

Diabetes 2006

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Life is But a DREAM



Important data on diabetes presented at the 42nd Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2006**, 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. E-mail or fax delivery to your office of **Diabetes 2006** will be followed by a **Diabetes 2006** booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing fee to the Yale Office of Continuing Education, 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 2006 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 interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, 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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Diabetes prevention strategies have become a major focus of clinical investigators throughout the world. The experimental designs of most trials in this area have used either lifestyle changes or pharmacotherapies. The goal in most has been to improve insulin sensitivity, either directly or indirectly, and to slow the progressive β -cell dysfunction that is the prime determinant of advancing hyperglycemia in patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

To date, there have been several successes in this area (Table 1). Several important concepts have emerged from these studies. First, untreated, the progression from IGT to diabetes is in the range of 10% per year, more so in those patients with higher fasting glucoses. Second, in the lifestyle change studies, it is weight loss that appears to be the major predictor of risk reduction. Third, most drugs appear to work at least modestly well, seemingly independent of their precise mechanism of action. Fourth, how durable any of these interventions might be over time is not at all clear. That is, is diabetes truly being prevented or just delayed? Finally, while the societal costs of diabetes are profound, there is a paucity of data on the actual cost-effectiveness of the regimens validated in these trials. Although lifestyle change in and of itself may be inexpensive, the resources necessary to keep patients engaged in these efforts may not be.

Into this discussion enters the Diabetes Reduction Assessment with ramipril and rosiglitazone

Table 1. Randomized, Controlled Type 2 Diabetes Prevention Studies

Study	Intervention	RRR
DaQing	TLC	31-46%
Finnish DPS	TLC	58%
DPP	TLC	58%
DPP	Metformin	31%
STOP-NIDDM	Acarbose	25%
TRIPOD	Troglitazone	55%
Xendos	Orlistat	37%

TLC = therapeutic lifestyle change.

RRR = relative risk reduction.

Medication (DREAM) study, the results of which were unveiled tonight during a standing-room-only session. This prospective, multi-national clinical trial involved 5,269 patients with either IFG or IGT. It employed a 2 X 2 factorial design with patients randomized to either the thiazolidinedione (TZD), rosiglitazone 8 mg qd, and/or the ACE inhibitor, ramipril 15 mg, vs. placebo. That is, 25% of patients received rosiglitazone alone, 25% ramipril alone, 25% both drugs, and 25% placebo only. In this manner the investigators could assess the effectiveness of the two agents simultaneously and also whether they might have an additive effect.

TZDs, which are PPAR- γ agonists with insulin sensitizing properties, have previously been tested in smaller studies for diabetes prevention. In the TRIPOD study, troglitazone, the original TZD, reduced progression to diabetes in a group of Hispanic women (n=133) with a prior history of gestational diabetes from 12.1% to 5.4% over 30 months, with an overall relative risk reduction (RRR) of 55% (p=0.02). A similar effect was seen with pioglitazone in the follow-up to the TRIPOD study using the same population (PIPOD; n=89). One of the important conclusions from these studies, which employed physiological testing of β -cell function, was that the drugs worked mainly by enhancing insulin sensitivity, reducing insulin secretory demands, and preserving islet activity.

Initially, the Diabetes Prevention Program (DPP) included two drug therapy arms, one involving metformin (Table 1) and a second involving troglitazone (n=585). Because of concern regarding its liver toxicity, the troglitazone arm was discontinued early in the study, although follow-up of all participants initially randomized to the TZD continued. At study conclusion, troglitazone therapy was compared with the other interventions, to determine both the short-term results during active therapy and the long-term results after the drug was stopped. During the mean 0.9 year (range 0.5 - 1.5 years) of troglitazone therapy, the diabetes incidence rate was 3 cases/100 person-years, compared with 12/100 person-years in the placebo group, for an impressive RRR of 75% (p<0.001)—one that even exceeded that of

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lifestyle change during the period. In the three years after troglitazone withdrawal, however, the diabetes incidence rate reverted back to essentially that of placebo. These data suggested that TZDs could markedly reduce progression to diabetes during active therapy but that there was no persistence of effect after drug discontinuation. Conclusions here were obviously limited by the relatively short TZD exposure during the DPP.

ACEI inhibitors have also been studied as diabetes prevention agents. Early studies with these drugs suggested a mild insulin-sensitizing effect. By modulating the renin-angiotensin axis, they also possess anti-inflammatory properties, which may attenuate β -cell dysfunction. In a secondary analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial, involving 5,720 older patients with vascular disease randomized to ramipril 10 mg/day vs. placebo, the relative risk of developing diabetes was 0.66 ($p < 0.001$) in the group assigned to active therapy. Similar data have since been reported from secondary analyses from several other ACE inhibitor trials, including PEACE, EUROPA, and D-SOLVD. Two *post-hoc* analyses involving angiotensin-II receptor blockers (LIFE and VALUE) have made similar conclusions. Therefore, there was a substantial body of evidence upon which the DREAM trial was formulated.

J. Bosch of McMaster University in Canada led off the session with DREAM's rationale and study design. Dr. Bosch pointed out that virtually all the studies to date exploring diabetes prevention with either ACE inhibitors or TZDs have been limited either by small numbers of patients, *post-hoc* or secondary analyses, and/or suboptimal diabetes ascertainment methods. DREAM's primary endpoint was the development of diabetes (by fasting glucose, OGTT, or physician diagnosis) or death. Several secondary analyses were also conducted, including regression to normal glucose homeostasis as well as a cardiovascular composite, including myocardial infarction, stroke, cardiovascular death, heart failure, new angina, and revascularization.

Inclusion criteria were age ≥ 30 years and IFG and/or IGT. Major exclusions were contraindication for an ACE inhibitor or a TZD, left ventricular ejection fraction $< 40\%$, other cardiovascular disease with an ACE inhibitor indication, diabetes, renal disease, diseases or other medications that might affect glucose tolerance, and pregnancy. Patient baseline characteristics are noted in Table 2.

S. Yusuf from Canada next presented data from the ramipril arm. As noted in Table 3, there

Table 2. DREAM—Baseline Characteristics

Age	54.7 years
Women	59.2%
BMI	30.9 kg/m ²
Waist circumference, men/women	34.3/32.6 in
IFG only	14.0%
IGT only	57.5%
IFG + IGT	28.5%
Mean fasting PG	104 mg/dl
Mean 2-hr PG	157 mg/dl

IFG=impaired fasting glucose; IGT=impaired glucose tolerance; PG=plasma glucose.

was no significant reduction in the primary endpoint or in its separate components. A predefined outcome was the regression to normal glucose tolerance. Here, ramipril demonstrated a modest effect, increasing the chance of normalization by 16% ($p < 0.001$). As far as the cardiovascular endpoints were concerned, the hazard ratio was 1.08 in favor of placebo but, due to small numbers of events, the confidence intervals were extremely wide (0.76-1.52) and the p -value (0.70) not significant. Side effects included cough in 10% of patients and hypotension in less than 1% (even though patients did not necessarily have hypertension upon enrollment).

H. Gerstein, also of McMaster University, next presented the rosiglitazone data (Table 3). The rosiglitazone-treated group experienced a marked 60% reduction in the primary outcome, with a 62% decrease in the development of diabetes. Active therapy patients also regressed to normal glucose 83% more frequently than did placebo patients. These benefits were independent of ramipril therapy. Stratified analysis showed that diabetes prevention occurred irrespective of BMI, gender, or ethnicity. However, greater effect was seen in the more obese. Regarding cardiovascular endpoints, there was a trend toward increased events in the rosiglitazone group (HR 1.37 [0.97-1.94]; $p = 0.08$), mainly driven by 14 (0.5%) vs. 2 (0.1%, placebo) cases of heart failure ($p = 0.01$). There were no cases of fatal heart failure.

Side effects of rosiglitazone also included an average weight gain of 2.4 kg, which led to

discontinuation of therapy in 1.9% (vs. 0.6%) of patients. Edema led to discontinuation of therapy in 4.8% (vs. 1.6%).

The session was closed by N. Wareham of Cambridge, UK who noted the impressive effects of rosiglitazone on diabetes prevention but tempered this with the trend toward increased cardiovascular events, mainly due to heart failure. Dr. Wareham then raised societal concerns about cost-effectiveness of a treatment that likely needs to be continued indefinitely for any benefit to persist. He also added that the prevention of cardiovascular complications from diabetes should be the primary concern, and this has not yet been demonstrated in this group of patients, at least in the short-term studies conducted to date. Wareham emphasized the importance of exercise and weight loss, which should remain the first recommendation to patients with pre-diabetes.

In conclusion, the DREAM trial shows that rosiglitazone has a marked benefit on the progression to diabetes and the regression to normal glucose tolerance in patients with IFG/IGT, while ramipril has only a modest effect on regression to normal glucose. Neither drug improved cardiovascular outcomes over a period of three years. In fact, there was a trend toward an increased risk of the secondary cardiovascular composite endpoint in the rosiglitazone arm, driven mainly by heart failure events.

Clearly, the diabetes prevention results are impressive and at this point we will need to strongly consider whether such a therapy should be applied more broadly in our practices. There are obvious concerns about heart failure, as was demonstrated in the PROactive trial (Dormandy *et al.*, *Lancet* 2005). Nonetheless the risk is small, and presumably treatable, since there was no excess in heart failure mortality. Since the mechanism of heart failure during TZD therapy is likely related to increased extracellular fluid through renal mechanisms, and not any impairment of ventricular function, this should be a side effect that can be monitored and addressed medically if it occurs. The ramifications of the DREAM trial results await our full digestion of the final manuscripts and the expected commentary from professional organizations.

Table 3. DREAM Primary Outcome (and Composites)

	Ramipril Arm			Rosiglitazone Arm		
	RR	95% CI	p -value	RR	95% CI	p -value
Diabetes or death	0.91	(0.81-1.03)	0.15	0.40	(0.35-0.46)	<0.0001
Diabetes	0.91	(0.80-1.03)	0.15	0.38	(0.33-0.44)	<0.0001
Death	0.98	(0.60-1.60)	0.93	0.91	(0.55-1.49)	0.70



That Old Gut Feeling



The glucagon-like peptide-1 (GLP-1) agonist, exenatide, as well as other members of this class of anti-hyperglycemic agents, continue to garner interest as a relatively new treatment option in Type 2 diabetes. GLP-1 is the major incretin—a peptide secreted by the intestine in response to food and stimulates pancreatic β -cell insulin secretion in a glucose-dependent fashion, while also reducing pancreatic α -cell glucagon secretion, slowing gastric emptying, and augmenting satiety.

In the first presentation of the opening day's sessions, Nauck of Germany and Duran of Spain (abstract 1) reported the results of a multinational (13 countries, 66 sites) 52-week trial comparing the efficacy and safety of exenatide with biphasic insulin aspart 70/30 in patients with Type 2 diabetes inadequately controlled on metformin and a sulfonylurea. Patients (mean age 58.7 ± 9.0 years, HbA1c $8.6 \pm 1.0\%$, and BMI 30.4 ± 4.1 kg/m²) were maintained on their existing oral agents and randomized to adjunctive exenatide 5 μ g twice daily for four weeks and 10 μ g twice daily thereafter (n=253) or biphasic insulin aspart with the dose individually titrated and administered twice daily (n=248).

Both treatments produced reductions in HbA1c (mean \pm SEM) from baseline to week 52 with a trend toward a greater decrease observed in those given exenatide (-1.04 ± 0.07 vs. $-0.89 \pm 0.06\%$ with insulin aspart, $p=0.069$ for between-treatment difference). Greater percentages of those given exenatide attained HbA1c levels of $\leq 6.5\%$ and $\leq 7.0\%$ compared to insulin aspart (Figure 2). Exenatide-treated patients experienced a steady decline in body weight (-2.5 ± 0.2 kg, $p < 0.001$) compared to insulin aspart-treated

patients who gained a mean of 2.9 ± 0.2 kg ($p < 0.001$). The rates of hypoglycemia were similar between the adjunctive-treatment groups (exenatide 4.7 ± 0.7 vs. insulin aspart 5.6 ± 0.7 events/patient-year). Nausea and vomiting were the most common adverse events reported with exenatide (incidence rates of 33% and 15%, respectively), with approximately 10% of those experiencing these symptoms withdrawing from the study (actual withdrawal rates of 3.5% and 1.6%, respectively). During the question and answer session, Dr. Nauck reported that blood pressure decreased among those given exenatide (-5 mmHg systolic and -2 mmHg diastolic) compared to slight increases observed among those on insulin (-1 mmHg systolic and diastolic).

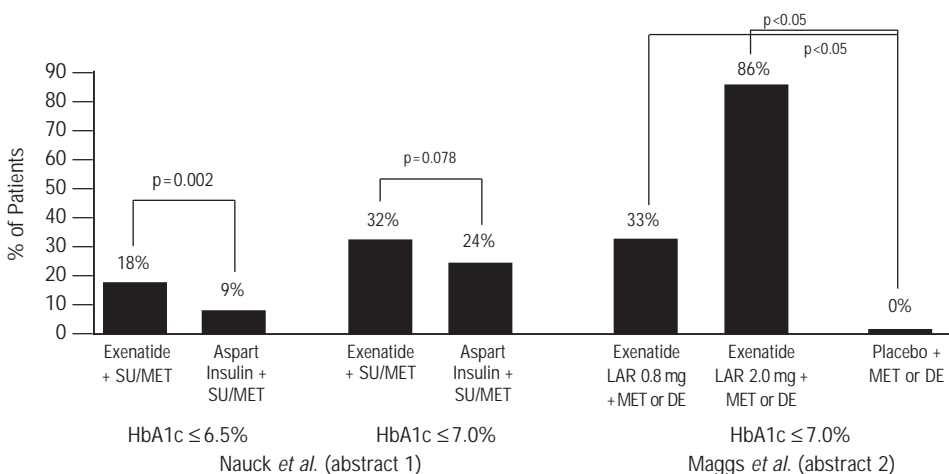
In the second of the opening day's presentations, Maggs of the US speaking on behalf of an international consortium (abstract 2) presented pharmacokinetic, efficacy, and safety data from a placebo-controlled trial of a long-acting release (LAR) formulation of exenatide that is based upon a biodegradable polymeric microsphere platform. A total of 45 patients (40% female, mean age 53 ± 11 years, diabetes duration 5 ± 4 years, BMI 36 ± 6 kg/m²) were studied. Their mean baseline HbA1c was $8.5 \pm 1.2\%$ and fasting blood glucose, 180 ± 36 mg/dl, on either metformin or diet and exercise (DE). The patients were given adjunctive subcutaneous (SQ) doses of 5 μ g exenatide or placebo twice daily for three days followed by once-weekly SQ doses of exenatide LAR 0.8 mg (n=16), exenatide LAR 2.0 mg (n=15), or placebo (n=14) for 15 weeks. Steady-state levels of exenatide administered as the LAR formulation were attained between weeks six and seven, with the levels of exenatide

LAR 2.0 mg attaining levels similar to those achieved with twice daily exenatide dosing. Both doses of exenatide LAR resulted in HbA1c reductions from baseline ($-1.4 \pm 0.3\%$ with 0.8 mg and $-1.7 \pm 0.3\%$ with 2.0 mg) compared to an increase of $0.4 \pm 0.3\%$ with placebo, with significantly greater percentages of exenatide-treated patients attaining HbA1c $\leq 7.0\%$ (Figure 1). There was no mean change in weight in the 0.8 mg exenatide LAR and placebo groups. With the 2.0 mg dose, however, the average patient lost 3.8 ± 1.5 kg. Mild nausea was the most frequent adverse event and was reported by 19%, 27%, and 15% of those given exenatide LAR 0.8 mg, exenatide LAR 2.0 mg, and placebo, respectively. A total of four hypoglycemic events were reported, all of which occurred with the exenatide LAR 0.8 mg dose. At week 15, 67% of patients given exenatide LAR were found to have anti-exenatide antibodies; however, this did not affect the magnitude of the glycemic response.

Madsbad and Danish colleagues (abstract 4) reported the results of a sub-analysis of a study involving liraglutide, a once-daily subcutaneously administered GLP-1 analogue under development. In the primary study, patients with Type 2 diabetes were randomized in a 1:1:1:1 ratio to liraglutide 0.65 mg/day, 1.25 mg/day, 1.90 mg/day, or placebo for 14 weeks. Prior to drug administration and at the conclusion of the treatment period, 28 patients underwent an insulin-modified frequently sampled IV glucose tolerance test and a hyperglycemic clamp (360 mg/dl) combined with IV L-arginine stimulation, all to test the integrity of β -cell function. The glucose tolerance test and clamp were also performed in 12 BMI-, gender-, and age-matched controls. β -cell secretory function was significantly increased in patients treated with liraglutide 1.25 mg (by 114%) and liraglutide 1.90 mg per day (by 97%), as compared to placebo ($p < 0.05$). The 1.25 mg/day and 1.90 mg/day liraglutide dosages increased first-phase insulin secretion significantly by 124% and 107%, respectively ($p < 0.05$). Second-phase insulin secretion increased significantly with liraglutide 1.25 mg/day ($p < 0.01$), but for some reason not with liraglutide 1.90 mg/day ($p = 0.17$).

Other studies of interest involving GLP-1 analogues, included that by Brodows *et al.* of the US who substituted exenatide (5 μ g twice daily for four weeks followed by 10 μ g twice daily thereafter for 12 weeks) for insulin in patients with Type 2 diabetes who were also receiving metformin, a sulfonylurea, or both (abstract 780).

Figure 1. Percentages of Patients Attaining HbA1c Targets in Exenatide Studies



SU=sulfonylurea, MET=metformin, DE=diet and exercise.

That Old Gut Feeling

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In this pilot study, 49 patients (mean age 54 ± 8 years, BMI 34 ± 4 kg/m², HbA1c $8.1 \pm 1.1\%$, fasting glucose 158 ± 247 mg/dl, daily insulin dose 45 ± 30 U, duration of insulin therapy 3 ± 3 years, and duration of diabetes of 11 ± 7 years) were randomized in a 2:1 fashion to either substitute exenatide (n=33) or to maintenance of their current insulin regimen (n=16). Of the 33 patients randomized to exenatide, a high percentage (14 patients, ~44%) were non-completers (four due to adverse events, four due to non-adverse event decisions, and six due to loss of glycemic control). Of the 19 exenatide-treated patients who completed the study, HbA1c decreased by -0.08%, which was similar to the decrease of -0.07% seen among the 15 completers who continued insulin. At the conclusion of the 16-week study, body weight decreased in the 19 exenatide-treated, completer patients (by 4.2 ± 3.2 kg, $p < 0.001$ compared to baseline) and increased by 0.5 kg in those who continued insulin. The high drop-out rate in this study makes it a difficult one to interpret.

GIP: The Other Incretin

Glucose-dependent insulinotropic peptide,

or GIP, is another incretin whose main effect appears to be to stimulate insulin secretion, also in a glucose-dependent fashion. While apparently less important than GLP-1, it is another potential target as a novel anti-hyperglycemic agent. GIP analogues are now under investigation. As reported in an earlier issue of *Diabetes 2006* (Volume 13, Issue 3 "DPP-4 Inhibitors: New Kid on the Block"), the therapeutic potential of these agents is limited by their rapid metabolism by the enzyme dipeptidyl peptidase-4 (DPP-4). At this week's EASD meeting, Irwin and colleagues of the United Kingdom presented animal model data on three long-acting, modified GIP molecules with DPP-4 resistance (abstract 172). Obese diabetic mice were given once daily intra-peritoneal injections of saline vehicle or one of the analogues (all dosed at 25 nmol/kg body weight) for 14 days. All three significantly ($p < 0.05$) reduced non-fasting plasma glucose and overall plasma glucose excursions as compared to saline vehicle. The metabolic and insulin secretory responses to native GIP were also significantly enhanced in all GIP analogue-treated mice compared to controls, indicating no evidence of GIP-receptor desensitization. These effects were accompanied by a significant increase in pancreatic islet area and islet number.

Lifestyle Impact on Incretin Physiology

Lifestyle intervention consisting of reduced caloric intake and increased physical activity improves glucose tolerance and, according to the results of Schaefer *et al.* of Germany and Denmark, these modifications increase GLP-1 concentrations in the two-hour oral glucose tolerance test (OGTT) (abstract 755). In their study, 47 subjects (35 normal glucose tolerance, 12 impaired glucose tolerance) of a mean age of 47 ± 1.6 years and BMI of 30.1 ± 0.9 kg/m² underwent an OGTT before and nine months following implementation of a calorie-restricted diet and regular physical activity. GLP-1 concentration at the nine-month OGTT was significantly higher compared to that at baseline ($p = 0.006$), with the increase in total GLP-1 secretion being positively correlated with a rise in insulin secretion relative to insulin sensitivity ($r = 0.32$, $p = 0.03$) as well as an improvement in glucose tolerance ($r = -0.43$, $p = 0.003$). A positive correlation was found between the increase in GLP-1 concentration and mean dietary fiber content ($r = 0.38$, $p = 0.01$). In contrast, no significant changes in GIP were observed after this lifestyle change.

These presentations demonstrate clearly that we still have much to learn about these very interesting gut peptides.



"Type 2 Diabetes Management: New Insights"

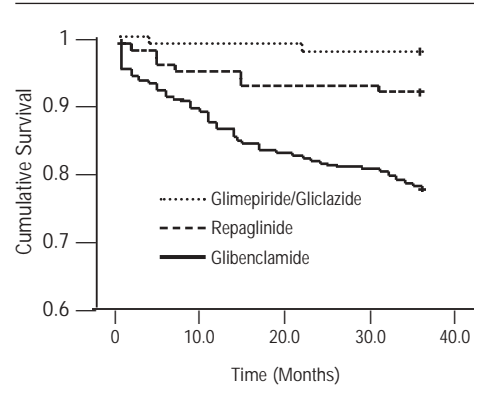


A major concern for clinicians treating patients with Type 2 diabetes is the long-recognized phenomenon of progressive β -cell dysfunction that results in loss of glycemic control over time, necessitating additional treatment strategies. Ultimately, a significant proportion of patients with Type 2 diabetes will require insulin. Elgzyri *et al.* from Sweden followed a cohort of 1,209 Type 2 diabetes patients from diagnosis over seven years to identify non-genetic predictors of β -cell deterioration (abstract 73). Mean time to insulin therapy was 2.5 years, with 47% of patients on insulin after seven years. After adjustments for age, gender, and BMI at diagnosis, the investigators found that the progressive increase in HbA1c (from 6.3% at year one to 7.0% during the subsequent six years) was associated with earlier age at diagnosis, but not with gender, BMI at diagnosis, ethnicity (i.e., Scandinavian origin vs. not), or insulin resistance.

Xu *et al.* from China followed 61 patients with Type 2 diabetes who had been successfully treated for severe hyperglycemia at diagnosis

(initial fasting glucose = 257 mg/dl) with two weeks of stringent control with a continuous subcutaneous insulin infusion (CSII) employing an insulin pump, followed by diet alone (abstract 74). Over a follow-up period of >24 months, near-normoglycemic control was maintained without medication in 26 patients (>50 months in four). According to the Cox proportional hazards model, high LDL-cholesterol (OR 2.5, 95% CI 1.3-4.8) and two-hour post-breakfast plasma glucose (OR 1.4, 95% CI 1.1-1.8) measured just after the completion of CSII were identified as risk factors that affected duration of near-normoglycemia, but, notably, not age, gender, weight, BMI, fasting glucose, insulin response, or insulin sensitivity. By Kaplan-Meier survival analysis, the median time to hyperglycemic relapse was 17 months. These data suggest a significant recuperative capacity of the pancreatic islet cells. With the initial attainment of normoglycemia using CSII, the effects of "glucose toxicity" were abolished, rendering markedly improved β -cell secretory capacity. Accordingly, while we typically see

Figure 2. Three-Year Mortality in Type 2 Diabetes Patients Treated With Different Combinations of Insulin Secretagogues and Metformin



insulin as a treatment of last resort, very aggressive insulin regimens early on in the disease course may have substantive benefits on disease progression.

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..New Insights

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Mannucci *et al.* from Italy conducted an observational cohort study of 2,002 outpatients with Type 2 diabetes, 696 (35%) of whom received combinations of metformin and an insulin secretagogue (abstract 78). After controlling for potential confounding factors (i.e., age, duration

of diabetes, BMI, lipid profile, HbA1c, insulin treatment, metformin doses, and comorbidities), the investigators determined a lower mortality rate over a three-year follow-up period among the patients treated with metformin and a sulfonylurea with greater β -cell selectivity (OR 2.09 for glibenclamide [similar to our glyburide] vs. repaglinide and glimepiride) (Figure 2). These

data, and other similar studies, while retrospective, suggest that glyburide should no longer be considered an optimal secretagogue.

These abstracts provide some insights into patients' metabolic and clinical progression in diabetes. Incorporating these observations into counseling and management of our patients may translate into improved outcomes.



What About Blood Pressure?



It could be argued that treatment of hypertension and dyslipidemia is as important as glycemic control in the overall management of our diabetic patients. Multiple agents are often required to achieve current blood pressure targets; as such, the development of novel agents may aid in the achievement of these goals. At the EASD, Tschoepe *et al.* of the US reported on a randomized, double-blind trial of the investigational drug, aliskiren, with or without ramipril, in the treatment of hypertensives with Type 1 or 2 diabetes (abstract 217). Aliskiren is a novel renin inhibitor that results in less conversion of angiotensinogen to angiotensin I and II, and so reduces sympathetic activation, vasoconstriction, and renal sodium re-absorption. Patients received either aliskiren 150 mg, ramipril 5 mg, or aliskiren + ramipril (150/5 mg) for four weeks followed by forced titration of aliskiren to 300 mg, ramipril to 10 mg, and aliskiren/ramipril to 300/10 mg for an additional four weeks. Results for mean change from baseline sitting systolic and diastolic blood pressures at the end of the trial are shown in Table 4. Aliskiren was shown to reduce plasma renin activity by 62-75% alone or by 46-51% when combined with ramipril. In contrast, ramipril monotherapy increased plasma renin activity by 92-118%. This potential new antihypertensive agent appears to be quite effective and may have some additional benefits. We

Table 4. Least Squares Mean Change From Baseline Sitting Blood Pressures (mmHg)

		<i>Aliskiren</i>	<i>Ramipril</i>	<i>Combination</i>
Overall population (n=826)	Systolic	-14.6	-11.9	-16.5*
	Diastolic	-11.3	-10.7	-12.7 [†]
HbA1c <7.0% (n=400)	Systolic	-14.9	-11.8	-15.6
	Diastolic	-11.3	-10.8	-13.3 [†]
HbA1c ≥7.0% (n=426)	Systolic	-14.9	-12.1	-17.8*
	Diastolic	-11.5	-10.8	-12.4

* $p \leq 0.001$ vs. ramipril, [†] $p \leq 0.05$ vs. aliskiren.

eagerly await more data from clinical studies, particularly outcomes trials on cardiovascular events.

Data from the Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm (ASCOT-BPLA) were also presented this week, focusing on effects in patients with Type 2 diabetes (Ostergren *et al.*, abstract 218). This trial compared two anti-hypertensive treatment strategies for the prevention of cardiovascular disease in more than 19,000 hypertensive patients who had no history of coronary disease. The study was stopped prematurely by its data safety monitoring committee due to a clear benefit of the amlodipine ± perindopril vs. the atenolol ± thiazide regimen. The current report involved a sub-analysis of the 5,137 patients who had Type 2 diabetes at study

entry. The trialists reported that the amlodipine-based regimen significantly lowered the incidence of combined major cardiovascular events (HR 0.86; 95% CI, 0.76-0.98). Fatal or non-fatal stroke was reduced by 25%, peripheral arterial disease by 48%, and non-coronary revascularization procedures by 57%. Interestingly, the absolute risk reduction in major cardiovascular events was very similar in the non-diabetic (2.6%) and diabetic (2.4%) subgroups. This major trial supports the preferential use of the calcium blocker, amlodipine, with or without an angiotensin converting enzyme (ACE) inhibitor, in the treatment of hypertension in diabetes. We remind the reader, however, that given the documented benefits of ACE inhibitors on renal endpoints, there is general agreement that they remain the drug of choice as first-line therapy in all patients with diabetes.



So Many Posters, So Little Time...



Implantation of a gastric stimulator produced near complete relief of nausea, vomiting, and abdominal pain in three of five patients with Type 1 diabetes and gastroparesis of several years duration that was previously resistant to standard treatment measures (Rask *et al.* of Denmark, abstract 1116).

A chewing gum formulation of metformin was found to have a pharmacokinetic profile similar to that of the oral tablet (Guevara-Aguirre *et al.* Ecuador, abstract 797). It is theorized that

this preparation may diminish gastrointestinal side effects seen with current oral preparations.

During the last decade there have been substantial changes in the bacteriologic pathogens isolated in diabetic foot ulcers, with Collina *et al.* of Italy finding significant increases in the prevalence of polymicrobial infections (56% today vs. 49% 10 years ago) as well as isolation of *Staphylococcus aureus* (50% vs. 21%) and *Pseudomonas aeruginosa*

(23% vs. 9%) (abstract 1130).

At present there remains insufficient evidence for an increased risk of diabetes in adults and children with schizophrenia who are prescribed an atypical compared with a typical antipsychotic, according to the findings of a meta-analysis of cross-sectional and cohort trials by Smith *et al.* of the UK and Australia (abstract 874).

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