. A total of 66% and 42% of the study participants achieved HbA1c  $\leq 7.0\%$  and  $\leq 6.5\%$ , respectively. Of note, there was an improvement in CV risk factors, with sustained reductions ( $p < 0.05$ ) in triglycerides ( $-18\%$ ,  $p < 0.05$ ), total cholesterol ( $-9$  mg/dl), and systolic ( $-3.0$  mmHg)/diastolic ( $-1.5$  mmHg) blood pressure values. With the exception of nausea, exenatide was well tolerated, with no reports of severe hypoglycemia. Nausea decreased over the extended treatment period, but did occur in 8% of patients.

Post-marketing reports of acute pancreatitis associated with exenatide therapy have raised concerns about the safety of this compound. Given these recent reports, Bloomgren and co-investigators from the US conducted a retrospective cohort study comparing patients

**Table 3. Differentiating Characteristics of Exenatide and Liraglutide**

	Exenatide	Liraglutide
Amino acid homology to native GLP-1	53%	97%
Half life, hr	2.4	13
Maximum daily dose	10 $\mu\text{g}^*$	1.8 mg
Renal elimination	yes	no
Antibody development	44%	8.6%

\*5  $\mu\text{g}$  twice daily.

who initiated exenatide therapy to those who initiated other antidiabetic drugs (abstract 6). The primary objective was to estimate the absolute and relative risk of acute pancreatitis in these patient groups. A health claims database representing 14 million covered lives was utilized over a 9-month continuous enrollment period. Exclusions were a history of pancreatitis and prior initiation of other medications to treat diabetes. A total of 25,719 patients were in the 'exenatide initiator' group and 234,536 were in the control group, who had started another anti-hyperglycemic medication. When compared to other drugs, the RR of pancreatitis for exenatide was 0.9 (95% CI 0.6 to 1.3) for current users, 0.9 (0.4 to 2.1) for recent use, and 1.4 (0.9 to 2.3) for past use. The

researchers concluded that the risk of acute pancreatitis in the exenatide group was not greater than that seen with initiators of other antidiabetic drugs. These data are comforting and do suggest that the recent reports may not represent a causal association. Nonetheless, any exenatide-treated patient developing abdominal pain or other symptoms associated with acute pancreatitis should be assessed quickly.

Buse *et al.* of the US reported the results of a 14-week extension of the LEAD-6 trial (abstract 2). LEAD-6 (previously reported, *Lancet* 2009) demonstrated that once-daily liraglutide, a GLP-1 receptor agonist still under investigation, had a greater effect on HbA1c and beta-cell function (as measured by HOMA-B) than did twice-daily exenatide over 26 weeks. In the extension trial, patients receiving liraglutide continued this therapy and those previously on exenatide were converted to liraglutide. Patients switched to liraglutide experienced statistically significant improvements ( $p < 0.0001$ ) in beta-cell function, fasting plasma glucose values, systolic blood pressure, and weight. Patients continuing on liraglutide maintained a durable glycemic response and continued improvement ( $p < 0.05$ ) in weight loss and systolic blood pressure control. Inherent differences between these two GLP-1 based therapies (Table 3) may explain the improved clinical response in the converted group.



## HbA1c: Where to Set the Target?



During a much-anticipated symposium, Dr. Irl Hirsch from the US and Dr. Siebenhofer-Kroitzsch from Austria conducted a heated debate on where to set the HbA1c target for diabetes— $<6.5\%$ ,  $<7\%$ , or even higher? Dr. Hirsch strongly believes that the target should be 6.5% based on the epidemiological data that points to the continuum of risk, whether it be for micro- or macro-vascular complications. The risk differences are attenuated at lower HbA1c levels, but are discernible even between 6.5% and 7%. As an example, he used the original DCCT trial, where the risk of retinopathy at HbA1c of 6.5% was lower than at 7%, albeit the difference was small. Similar data were presented from the UKPDS. The notion that lower is better was further illustrated in the observational EPIC-Norfolk study (*Annals Int Med* 2004) in which the RR of death was 1.24 for men and 1.28 for women per each 1% increase in HbA1c.

His second argument rested on the fact that whenever glycemic targets are set, the actual achieved HbA1c values are at least 0.5% higher,

**Table 4. Treatment Targets for HbA1c Endorsed by Various Professional Societies**

Organization	HbA1c Target
ADA/EASD	$<7\%$
AACE/ACE	$<6.5\%$
IDF	$<6.5\%$
Canadian Diabetes Association	$<6.5\%$

AACE=American Association of Clinical Endocrinologists, ACE=American College of Endocrinology, ADA=American Diabetes Association, EASD=European Association for the Study of Diabetes, IDF=International Diabetes Federation.

even in rigorously conducted clinical trials. He speculated that the differences may be much greater in clinical practice. Moreover, most clinicians will not start or change treatment until the HbA1c is at least 0.5-1% above the target. Therefore, the goals should be set sufficiently low to accommodate this reality (see Table 4 for current recommendations).

The main reason for avoiding intensive glucose control is the risk for hypoglycemia. Hirsch showed the data from the 1993 DCCT trial demonstrating exponentially increasing frequency of severe hypoglycemia with decreasing HbA1c. He argued, however, that in a current JDRF glucose sensor study, the risk of hypoglycemia was well below that seen in the DCCT. The ACCORD data was next reviewed, showing that the risk for mortality in this Type 2 diabetes study was significantly increased by 66% (HR=1.66 [95% CI 1.46-1.89]) per each 1% increase in HbA1c in the intensively-treated group. In stratified analyses, it was suggested that the excess risk in the intensive cohort occurred in the subgroup who were not able to achieve an HbA1c  $<7\%$  and in those with the smallest change in HbA1c ( $<0.5\%$ ). These data suggest that those starting with high HbA1c who fail to improve are at the highest risk.

In conclusion, Dr. Hirsch agreed that the difference between HbA1c of 6.5% and 7% is small, but that we should aim for HbA1c as close to normal

Continued on page 7

## HbA1c: Where to Set the Target?

Continued from page 6

as possible. He reminded the audience that treatment goals need to be individualized and based on sound clinical judgment.

Siebenhofer-Kroitzish began her talk by reminding us that observational studies are able to show association, but not causality. Therefore, only RCTs and their meta-analyses are able to adequately address the question of glycemic targets. The recent meta-analyses by Ray *et al.* (*Lancet* 2009) and Kelly *et al.* (*Annals Int Med* 2009) showed no significant difference in all-cause mortality or CV death between intensive and standard glucose control, although they did find decreased risk for CHD events. Siebenhofer believes that the benefits of intensive treatment have been over-emphasized and the risks have been under-estimated. For example, the risk of severe hypoglycemia in Type 1 diabetes in the DCCT trial translates to roughly 2.3 'persons needed to harm.' In the Type 2 diabetes trials (UKPDS, ACCORD, ADVANCE, VADT), the risk of severe hypoglycemia was roughly double in the intensive-treated groups, as recently shown in a review of data by Montori *et al.* (*Annals Int Med* 2009).

Siebenhofer also showed the number of



If the medical world united with the common goal of preventing diabetes, pregnancy might be at the center of the discussion. All preventative public health campaigns begin with women and children. Why should diabetes be any different? Not only do women with a history of gestational diabetes (GDM) have a significant risk of developing Type 2 diabetes, but also there is increasing and fascinating evidence that the burden of insulin resistance is passed on to their offspring. The terms applied to this phenomenon range from the 'intrauterine metabolic environment' to 'epigenetics.' But even in 2009, there remains no international consensus on the diagnosis or screening for GDM. A symposium on *Diabetes and Pregnancy* this year presented the most recent research on this condition and the efforts to build such a consensus. The overall theme was to prompt more aggressive diagnostic criteria for GDM, with the underlying goal being prevention of adverse pregnancy outcomes as well as childhood obesity. The controversy, of course, lies in how robust the data are to warrant 'medicalization' of a significantly greater number of pregnant women.

Moshe Hod, MD from Israel started the

**Table 5. NNT for 10 Years to Prevent One Event by Reduction of HbA1c, Blood Pressure, or Cholesterol**

Event Prevented	Glycemia reduction (1% HbA1c)	Blood pressure reduction (10/5 mmHg*)	Cholesterol reduction (39 mg/dl)
	UKPDS, ACCORD, ADVANCE, VADT	UKPDS	UKPDS
CHD	46	26	25
Stroke	3333	49	118
CV disease	45	17	21

NNT=Number Needed to Treat.

\*Systolic/diastolic blood pressure.

Source: Dr Siebenhofer, adapted from Yudkin *et al.*, *Lancet* 2009.

individuals needed to treat (NNT) to prevent CV events by lowering HbA1c 1%, blood pressure by 10/5 mmHg, or cholesterol by 39 mg/dl (see Table 5), making the point that a multi-interventional approach is needed, and that lowering lipids and blood pressure reduces CV events to a greater extent than does glycemic control. Importantly, she reminded us that Type 2 diabetes has a very high prevalence in the older population, a group that is particularly vulnerable to the risks of hypoglycemia. There are currently no RCTs assessing the benefits of intensive glucose control in this

growing population.

Therefore, she cautioned that treatment should be individualized, keeping in mind the age of the patient, other co-morbidities, duration of diabetes, risk for hypoglycemia, and impact on quality of life.

At the end of the debate, the chair asked the audience to clap in support of the two targets: <6.5% vs. 7% and higher—it was clear that the audience remained very much divided despite excellent arguments presented by both sides.



## Gestationally Yours

symposium with data and perspective from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. This international observational study included over 25,000 healthy pregnant women to answer the question of what level of glucose during pregnancy causes undesired outcomes such as macrosomia, fetal hyperinsulinemia, neonatal obesity, and neonatal hypoglycemia. With these as primary outcomes, the values of a 2-hour 75-gram OGTT in the late second trimester were correlated after adjustment for potential confounders such as BMI, ethnicity, and study center differences. The results clearly show a continuous relationship between increasing glucose and incidence of large gestational age babies and neonatal adiposity, regardless of whether fasting, 1- or 2-hour glucose values were used. Among the secondary outcomes, the risk of pre-eclampsia also clearly increased with increasing glucose values.

HAPO (*NEJM* 2008;359:1991-2002) provided evidence that glucose values within a previously considered mildly elevated or normal range do pose neonatal health risks. Other studies have also suggested that treating pregnant women at lower glucose thresholds might improve clinical

outcomes. International groups are now reviewing these data and may shortly redefine the specific cutpoints used to diagnose GDM.

In a related oral session, Anastasiou *et al.* presented data from their study of 6671 pregnant women in Greece, who underwent 100 g OGTT in their third trimester with plasma glucose measurements at baseline (fasting), and then 1, 2, and 3 hours post-challenge (abstract 99). The patients were then categorized by their results: normal (NGT), one abnormal value, and two or more abnormal values (GDM). Not surprisingly, the women with GDM were older, heavier, and more likely to have a family history of diabetes. The same, however, was true of women with a single abnormal OGTT glucose value, who are not currently categorizable. Women with one abnormal value were also evaluated as to the timing of the abnormal results: it occurred fasting in 28.5%, at 1 hour in 42.5%, and at 2 or 3 hours in 29%. There were no differences in insulin sensitivity index (ISI) between these groups, however. The investigators concluded that women not currently categorized as having GDM, but with clear abnormalities on OGTT, share some clinical features with their GDM counterparts and

Continued on page 8

## Gestationally Yours

Continued from page 7

that the abnormal glucose result can occur at anytime during the monitoring period.

Todorova-Ananieva and colleagues from Bulgaria discussed results from their prospective case-control study comparing metabolic indices and birth outcomes from 66 pregnant women with one prior unsuccessful pregnancy. A 75-g OGTT with insulin levels was performed at 12 weeks, and the patients were then defined as either

normal (n=21), IGT with concurrent hyperinsulinemia (n=24), or GDM with hyperinsulinemia (n=21). Women with IGT or GDM were placed on metformin (0.75-1.5 g/day), and a repeat OGTT was performed at 36 weeks. During this follow-up test, both groups of metformin-treated women had lower insulin levels while fasting and at one hour than was measured during the baseline study. Moreover, and surprisingly, these values were actually lower as compared to the group of women without GDM at 36 weeks. There were no maternal or fetal complications attributable to

metformin therapy. Newborn body weight was similar in all groups, and the overall miscarriage rate was 13.6% (9/66). The frequency of miscarriages was, interestingly, highest (28.5%) in the normal OGTT group. These data suggest that metformin may have a role in improving fetal outcomes in women with early glucose intolerance and hyperinsulinemia in pregnancy. The study is provocative but needs to be repeated in a randomized, controlled fashion.

We look forward to upcoming changes in the GDM guidelines, based on these emerging data.



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



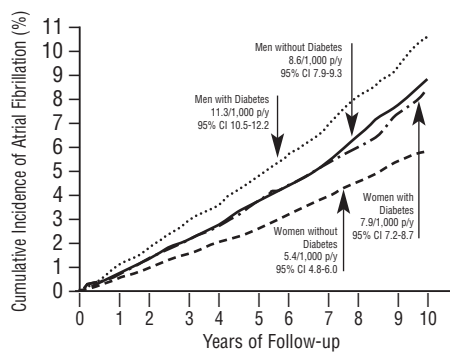
### Exercise Intensity and Effects on Glycemia

Exercise has been shown to improve blood glucose homeostasis. Manders and associates from the Netherlands determined the impact of a single session of either low- or high-intensity exercise on the prevalence of hyperglycemia throughout the subsequent 24-hour period in patients with long-standing Type 2 diabetes (abstract 692). Nine sedentary male patients (mean age 57 years, BMI 29 kg/m<sup>2</sup>) were enrolled in a randomized cross-over study in which they performed an equaloric session of exercise for 60 minutes at 35% of maximal capacity or 30 minutes at 70% of capacity vs. no exercise (control), after which blood glucose homeostasis was assessed by continuous glucose monitoring under strict dietary standardization. Mean glucose concentrations over the 24-hour post-exercise period were reduced following low-intensity exercise (p<0.05), but not by high-intensity exercise (p=0.14), as compared to no exercise. A single bout of exercise reduced the prevalence of hyperglycemia from 35% of the day in the control period to 17% and 28% of the day with the low-intensity (p<0.05) and high-intensity (p=0.13) session, respectively. Whether these differences from exercise intensity persist in the long-run remains to be determined. This provides yet further evidence, however, for the benefits of modest exercise for all our patients.

### A-fib and Diabetes

While the relationship between diabetes and CVD is well described, there is less data on the prevalence and incidence of atrial fibrillation in this patient population. US researchers, Nichols *et al.*, used electronic medical records from Kaiser Permanent Northwest to evaluate the potential association (abstract 137). Records from 17,372 patients with diabetes were compared with age-

Figure 4. Incidence of Atrial Fibrillation by Gender and Diabetes Status



matched controls without diabetes from the same time period. Prevalence of atrial fibrillation was estimated at baseline and patients were followed to determine incidence in those with and without diabetes during the follow-up period (average 7.2±2.8 years). After controlling for age, sex, race, BMI, systolic blood pressure, smoking, and other CV co-morbidities, patients with diabetes had a higher incidence of and much greater risk of developing atrial fibrillation than those without diabetes (Figure 4). Specifically, the risk in women (RR 1.23 [1.07-1.43]) was greater than in men (RR 1.14 [1.01-1.29]). The investigators concluded that a link exists between atrial fibrillation

and diabetes and the impact of gender merits further investigation. Whether this relationship may stem from underlying epicardial coronary disease or microvascular pathology has not yet been adequately explored.

### Gastric Emptying and Post-Prandial Glucose

Piswanger-Soelkner and fellow Austrian researchers investigated the impact of diabetic gastroparesis on glycemia in 26 patients with Type 1 diabetes (mean diabetes duration 32±10 years, mean age 50±13years) (abstract 978). They observed different gastric emptying patterns, as assessed by scintigraphy, which affected post-prandial glucose profiles. Emptying rates were normal in 13 patients, accelerated in 8 patients, and delayed in 5 patients. While baseline glucose values were similar across the groups, patients with accelerated gastric emptying had an increase in glucose that peaked at 90 minutes and decreased thereafter, whereas those with delayed gastric emptying showed a continuous increase in prandial glucose, with peak values 150 minutes after ingestion of the test meal (Table 6). Altered emptying rates due to diabetic gastropathy affect post-prandial glucose, a finding that should be taken into account in the management of Type 1 diabetes in order to optimize prandial insulin replacement.

Table 6. Post-Prandial Plasma Glucose (mg/dl) by Gastric Emptying Status in Type 1 Diabetes Patients

Emptying Status:	Minutes Following Standard Semisolid Test Meal					
	0 min	30 min	60 min	90 min	120 min	150 min
Normal	205	231	254	266	257	286
Accelerated	225	255	299	315	289	267
Delayed	206	258	275	290	326	363

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