

Diabetes 2007

From the 43rd Annual Meeting of the European Association for the Study of Diabetes ■ Amsterdam, The Netherlands

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Like an Old Friend...



Important data on diabetes presented at the 43rd Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2007**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2007** will be followed by a **Diabetes 2007** 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 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

Diabetes 2007 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

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

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The most popular anti-hyperglycemic agent in the world is also one of the oldest—metformin. This drug is the only one demonstrated as monotherapy to have a beneficial effect on cardiovascular outcomes (UKPDS, *Lancet* 1998). It is reasonably well tolerated, safe, and effective in the vast majority of patients. One specific clinical advantage to metformin is the lack of hypoglycemia associated with its use as monotherapy. Metformin's primary mechanism of action is to reduce hepatic glucose production, predominately gluconeogenesis. There is less consistent evidence for other proposed mechanisms, such as improved peripheral glucose disposal and reduced gut carbohydrate absorption. It is widely used as monotherapy, as well as in combination regimens with essentially any other anti-diabetic drug, including insulin. Some new data concerning this old drug emerged this week, underscoring its important role in clinical practice.

Zeller and colleagues from France were interested in the impact of chronic oral anti-hyperglycemic agents on outcomes in patients with acute myocardial infarction (AMI) (abstract 243). Using a national registry of AMI patients, the group studied 1316 diabetic individuals presenting with an acute coronary event during a two-month period in 2005. Four groups were defined: those receiving neither metformin nor a sulfonylurea on admission ("S-/M-", n=594), those on sulfonylureas alone ("S+", n=264), those taking metformin alone ("M+", n=257), and those on combination therapy ("S+/M+", n=201). S-/M- and S+ patients were

slightly older (71 years) than the other two groups (67-68 years). S+/M+ patients had a higher average HbA1c ($8.0 \pm 1.6\%$) than the others (S-/M-, $7.5 \pm 1.6\%$; S+, $7.3 \pm 1.4\%$; M+, $7.4 \pm 1.4\%$; $p < 0.005$). Unadjusted mortality data are displayed in Table 1.

In a Cox multivariate analysis, which incorporated among several clinical factors the glycemic status of the patient, the odds ratios (OR) for mortality at six months compared to the M-/S- group were: 0.84 (95% CI, 0.56-1.25, $p = \text{NS}$) for M+ patients, 0.65 (0.43-0.97, $p < 0.05$) for S+ patients, and 0.27 (0.13-0.54, $p < 0.001$) for M+/S+ patients. Therefore, in this registry, the combined use of sulfonylurea plus metformin was associated with improved survival following AMI. One of the peculiar findings in the UKPDS is that all-cause mortality was increased in those Type 2 diabetes patients who had failed sulfonylurea monotherapy and had metformin added to their regimen. The Zeller data are not consistent with those findings.

Herman *et al.* from the ADOPT study reported this week on the effectiveness of metformin or glyburide in recently diagnosed patients with Type 2 diabetes (abstract 877). This three-year study tested the efficacy over time of three diabetes therapies, metformin, glyburide, and rosiglitazone. In the main paper from this group, published last year (Kahn *et al.*, *N Engl J Med* 2006), rosiglitazone was reported to have the more durable effect on glucose control. In this presentation, the investigators reported on the time to monotherapy failure (defined as time to persistent fasting glucose levels >180 mg/dl) for patients randomized to metformin versus glyburide. Eligibility criteria included ages 30-75 years, Type 2 diabetes diagnosed within the past three years, and fasting glucose 126-180 mg/dl with lifestyle management alone. The mean BMI was 32.2 kg/m². Metformin and glyburide were titrated to 2,000 mg and 15 mg, respectively. Compared with patients randomized to glyburide, the risk of monotherapy failure was reduced by 46.5% with metformin ($p < 0.01$). At four years, 36% of patients in the metformin group had a HbA1c $<7\%$, compared with 26% in the glyburide group ($p < 0.01$).

Table 1. Unadjusted Mortality Following AMI by Type of Anti-Hyperglycemic Drug(s) Used

Drug Regimen	5-day Mortality	6-month Survival
S-/M-	6.1%	80%
S+	3.5%	86%
M+	2.3%	87%
S+/M+	0.5%	95%
<i>p</i> -value	<0.001	<0.001

M = Metformin, S = sulfonylurea.

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Longitudinal linear modeling revealed that metformin maintained the group mean HbA1c <7% to month 45, while glyburide did so to month 33. Metformin therapy was associated with more gastrointestinal side effects (38% vs. 22%, $p < 0.01$), but less hypoglycemia (12% vs. 39%, $p < 0.01$), and more favorable changes in body weight (-2.53 kg vs. +1.81 kg, $p < 0.01$). The ADOPT study demonstrates that in recently diagnosed Type 2 diabetes patients, metformin has a more durable effect on glucose control than does glyburide. Importantly, most, if not all therapies have secondary failure rates over time, necessitating combination therapy in many circumstances.

Jacobsen and Danish collaborators assessed the effect of metformin in patients with Type 1 diabetes (abstract 242). This drug is obviously approved solely for use in patients with Type 2 diabetes. Nonetheless, the scenario of the obese Type 1 diabetes patient with increasing insulin requirements is not an uncommon one in our offices. Whether an insulin sensitizing drug should be tried in these individuals is an interesting but still unanswered question. These investigators examined 100 Type 1 patients with poor glycemic control, manifested by a HbA1c of $\geq 8.5\%$. They

were randomized to either metformin (1,000 mg BID) or placebo, added to their usual insulin regimen, and followed for one year. Changes in the insulin dose over time were allowed, based on clinical response. There were no significant baseline differences between the two groups, with a mean HbA1c of 9.5-9.6%. After 12 months, the mean baseline-adjusted change in HbA1c was not significantly different between groups: metformin, -0.10% (95% CI, -0.32 to 0.12); placebo, -0.23% (-0.45 to -0.01). Subgroup analysis based on initial HbA1c level also found no specific category that benefited from metformin. The reported number of minor and major hypoglycemic events was also not significantly different. As compared to placebo, the total insulin dose by the end of the study was slightly lower with metformin (-5.6 units/day [-8.4 to -2.7, $p < 0.001$], as was body weight (-1.74 kg [-3.32 to -0.17, $p = 0.030$]). The investigators concluded that metformin therapy does not improve glycemia in poorly controlled patients with Type 1 diabetes.

Finally, a Canadian group led by Eurich conducted a meta-analysis of the literature between 1966 and 2007 concerning patients with heart failure and diabetes (abstract 873). Of 968 references initially identified, only six met the rigorous inclusion criteria. Three studies (total patient

number=21,125) involved metformin therapy. In two, the use of metformin was associated with a significant reduction in all-cause mortality (risk estimates 0.61-0.86), with a similar trend in the third. The researchers noted that metformin is the only anti-hyperglycemic agent not found to be associated with any measurable harm in diabetic patients with heart failure. In this cohort, insulin has been associated with increased mortality, and the TZDs, while associated in one study with decreased mortality, do appear to increase heart failure readmission rates. (Sulfonylureas and alpha-glucosidase inhibitors have not been adequately studied in this group of patients.) These data recently persuaded the FDA to recommend lifting the contraindication for metformin therapy in heart failure (although it is still mentioned in the "Warnings" section of the package label that deals with lactic acidosis risk.) Clearly, the drug should still not be used in those with acute or unstable heart failure, but in patients with stable ventricular dysfunction and normal renal status, metformin may, if anything, provide a unique advantage.

For most patients with Type 2 diabetes, metformin remains the optimal first drug choice. Indeed, the more we learn about metformin, the better a drug it appears to be.



Insulin Therapy: Titrating to Target



Insulin therapy is obviously the only effective treatment for Type 1 diabetes. In Type 2 diabetes, many patients will ultimately require it for optimization of glycemic control. This is predominately due to β -cell failure over time. Despite what is now a wide array of oral anti-hyperglycemic agents available for our patients, many still do not achieve target glucose levels despite complex combination therapy regimens. Over the past decade, the availability of both rapid-acting and long-acting insulin analogues have changed the treatment standards for our insulin-using patients. Other than an insulin pump, the most physiological way to give insulin is using these newer insulins in combination—the so-called "basal-bolus" technique with a single long-acting or "basal" insulin given once daily along with multiple smaller doses of rapid-acting "boluses" before meals. Clearly, this more complex method requires a willing patient and frequent glucose monitoring. Many patients either refuse or simply don't have the capacity to engage in such intensive regimens. One of the arts of diabetes management is choosing an insulin regimen that is individualized, based on a variety of factors, including the degree of hyperglycemia, the relative need for fasting vs. post-prandial control, the presence of hypoglycemia unawareness, and the patient's coopera-

Table 2. Pre-meal Rapid Insulin Titration Schedule

The pre-meal BG goal is <100 mg/dl, while avoiding recurrent (>2 events per week) hypoglycemia.

Insulin Dose	"Low" Pre-Meal BG Pattern*	"High" Pre-Meal BG Pattern†
≤ 10 units	↓ by 1 unit	↑ by 1 unit
> 10 units	↓ by 2 units	↑ by 2 units

BG=blood glucose

* 2 BG values ≤ 70 mg/dl during one week.

† 4 BG values ≥ 100 mg/dl during one week

OR 4 bedtime BG values of ≥ 130 mg/dl during one week.

tion and willingness to engage in the process.

Dozens of abstracts were presented in Amsterdam this week focusing in on highly clinical aspects of insulin management. One problem that was addressed by several groups was the need for simple, yet aggressive strategies to control blood glucose once the decision to use insulin is made. It is not enough to simply start insulin—the dose must be titrated in order to reach targets. Sometimes, in Type 2 diabetes, because of insulin resistance, the doses can actually reach quite impressive levels.

One of the specific difficulties in managing Type 2 diabetes is to control post-prandial hyperglycemia, especially if the patient is unaware of his or her carbohydrate intake. In an interesting study from the US, Johnson *et al.* (abstract 983) addressed the possibility that prandial insulin dosed using a fixed algorithm could be as effective as the method based on "carbohydrate counting," within the context of a basal-bolus insulin regimen. (See Table 2 for study algorithm.) 273 obese subjects, aged 18-70 years old, with uncontrolled Type 2 diabetes on a mean of 102 units of insulin per day were randomized to either group, and monitored over a 24 month period. On follow up, both groups achieved similar goal glycemic control (HbA1c of 6.6% with algorithm and 6.5% with carbohydrate counting), with most of the improvement seen by 12 weeks. However, the algorithm group required a significantly larger daily insulin dose (209.5 units/day vs. 163 units/day) and gained more weight (4.0 kg vs. 2.4 kg) than the carbohydrate counters. The rates of hypoglycemia were not statistically different.

Meneghini *et al.* (abstract 224) presented a large randomized study ($n = 5604$) that compared a simplified patient self-adjusted dosing algorithm to standard-of-care physician-driven adjustments

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of detemir basal insulin in Type 2 diabetes. The patient-based algorithm entailed adjusting the evening detemir every three days based on mean fasting blood glucose (FBG): reducing the dose by 3 units if FBG <79 mg/dl, maintaining same dose if FBG between 79-110 mg/dl, and increasing by 3 units for FBG >110 mg/dl. After 26 weeks of treatment, with 88% of the subjects remaining, both groups showed significantly better glycemic control. The self-titrated group had better lowering of the FBG (-32 vs. -22 mg/dl, $p < 0.001$) and HbA1c (to 7.9% vs. 8.0%, $p = 0.01$) compared to the physician-titrated group, albeit with a higher mean daily detemir dose (0.7 vs. 0.5 units/kg). However, the self-titrated group also had more hypoglycemic events (6.4 vs 4.9 events per patient year, $p < 0.001$).

Ahmann and American colleagues randomized 187 patients who were sub-optimally controlled (HbA1c 7.5-12%) on the combination of glargine insulin with oral agents to one of two insulin regimens (abstract 991). The first was pre-meal (TID) premixed lispro 50/50 (consisting of 50% lispro and 50% protamine lispro, the latter component having pharmacokinetics similar to NPH). The second was a traditional basal-bolus approach using glargine and three doses of pre-meal lispro. A structured insulin titration schedule was used in all patients. Baseline characteristics of the study population included age 55 years, diabetes duration 11 years, BMI 34 kg/m², and HbA1c of 8.8-8.9%. After 24 weeks, both groups had markedly improved their glycemic control, slightly more so in basal-bolus patients (Table 3). The authors concluded that basal-bolus therapy resulted in mildly better overall glucose control but that many issues need to be considered in deciding which method is best for a patient who requires advancement in their insulin therapy.

Milek *et al.*, Germany, wondered if a fixed dose basal-bolus regimen is as good as a self-titrated approach. They conducted a 52 week, open-label, randomized trial involving 373 patients with suboptimally controlled Type 2 diabetes on oral agents, basal insulin, or premixed insulin. One half of participants were randomized to either flexible therapy, involving extended patient education, daily blood glucose profiles, carbohydrate counting and patient-driven insulin dose adjustment ("FLEX"). The other half were assigned to a simple, fixed-dose regimen with rare blood glucose monitoring up to two profiles per week ("FIX"). All other medications for diabetes were stopped, but detemir and metformin could be added as needed. The endpoints were blood glucose control, safety, and quality of life. Approximately 55% of patients were male, with a mean age of ~62 years, diabetes duration ~10 years, BMI 31-32 kg/m², and HbA1c ~8.2%. After

Table 3. Glycemic Outcomes, TID Premix vs. Basal-Bolus Insulin

	Pre-mixed TID	Basal-Bolus	p-value
A1C (%)			
Baseline	8.8±1.0	8.9±1.1	0.6041
Endpoint	6.9±0.1	6.8±0.1	0.0208
Change from baseline	-1.87±0.07	-2.09±0.07	0.0208
<7.0%, n (%)	81 (54)	101 (69)	0.0075
≤6.5%, n (%)	53 (35)	74 (50)	0.0072
Daily insulin dose (units/kg)	1.17±0.54	1.38±0.79	0.0019
Overall hypoglycemia (episodes/patient/year)	51.2±50.1	48.7±48.4	0.6189
Nocturnal hypoglycemia	4.8±7.2	6.2±10.7	0.1390
Severe hypoglycemia, n (%)	6 (3.21)	4 (2.14)	0.7506

Data presented as mean±SD, except as otherwise noted.

one year, the FIX group's HbA1c had been reduced to 6.97±0.07%, whereas in FLEX patients the value was 6.72±0.07% ($p = 0.007$). 78% of FIX patients and 75% of FLEX patients achieved this goal (with the addition of detemir at a mean total dose of 27±16 and 25±17 units in the respective groups). The authors concluded that both methods improved glucose control nicely, getting the majority of patients to <7%. However, a patient-adjusted, flexible, pre-meal aspart regimen, which involves more education and effort, appears to provide a modest ~0.2% HbA1c advantage over a fixed-dose aspart regimen.

One of the big announcements at this year's EASD annual meeting concerned the first phase results of the three-year study known as "Treating to Target in Type 2 Diabetes (4 T)." This is a multicenter, randomized, parallel-group trial that is being conducted in the UK to determine the best regimen for initiating insulin in Type 2 diabetes patients failing oral agent therapy. 708 adult subjects were included, with HbA1c 7.0-10.0% (mean 8.5%) on maximum doses of metformin and sulfonylureas. On initiation of insulin therapy the goal was to achieve an HbA1c <6.5% within 12 months, as well as glucose levels pre-meal of 72-99 mg/dl and two-hours post-meal of 90-126 mg/dl. The three insulin regimens included: basal insulin (detemir) QD or BID, "biphasic" premixed aspart 70/30 (consisting of 30% aspart and 70% protamine aspart, the latter component also having NPH-like pharmacokinetics), or solely prandial insulin (aspart) TID. An initial insulin dose was determined by assessing the fasting plasma glucose, body weight, and gender. The frequency of blood glucose monitoring varied between the groups, with biphasic and basal regimens requiring BID monitoring, versus seven times a day for the prandial regimen.

Professor Holman of the Oxford Center presented the results showing a significant lowering of the HbA1c, with mean values at one year 7.3±0.9% (biphasic), 7.2±0.9% (prandial), and 7.6±1.0% (basal), achieved mainly in the first three months, but maintained over the remaining nine months. It was quickly apparent that the basal insulin regimen was

less effective in lowering HbA1c ($p < 0.001$), had fewer subjects meeting goal HbA1c <6.5% (8.1%, $p < 0.001$), and resulted in higher rates of unacceptable hyperglycemia at six months requiring increased frequency of dosing to BID (17.9%, $p < 0.001$). However, it was also noted that the mean total amount of insulin used in the basal group (0.49 units/kg/day) was less than that of the biphasic (0.53 units/kg/day) or prandial groups (0.61 units/kg/day). In support of using the basal insulin regimen, it resulted in a statistically significantly better lowering of fasting plasma glucose, less weight gain, and fewer episodes of hypoglycemia than either the biphasic or prandial insulin regimens. In general, the rates of hypoglycemia were low, and there were no detectable differences from baseline in quality of life for any group, despite the differences in number of daily glucose monitoring and insulin injections.

The conclusions of the trial were that the addition of any insulin regimen can lower the HbA1c, but steadily increasing doses were required to maintain the initial improvement. The results also suggested that most patients would require a second type of insulin to be added after the first year. The second phase of the trial, with results to be reported in 2009, will address the predetermined addition of a second insulin in subjects who did not meet target HbA1c, as well as publishing a much-needed, evidence-based algorithm for the titration of insulin in the primary care setting.

In a critical analysis of the trial, Dr. Roden from Vienna questioned whether the effect of added insulin is due to the total dose, instead of the mode of administration. He recommended the initial use of basal insulin, since it lowered HbA1c, was simpler and was associated with less weight gain and hypoglycemia.

These abstracts demonstrate that successful use of insulin requires aggressive titration schedules. QD basal insulin is a reasonable starting point in most Type 2 patients. Self-mixed or pre-mixed products are a good next step. Ultimately, in many patients, a titrated basal-bolus regimen may be the optimal method.



Preserving Function



The detection of micro- or macroalbuminuria identifies those individuals with Type 2 diabetes who are at increased risk of not only renal failure but also of cardiovascular disease. More recently, decreased renal function has been implicated as a potentially important risk indicator for all-cause mortality. Ubink-Veltmaat *et al.* (abstract 1081), from the Netherlands, investigated the predictive value of these renal measures in subjects from the ZODIAC study. This prospective study of 1145 patients with Type 2 diabetes began in 1998. The presence of micro- or macroalbuminuria at baseline was assessed by the urinary albumin-creatinine ratio (ACR, normal being <21 mg/g in males and <30 mg/g in females). Baseline renal function was assessed by estimating glomerular filtration rate (eGFR) using the Cockcroft-Gault formula (normal ≥ 60 mL/min). Comparisons of mortality (average follow-up, 5.8 years) were made for the total group and between age categories (<70 versus ≥ 70 years). At baseline the subjects were 68.7 ± 11.5 years old, 42% were male, and their mean serum creatinine was 1.1 ± 0.2 mg/dl. Baseline eGFR could be calculated for all subjects; baseline ACR was available in 96%. Of these, 34% had microalbuminuria and 8% had macroalbuminuria. The investigators found that both low eGFR and the presence of micro- or macroalbuminuria were associated with increased mortality (Table 4). When combining both risk indicators, the all-cause mortality rate further increased to 56% compared to 14% in patients with normal renal function. They concluded that a decreased eGFR and the presence of albuminuria predicts all-cause mortality risk in Type 2 diabetes patients, and that the combined presence of these two "renal risk factors" predicts a very poor prognosis.

Following the detection of microalbuminuria, intervention with an ACE inhibitor (ACE-I) or angiotensin receptor blockers (ARBs) is now standard therapy for individuals with both Type 1 and Type 2 diabetes. Recently it has been proposed that high-dose ACE inhibition or ACE-I/ARB combination therapy may have additional benefits in this regard. Exploring this issue further, Schjoedt *et al.* (abstract 1119) from Denmark, evaluated the impact of high-dose lisinopril therapy in a double-blind, randomized, crossover trial consisting of three treatment periods in 56 subjects with Type 1 diabetes. At inclusion, ongoing antihypertensive treatment was discontinued and replaced with slow-release furosemide in individual but fixed doses (median 60 mg daily), for the duration of the study. After a two-month washout period (baseline), patients

Table 4. Six-Year All-Cause Mortality in Type 2 Diabetes Patients by Age and Presence of Reduced Renal Function, Albuminuria, or Both

6-Year Mortality	eGFR		ACR		eGFR + ACR	
	normal	abnormal	normal	abnormal	normal	abnormal
All patients	138/744 18%	195/398 49%†	143/503 21%	171/459 37%†	66/456 14%	108/194 56%†
< 70 yrs	48/497 10%	9/51 18%	24/355 7%	31/180 17%†	22/324 7%	7/22 32%†
≥ 70 yrs	90/247 36%	186/347 54%†	110/282 39%	140/279 50%*	44/132 33%	101/172 59%†

Data presented as ratio and percentage of deceased patients per total patients per group.

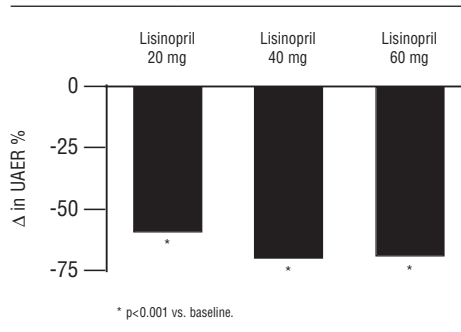
Chi-square tests; * $p < 0.01$, † $p < 0.001$ normal vs. abnormal.

were treated in random order with lisinopril 20, 40, and 60 mg once daily, each dosed for two months. Outcome measures included urinary albumin excretion rate (UAER), 24-hour ambulatory blood pressure, and eGFR (using the MDRD equation). GFR was also measured as ⁵¹Cr-EDTA clearance at baseline. Forty-nine of 56 randomized patients completed the study (failure to complete was mainly due to dizziness in 6/7 patients). When compared to baseline, all doses of lisinopril significantly reduced UAER (Figure 1, $p < 0.001$), ambulatory blood pressure, and eGFR. After adjustment for changes in 24-hour blood pressure, there were no statistically significant differences between dose groups ($p = 0.14$, 20 mg vs. 40 mg). With increasing doses of lisinopril, systolic ambulatory blood pressure was reduced from baseline by 10 (95% CI, 6 to 15), 13 (9 to 19), and 12 (8 to 17) mm Hg, and diastolic by 6 (4 to 8), 8 (6 to 10), and 7 (5 to 10) mm Hg ($p < 0.05$ for diastolic, 20 vs. 40 mg, otherwise NS between doses). The investigators concluded that a high dose of lisinopril (40 mg once daily) is generally

safe and offers additional renoprotection as reflected by greater reductions in UAER in comparison to the more commonly prescribed 20 mg. This benefit appears, however, to be linked to better reduction in blood pressure.

In a related presentation by investigators from Helsinki, Finland, Hiukka *et al.* (abstract 216) reported on the impact of fenofibrate on markers of renal function. Their study cohort consisted of 170 patients with Type 2 diabetes recruited to the FIELD study who had been randomly assigned to fenofibrate 200 mg/day or placebo in a double-blind design and followed for five years. No FIELD patient was taking statin therapy at baseline. The FIELD study (see *Diabetes 2005*, Volume 12, pages 23-24) was a multicenter study examining the effect of this fibrate drug on coronary artery disease endpoints in patients with Type 2 diabetes. Plasma creatinine, overnight UAER, calculated creatinine clearance, and eGFR by the Cockcroft-Gault equation were measured. In this trial, both groups showed comparable and significant decreases in mean blood pressure (from 144/88 to 137/80 mm Hg, $p < 0.001$) and mean fasting plasma glucose (from 144 to 135 mg/dl, $p = 0.007$), but HbA1C remained stable at 7.2%. The investigators found that plasma creatinine increased with fenofibrate but urinary creatinine remained comparable between the groups, resulting in a decrease in both creatinine clearance and eGFR with active therapy. There were no substantive changes in the other measures of renal function. In contrast to earlier reports from this study, fenofibrate does not have a beneficial effect on albumin excretion and, if anything, reduces creatinine clearance and glomerular filtration rate.

Figure 1. Change in UAER vs. Baseline



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Preserving Function

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Overall, these presentations confirm the importance of screening, detecting, and treating renal disease at the earliest possible stage in diabetic

patients. Renal dysfunction identifies those individuals at risk for diabetic nephropathy, and at high risk for coronary disease as well as all-cause mortality. Aggressive management of blood pressure with ACE-Is and/or ARBs is essential, with more

data needed before higher doses of ACE-Is or combination therapy can be routinely recommended. The findings also lend further support to the first-line use of statins, rather than fibrates, in individuals with diabetes, dyslipidemia, and renal disease.

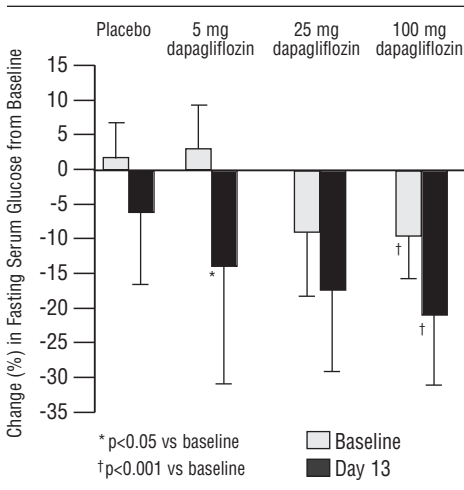


So Many Posters, So Little Time....



The results of a dose-ranging study of dapagliflozin (BMS-512148), a selective sodium-glucose reuptake cotransporter-2 (SGLT-2) inhibitor, were presented this week at the EASD meeting. Located in the proximal tubule, SGLT-2 is a major pathway for renal glucose reabsorption; its inhibition comprises a novel, albeit somewhat peculiar, therapeutic modality for Type 2 diabetes (abstract 763). Drugs in this class essentially lower plasma glucose levels by increasing urinary glucose excretion. In a double-blind study 47 Type 2 diabetes patients who were drug-naïve or on a stable dose of metformin were randomized to placebo (n=8) or dapagliflozin 5 mg (n=11), 25 mg (n=12), or 100 mg (n=16) for 14 days. Patients in the 25 mg and 100 mg dapagliflozin groups had increased urinary glucose excretion corresponding to ~40% inhibition of renal glucose reabsorption versus baseline. A significant decrease in fasting glucose was also observed across the active dose groups (Figure 2).

Figure 2. Change in Fasting Glucose from Baseline



Despite the recent developmental history of rimonabant, there is continued interest in the mechanism(s) by which cannabinoid-1 (CB1) receptor antagonists affect body weight. In a double-blind, double-dummy, four-period crossover study, Addy and multinational co-workers randomized 17 overweight and moderately obese (mean BMI=29.3 kg/m²) male subjects to single doses

of taranabant (an investigational CB-1 receptor antagonist) 4 mg or 12 mg, sibutramine 30 mg (active control), and placebo (abstract 832). Resting energy expenditure (REE) was assessed using indirect calorimetry over a five-hour post-dose period and at 24 hours later. In comparison to placebo, the peak REE geometric mean ratio (90% CI) for taranabant 4 mg, taranabant 12 mg, and sibutramine 30 mg were 1.02 (95% CI 0.98, 1.05), 1.06 (1.02, 1.09), and 1.03 (0.99, 1.07), respectively. These data suggest that increases in REE may partially explain weight loss with CB1 receptor antagonists. Reduction in food intake may also be at work. Using a similar study design, Wright *et al.* studied 36 overweight/obese (BMI range 24.6-35.7 kg/m²) male subjects who were permitted *ad libitum* energy intake (abstract 833). The mean change (95% CI) in energy intake over 24 hours, relative to placebo, was -3% (+5%, -10%), -22% (-16%, -28%), and -12% (-5%, -18%) for taranabant 4 mg, taranabant 12 mg, and sibutramine 30 mg, respectively, with effects equally distributed across all macronutrients. The future of this drug class, however, remains nebulous, since the FDA did not approve rimonabant primarily because of its psychiatric effects (depression).

Thiazolidinedione (TZD) drugs (rosiglitazone, pioglitazone) are activators of the nuclear transcription factor known as peroxisome proliferator-activated receptor (PPAR)- γ . Fibrate drugs (gemfibrozil, fenofibrate) are PPAR- α activators. Initial forays into the development of single agents that serve as agonists to both these receptors (so-called "dual PPAR activators") were ultimately unsuccessful, with muraglitazar associated with an increase in cardiovascular events and tesaglitazar associated with impairment of renal function. These agents did, however, demonstrate a glucose-lowering effect equal to the TZDs, with added beneficial effect on triglycerides and HDL-cholesterol. This experience has not dissuaded the development of "pan-PPAR" agonists, which activate PPAR- α , - γ , and - δ . Theoretically, activation of PPAR- δ may result in improved lipid profiles and, potentially, no weight gain or even weight loss. Katz and US investigators presented

efficacy and safety results from a study of 87 treatment-naïve Type 2 diabetes patients (53 male, mean age 56.6 years, BMI 30.8 kg/m², fasting glucose 158.4 mg/dl) who were randomized to receive a novel pan-PPAR agonist, PPM-204 (25, 75, or 225 mg/day), pioglitazone 30 mg/day, or placebo once daily for 28 days (abstract 220). Statistically significant decreases were observed in fasting glucose (in the PPM-204 225 mg and pioglitazone groups) and fasting insulin (in the PPM-204 225 mg group). The drug was well tolerated and no significant increases in weight were observed. Mild edema was reported in four study patients (one in the placebo group and two and one in the PPM-204 75 mg and 225 mg groups, respectively). It will be interesting to see reports from larger clinical trials with these novel compounds.

vanBallegooye and Dutch colleagues (abstract 223) reported successful results utilizing intraperitoneal (IP) insulin administration (via implantable pump) in patients with poorly controlled Type 1 diabetes. Interim data examining glycemic control, treatment satisfaction, and quality of life (QOL) in the first phase of this on-going, crossover trial comparing IP and subcutaneous (SubQ) insulin administration were presented. There were no significant differences in the treatment groups for the first phase (9 received IP and 10 received SubQ). At the six-month mark, patients receiving IP insulin demonstrated significant improvement in treatment satisfaction, QOL, and glycemic control indices when compared to SubQ administration. Treatment satisfaction measured by DTSQ scores increased by 8.4 points in the IP group (95% CI, 4.8-12.1, $p<0.001$) and WHO-5 measures, a QOL indicator, improved in the IP group by a mean difference of 21 points (95% CI, 6.1-35.6, $p=0.01$). Time spent in euglycemia was significantly greater in the first 3 of 6 months in the IP group, but this was not sustained. However, perceived hypo- ($p=0.020$) and hyper- ($p=0.24$) glycemia significantly decreased with IP insulin. Although quite promising, the results following the crossover phase will assist in determining if favorable results due to IP insulin administration are real and sustainable.

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