

Diabetes 2005

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Important data on diabetes presented at the 65th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$10 certificate 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 2005 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.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians. Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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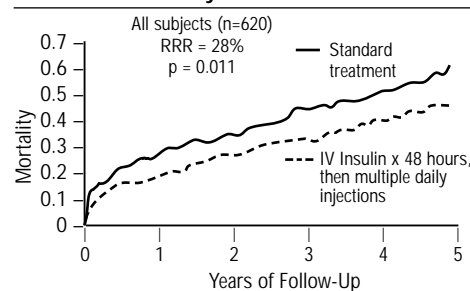
Intensive Insulin Infusion in Acute Myocardial Infarction?



In a debate during the opening session of this week's American Diabetes Association's (ADA) Scientific Sessions, Drs. Hertzell Gerstein from McMaster University and Silvio Inzucchi from Yale University squared off on opposite sides of this contentious issue. First, Dr. Inzucchi, taking the "con" position, pointed out that the best randomized data that adequately demonstrate a benefit from insulin infusion in critically ill patients come mainly from surgical intensive care units. There is extensive observational evidence that admission plasma glucose concentrations are closely associated with patient outcomes following not only acute myocardial infarction (AMI), but a variety of other cardiovascular events. However, a "cause and effect" association cannot be proven from such investigations. Stress hyperglycemia is known to result from the counter-regulatory factors (catecholamines, cortisol) that surge during acute illness. As a result, the plasma glucose is likely to be a parphenomenon, merely a reflection of the sickest (or the "most diabetic") patients. The answer as to whether hyperglycemia during acute cardiovascular events is worthy of treatment must come from randomized clinical trials.

The DIGAMI study (Malmberg, *BMJ* 1997) did show a mortality benefit in those AMI patients with diabetes who were treated with a two-component insulin program (Figure 1). The first involved IV insulin (with dextrose), targeting a plasma glucose of 126-196 mg/dl, relatively conservative by some of the standards currently being proposed.

Figure 1. DIGAMI Study: All-Cause Mortality After AMI



Source: Malmberg et al., *BMJ* 1997.

The second involved an intensive insulin regimen of at least three injections per day upon discharge and extending at least three months. An approximate 30% all-cause mortality benefit was demonstrated at one year and persisted to the study's conclusion at five years. This landmark study set the stage for future investigations in this field. Dr. Inzucchi noted, however, that firm conclusions could not be made from the DIGAMI study because it is impossible to know whether the mortality benefit was attributable to one or the other treatment component. In the DIGAMI-2 study, which was recently published (Malmberg, *Europ Heart J* 2005), the same group of Swedish investigators tackled this specific issue. By randomizing diabetic AMI patients into three groups—intensive IV insulin + intensive outpatient insulin (Group 1) vs. intensive IV insulin only and conventional outpatient care (Group 2) vs. conventional inpatient and outpatient diabetes care (Group 3)—they attempted to tease out the individual effects of the various treatment regimens. (The glucose target in the intensive groups was 126-180 mg/dl.) Unfortunately, as reported in *Diabetes 2004* from Munich, Germany (Volume 10, pg 4), the DIGAMI-2 steering committee stopped the study due to poor patient recruitment and less than anticipated glycemic differences between the three groups of patients. In addition, the overall event rate was much lower than had been predicted, due to implementation of evidence-based cardiovascular risk factor reduction strategies in all groups (aspirin, statins, beta-blockers, ACE inhibitors). In the end there were no statistical differences in cardiovascular and all-cause mortality (Figure 2). In fact, there appeared to be some trends toward fewer events in the conventionally treated group. Based on DIGAMI-2, the use of IV insulin cannot be supported in and of itself, since it had no demonstrable effects on patient outcomes.

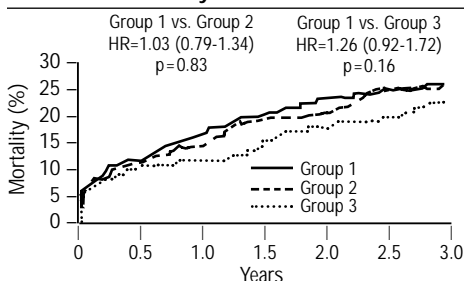
Glucose-Insulin-Potassium (GIK) infusion has been proposed for decades as important adjunctive therapy in AMI patients, with multiple theoretical benefits including increasing intracellular potassium to stabilize cardiac membranes, augmenting intracellular glycolytic flux, decreasing

Continued on page 2

Intensive Insulin Infusion...

Continued from page 1

Figure 2. DIGAMI-2: All-Cause Mortality After AMI



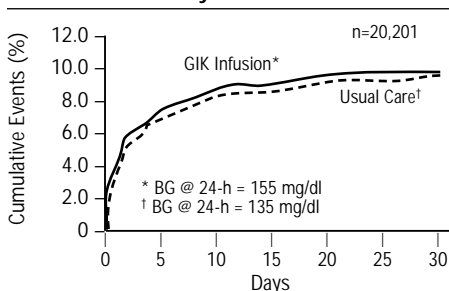
Group 1: Intensive IV insulin + intensive outpatient insulin
 Group 2: Intensive IV insulin only
 Group 3: Conventional diabetes care

Source: Malmberg et al., *Europ Heart J* 2005.

fatty acid availability and oxidation to lower myocardial oxygen demands, and directly reducing cardiac myocyte apoptosis, ultimately decreasing myocardial damage and the chance of arrhythmia. Small randomized GIK studies have previously suggested benefit, but with large confidence intervals. A meta-analysis (Fath-Ordoubadi and Beatt, *Lancet* 1999) was inconclusive, indicating a possible small benefit, but with only a statistical trend ($p = 0.06$). Accordingly, a large international GIK study involving over 20,000 AMI patients was conducted and recently published (CREATE-ECLA Study Group, *JAMA* 2005). Patients were randomized to high-dose GIK vs. conventional care. No benefit on mortality after 30 days was demonstrated in the GIK group (Figure 3).

Administration of IV insulin is not without risk, most notably hypoglycemia, which is considered "the cost of doing business" for intensive glucose control in the inpatient setting. However, the implications of hypoglycemia for the ischemic myocardium are not well known. Several studies have clearly shown a marked increase in circulating epinephrine levels even with mild hypoglycemia (<50-60 mg/dl). Insulin also stimulates the sympathetic nervous system by itself, augments

Figure 3. CREATE-ECLA Study: Mortality Results



Source: CREATE-ECLA Study Group, *JAMA* 2005.

ventricular stroke volume, thereby increasing myocardial oxygen demands, leads to important potassium and phosphate shifts, and may have under-appreciated mitogenic effects. A small observational study recently published from Sweden actually suggested that *both* admission hyperglycemia and any hypoglycemia occurring during hospitalization for acute coronary syndrome significantly increases mortality.

The issue of competing clinical priorities was next reviewed. The cardiovascular field is replete with extensive guidelines concerning the acute and chronic management of AMI patients. The question was posed as to whether the recently published inpatient guidelines from the American Association of Clinical Endocrinologists (AACE) and the ADA are evidence based enough to be added to the "table." Finally, patient groups in the various intensive care units were compared, and the issue that a surgical ICU or medical ICU patient is different from a Coronary Care Unit (CCU) patient was raised. These groups have distinct diagnoses, lengths of stays, and complication and mortality rates. Therefore, the benefit of tight glucose control demonstrated in some of these other settings may not necessarily extend to AMI patients.

Dr. Gerstein next provided an excellent overview of the relationship between glucose and cardiovascular disease. He pointed out that the vast majority of acute coronary syndrome patients has either diabetes or prediabetes. Some studies have shown that only about one-third to one-quarter of patients with acute coronary syndromes or being invasively assessed for coronary artery disease actually has normal glucose metabolism. Also, the degree of hyperglycemia in these patients, whether assessed by admission plasma glucose, average in-hospital glucose control, or oral glucose tolerance testing after cardiac events, was closely aligned with outcomes. In fact, the prognostic implications of hyperglycemia in these settings are very strong and not well appreciated by physicians. Hyperglycemia also has many well-recognized deleterious effects on the vasculature. Moreover, since any degree of hyperglycemia in any setting indicates at least relative insulin deficiency, it is logical to focus on providing adequate insulin to reduced glucose levels to normal or near-normal in these patients.

The biochemical and cellular benefits of insulin on the ischemic myocardium were described, with a focus on glycolytic pathways and mitochondrial fatty acid metabolism. Essentially, insulin improves coronary blood flow while at the same time decreasing myocardial oxygen demands by enhancing metabolic efficiencies of energy generation.

Dr. Gerstein emphasized the important findings of DIGAMI-1, pointing out that the negative

results of DIGAMI-2 do not nullify those of the earlier study. DIGAMI-2 was ultimately underpowered to show benefit, particularly since the treatment groups were not, in the end, distinct enough to make any conclusive statements about the effect of glucose control in the acute setting. Dr. Gerstein pointed out that the glucose differences between the intensive and conventional groups in DIGAMI-1 were marked, whereas those in the follow-up study were minimal, and only at earlier time points. Also, DIGAMI-2's event rates were too low to easily detect any superimposed effects of glucose control. Next, Dr. Gerstein addressed the CREATE-ECLA study results, emphasizing that the GIK group actually had higher, not lower, glucose levels than did conventionally treated patients. Therefore, all that could be concluded was that if insulin is given in AMI but not in a manner that normalizes glucose, it will be ineffective. He underscored the need for a new GIK study with adequate methodology—to provide enough insulin to substantially lower glucose. Only then can the benefits of GIK be really known. Other methodological flaws of the study were also proposed, including lower than ideal primary reperfusion rates and the likelihood that the GIK infusions were not started early enough upon patient presentation.

Dr. Gerstein then reviewed data from the literature showing widespread benefits of tight glucose control in a number of critical care settings. He highlighted the landmark Leuven Study (van den Berghe, *N Engl J Med* 2001), conducted in the surgical ICU. This investigation showed a 42% reduction in ICU mortality in mechanically ventilated patients placed on an aggressive IV insulin infusion that targeted a blood glucose of 80-110 mg/dl. Other important benefits of tight glucose control in the Leuven study included a reduced need for dialysis, blood transfusion, and prolonged mechanical ventilation. Dr. Gerstein believes that such benefits would be extended to other critically ill patients, but only if the same glucose targets are achieved.

In the Q & A session that followed, audience members underscored the reticence on the part of the cardiology community to readily embrace the notion of tight glucose control in their AMI patients. Some remarked that hyperglycemia remains a major problem in their CCU patients. Others pointed out the recognized vasodilatory and anti-inflammatory effects of insulin and their potential benefits in the acute coronary syndrome setting.

In the end, it was agreed that moderate-severe hyperglycemia must be avoided in AMI patients, that IV insulin by itself has no benefit unless glucose levels are also targeted, and that more data are needed to better understand the benefits of euglycemia during AMI.



Diabetic Dyslipidemia: The Troublesome Triad

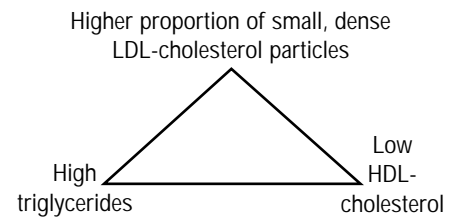


Dyslipidemia—characterized by low HDL-cholesterol, high triglycerides, and a higher proportion of small, dense LDL-cholesterol (LDL-C) particles—is highly prevalent among patients with Type 2 diabetes (Figure 4). LDL-C is a long-established risk factor for coronary heart disease. In a symposium on “Lipid Targets for Cardiovascular Disease in Diabetes,” Dr. Neil Stone from Northwestern University reviewed the benefits of LDL-C reduction as observed in both the general population and in those with diabetes from randomized, controlled clinical trials. He pointed out that reduction in coronary heart disease risk (~25%) has been confirmed through the spectrum of baseline LDL-C levels. Based on results of the Heart Protection Study (*Lancet* 2003) and CARDS (*Lancet* 2004), the ADA recently revised their LDL-C goals to <100 mg/dl (<70 mg/dl in high-risk patients, e.g., those with overt cardiovascular disease) (*Diabetes Care* 2005). Parenthetically, the results of a recent study suggest that 25% of diabetics will require more than two lipid-lowering drugs to decrease their LDL-C below 70 mg/dl (*Diabetes Care* 2005), underscoring how difficult this goal will be for many of our patients.

Drs. John Brunzell from the University of Washington School of Medicine and Henry Ginsberg from Columbia College of Physicians and Surgeons next discussed low HDL-cholesterol (HDL-C) and high triglycerides as secondary therapeutic targets. Each has been demonstrated to be independent risk factors for coronary disease. Both speakers emphasized the physiologic inter-relatedness of the lipoproteins, as well as the atherogenic properties each has beyond its association in the dyslipidemic triad. Aside from the VA-HIT study, however, there are few data that indicate a benefit on cardiovascular disease endpoints from targeted lowering of triglycerides or attention to low HDL-C. Moreover, there are essentially no data in diabetic patients. Yet, both of these lipoprotein abnormalities remain highly predictive of vascular risk and both are intimately linked to the metabolic syndrome. Several studies are underway to further explore the potential benefit of modulating the levels of lipoproteins other than LDL-C.

In the Q & A session, the speakers were asked what triglyceride and HDL-C targets should be used after the guideline LDL-C level has been achieved. The discussants emphasized that for both HDL-C and triglyceride-targeted therapeutics, drugs will need to be evaluated for their *incremental* benefits on top of guideline-based LDL-C lowering. For instance, in the ACCORD trial, fenofibrate is being added to simvastatin to determine the

Figure 4. Dyslipidemic Triad of Diabetes



effects of the fibrate therapy to the LDL-C lowering of the statin. Some of the thiazolidinedione (TZDs) end-point studies, including PROACTIVE (due later this year), may allow us to better understand the impact of reducing triglycerides and raising HDL-C in diabetic patients. Of course, these effects of the TZDs (see below) will be difficult to sort out from the well-known effects of these drugs on insulin resistance itself as well as glucose concentrations. It is anticipated that the results of these types of studies, and others, will guide the future comprehensive approach to the treatment of dyslipidemia in patients with diabetes and/or metabolic syndrome.

In a related abstract, a double-blind, multicenter, randomized trial of 1902 diabetic patients with hypercholesterolemia was presented by Ballantyne *et al.* (962-P). Those patients randomized to combination ezetimibe/simvastatin vs. atorvastatin (at mg-equivalent statin doses between 10 mg and 80 mg for six weeks) showed greater improvements in LDL-C, total cholesterol, and HDL-C (-10.6%, -6.4%, and +2.5% treatment differences, respectively) with similar improvement in triglyceride (~ -26% each).

The effects of the TZDs on lipid metabolism have been a point of some controversy. Moreover, their impact in patients already aggressively treated

with statins is largely unknown. Khan *et al.* conducted an open-label study (COMPLEMENT) in which 305 patients with Type 2 diabetes and fasting triglyceride between 200 - 1000 mg/dl who had received stable (>90 days) statin and rosiglitazone therapy were switched at baseline from rosiglitazone to pioglitazone (30 mg/day titrated to 45 mg/day, at the discretion of the investigator) (553-P). Lipid-lowering agents were maintained at stable, pre-study doses throughout the 17-week study. Statistically significant mean decreases in triglyceride and total cholesterol levels were observed (Table 1), as was a significant mean increase in apolipoprotein A-1 (+9.7 mg/dl, $p < 0.001$) and a significant mean decrease in apolipoprotein B (-2.6 mg/dl, $p < 0.05$). These lipid changes were apparently independent of glycemic control. Furthermore, lipid fractionation showed a shift in LDL-C composition toward larger, more buoyant, less atherogenic particles (555-P). The impact of such changes on cardiovascular risk remains debatable. We would also point out that the methodology of this study (open-label design) was suboptimal, although it did echo results from a recent randomized, controlled trial in patients not taking statins (*Diabetes* 2004, Volume 10, pg 26).

Finally, La Choice and Canadian coworkers studied the contribution of visceral adiposity to postprandial lipemia in patients with Type 2 diabetes (5-OR). Postprandial triglyceride (TG)-rich lipoprotein levels (chylomicron, chylomicron remnants, and very low density lipoprotein [VLDL]) were measured following a standardized breakfast of high fat content (60 g fat/m² body surface area) among 65 men with normal glucose tolerance and 14 males with newly diagnosed but yet untreated Type 2 diabetes. The diabetic patients had significantly higher postprandial TG-rich lipoprotein levels at all timepoints (0, 2, 4, 6, and 8 hours; $p < 0.03$) as well as increased visceral adipose tissue mass (287.2 vs. 125.1 cm² in those with normal glucose tolerance; $p < 0.0001$). However, after adjustment for visceral adiposity, there was no significant difference in post-prandial TG response between the groups. These data underscore the important role of abdominal adiposity in deranged lipoprotein metabolism in our patients with Type 2 diabetes. Since most lipid trials have assessed the less dynamic fasting lipoprotein profile, this has become the standard way to measure lipids in clinical practice. The optimal ways to assess and treat post-prandial hyperlipemia and its clinical import remain largely unknown.

Table 1. Incremental Lipid Effects of Switching From Rosiglitazone to Pioglitazone in Patients Taking Statins

	Baseline Mean (n=303)	Week 17 Mean Change (n=280)	% Mean Change
Triglyceride	303 mg/dl	-64.9 mg/dl	-15.2 [†]
Total cholesterol	199 mg/dl	-20.6 mg/dl	-9.0 [†]
LDL-cholesterol	104 mg/dl	-2.6 mg/dl	2.2
HDL-cholesterol	42 mg/dl	0.0	1.8*

* $p < 0.05$; [†] $p < 0.0001$.



Farewell to Fingersticks?



Strict control of glycemia decreases the risk of microvascular complications, but when such a treatment strategy involves insulin, the risk of hypoglycemia is increased. Periodic monitoring of blood glucose with fingerstick meters has enabled patients to better assess their day-to-day control, but often misses hypoglycemic periods and post-prandial hyperglycemic excursions. Optimally, the measurement of blood glucose should be accurate, precise, reliable, and continuous. Various sensors that provide the patient minute-to-minute blood or interstitial glucose information are being evaluated to address this need. Several studies were described at this week's ADA Scientific Sessions, highlighting the utility of various glucose monitoring technologies.

Miller *et al.* reported on a total of over 20+ patient-years of experience in 26 Type 1 diabetes patients with a long-term sensor system, which is comprised of an intravascular glucose sensor electronically connected to an implanted insulin pump that is refilled every 90 days (Medtronic) (404-P). Although these components are operating independently during the ongoing multicenter feasibility study, a link can be made through software, resulting in a fully implanted "artificial pancreas." Calculated glucose sensor output was determined using a prospective calibration routine based on previously measured home glucose meter data. The sensor's accuracy is determined by comparing its output to home glucose meter data and computing the mean absolute difference (MAD). When MAD exceeds 25% for more than 21 days, the sensor is replaced. Based on this procedure, the mean sensor life is currently 259 days (operational range 90-431 days). After 11 months of use, the implanted sensors had a MAD of 16.4% with over 6000 paired sensor and measured blood glucose values—fairly good by current industry standards. Over 95% of all data points were in the A + B zones of the "Clarke Error Grid." (In these grid zones on a conventional x-y axis graph, proper clinical decisions would have been made by the patient as a result of the sensor reading as compared to the meter reading).

Jovannovic *et al.* prospectively evaluated the accuracy and reproducibility of a transcutaneous glucose sensor (DexCom, Inc.) in 15 patients with Type 1 diabetes (398-P). Two of the enzyme-electrode sensors were inserted under the skin of each study patient, with one sensor providing real-time continuous glucose data to

the patient and the other used in comparisons to fingerstick values. During the first 12 hours of the study, comparative blood glucose values were measured every 20 minutes in a clinic setting; home use data (seven values per day) were collected over the subsequent 60 hours. Of 1139 matched blood/sensor glucose values, 97.5% were in the A + B region of the Clarke Error Grid. Mean absolute relative difference (MARD) was 21.1%. Sensitivity/specificity at established high (200 mg/dl) and low (80 mg/dl) thresholds were 84.8%/88.5% and 84.0%/83.1%, respectively. Reproducibility between the sensors in each patient was assessed using Mean Relative Difference (MRD), which was -1.7% and MARD, which was 16.2%. Patients did not report any adverse events related to the sensors. We feel these results are noteworthy, but such a system may not yet be accurate enough for clinical use.

Interstitial continuous glucose monitoring technology was the subject of several investigations. For example, Deiss and European co-workers described the findings of a pilot study of the Guardian® RT (Real Time) (Medtronic MiniMed) used at home for 10 days by 12 children and 12 adults with Type 1 diabetes (393-P). The Guardian is an adaptation of MiniMed's Continuous Glucose Monitoring System (CGMS®) that has been available for several years mainly for physician use. It is a telemetered glucose monitoring system with continuous display of glucose values and low/high alerts for preset glucose values. Patients changed their own sensor every three days. Based on alarm settings for hypoglycemia (mean 63 mg/dl, range 50-81 mg/dl) and hyperglycemia (mean 200 mg/dl, range 162-234 mg/dl), patients experienced a mean of 0.6 hypoglycemia and 0.8 hyperglycemia alarms overnight and 1.4 hypoglycemia and

2.4 hyperglycemia alarms during daytime hours. As compared to the first day, there was a 38% decrease ($p < 0.05$) in the number of excursions over 200 mg/dl. Fourteen patients reported greater satisfaction with their glycemic management. Four patients reported six mild adverse events, four related to sensor insertion.

Farhy *et al.* from Charlottesville, VA compared the accuracy of two continuous glucose sensors, the FreeStyle Navigator™ (Abbott Diabetes Care) and CGMS® (Minimed), which were concurrently placed on 16 Type 1 diabetes patients (394-P). Patients underwent two hyperinsulinemic clamp studies, each consisting of 70-210 minutes of euglycemia (goal 110 mg/dl) followed by a 1 mg/dl/minute decrease in blood glucose to hypoglycemia (goal 40 mg/dl). Arterial blood glucose was measured every five minutes. While the performance of both sensors was similar in the euglycemic range, the FreeStyle Navigator appeared more accurate in the setting of hypoglycemia (82.4% vs. 61.6% with CGMS, $p < 0.0005$) (Table 2).

In late-breaking posters, a feasibility study of continuous glucose monitoring using near-infrared spectroscopy (1-LB) was described, as were preliminary findings of a biodegradable glucose sensor measuring transcutaneous fluorescence lifetime (3-LB).

Such glucose sensor devices, while interesting, are not ready for widespread use in all diabetes patients. There remain concerns about reliability and cost. It is our hope that research efforts, such as those presented this week, will culminate in one or more of these emerging technologies eventually replacing fingerstick glucose monitoring. This will be a benefit to our patients not only for convenience. With more data, as long as properly interpreted and acted upon, better control should follow.

Table 2. Accuracy of Continuous Glucose Sensors in Euglycemia vs. Hypoglycemia

	Hypoglycemia (BG ≤ 70 mg/dl) (n = 250)		Euglycemia (70 mg/dl < BG < 180 mg/dl) (n = 1104)	
	Navigator	CGMS	Navigator	CGMS
Accurate readings (A zone)	82.4%	61.6%	88.8%	89.3%
Benign errors (B zone)	5.6%	1.2%	10.2%	9.0%
A + B zone	88.0%	62.8%	99.0%	98.3%
Erroneous readings	12.0%	37.2%	1.0%	1.7%

BG = blood glucose; CGMS = continuous glucose monitoring system



Diabetes Prevention: Drugs vs. Lifestyle



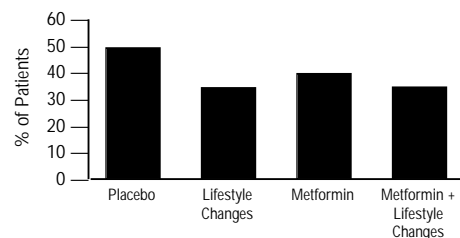
Since publication of the Finnish Diabetes Prevention Study (DPS) and the US Diabetes Prevention Program (DPP) results in 2003, there has been extensive interest in halting the deterioration in glycemic status in at-risk individuals. Clearly, preventing progression of hyperglycemia in patients with prediabetes (i.e., Impaired Glucose Tolerance [IGT] and Impaired Fasting Glucose [IFG]) may be the most effective way of preventing diabetes-related vascular complications. Several related abstracts from around the globe were presented this week.

In a follow-up to his often-cited TRIPOD (Troglitazone in the Prevention of Diabetes) Study, Dr. Tom Buchanan and colleagues from the University of Southern California reported on their experience with a follow-up investigation using pioglitazone (157-OR). In the PIPOD (Pioglitazone in the Prevention of Diabetes) Study, the collaborators treated 89 women with a previous history of gestational diabetes with open-label pioglitazone 45 mg/day. Oral glucose tolerance tests (OGTTs) were performed annually for three years and also at the end of a post-drug wash-out period. Insulin sensitivity and β -cell function were also measured using the intravenous glucose tolerance test (IVGTT)—minimal model. The mean age of PIPOD participants was 39 years and BMI 30.6 kg/m². Two out of three women had IGT. The annual diabetes incidence was 4.6%, equivalent to the 5.3% per year rate in the active therapy group (troglitazone) in TRIPOD. Although there was no placebo control in PIPOD, this rate compares favorably to the

12.4% annual incidence observed in placebo-randomized TRIPOD subjects. Upon further metabolic assessment, those women who did *not* develop diabetes in PIPOD had lower baseline blood glucose levels ($p < 0.01$), slightly higher insulin levels ($p = 0.08$), and slightly better β -cell compensation for their insulin resistance. Also, they demonstrated, at one year, a greater reduction in plasma insulin concentrations (“ β -cell unloading”) during OGTTs and IVGTTs on drug therapy. The authors concluded that unloading the β -cell from insulin resistance is closely associated with protection from diabetes during TZD treatment of women with a history of gestational diabetes—echoing the findings of TRIPOD.

The results of the Indian Diabetes Prevention Program were announced this week (Ramachandran *et al.*, 366-OR). Modeled after the US DPP, this study additionally looked at the effects of *combined* metformin therapy with lifestyle change, metformin alone, and lifestyle change alone in 531 patients with IGT. Notably, the patients studied in India were generally not obese, in sharp contrast to the patients in the US study. After a median follow-up of 30 months, data from 95% of patients were available for analysis (Figure 5). The relative risks of developing diabetes were 0.70, 0.80, and 0.71 in the three intervention groups, respectively. Of note, these results were not as impressive as the 58% risk reduction with lifestyle change and 31% risk reduction with metformin observed in the US DPP study. Moreover, there appeared to be no additional ben-

Figure 5. Incidence of Diabetes Over 30 Months in the Indian Diabetes Prevention Program



efit with diet and exercise on top of metformin.

In trying to translate the results of the US DPP to the “real world” setting, Giri and Feyen from Belgium implemented a similar program in 48 obese, insulin resistant non-diabetic patients. They were randomized into two groups receiving either metformin 850 mg twice daily or placebo, but both combined with moderate calorie restriction (-500 kcal/day) and 30 minutes of daily exercise for one year. Both groups experienced equivalent reductions in weight, BMI, percent body fat, fasting glucose, CRP, and in total cholesterol and triglyceride levels. Interestingly, and in contrast to the US study, however, significant weight loss was maintained at one year only in the metformin group. Clinical outcomes are not yet available.

We look forward to ongoing investigations on the optimal and most cost effective way to prevent the development of Type 2 diabetes in high-risk patients.



So Many Posters, So Little Time...



Foot ulcerations are a major source of morbidity in our patients with diabetes, particularly in those with peripheral vascular disease and advanced neuropathy. Schwegler and Swiss colleagues compared magnetic resonance imaging (MRI) with ¹⁸F-deoxyglucose positron emission tomography (PET) and anti-granulocyte scintigraphy (^{99m}Tc-MOAB) (66-OR). In this prospective study of 20 diabetic patients with chronic (>8 weeks) foot ulcers, seven were ultimately found to have biopsy-confirmed osteomyelitis. MRI was positive in all seven, whereas the other two modalities were only positive in two (same patients). The investigators concluded that unsuspected osteomyelitis may be present in more than one-third of diabetic patients with chronic foot ulcers and that MRI is superior to PET and scintigraphy to detect it.

Chromium has been considered in some circles to be a nutritional supplement with beneficial effects on insulin resistance. Two abstracts this week appeared to confirm this. Martin and US collaborators reported that three months of therapy with 1000 mg of chromium picolinate in diabetic patients improved insulin sensitivity and glycemic control (1778-P). Twenty-seven patients with Type 2 diabetes (mean age, 59.7 years) had previous oral drug therapy stopped and were then randomized to glipizide plus placebo or glipizide plus chromium. Those assigned to the double active therapy group experienced an improvement in insulin sensitivity as well as a 1.2% ($p < 0.005$) decrease in HbA1c (vs. 0.4% in the placebo group). Additionally,

chromium therapy was associated with a reduction in free fatty acid concentrations and a relative attenuation of body weight and visceral fat mass accumulation. Albarracin *et al.* from the US used 600 mg of chromium picolinate with 2 mg of biotin in a three-month, placebo-controlled study involving 368 subjects with Type 2 diabetes on a variety of antihyperglycemics (1784-P). Improvements in HbA1c ($p < 0.001$), total cholesterol ($p < 0.02$), and TG/HDL ratio ($p < 0.0001$) were greater with active therapy. The effect of chromium appeared to be greatest in those with higher baseline HbA1c (as is usually observed in clinical trials), with those having HbA1c >10% experiencing a mean reduction of 1.78% on therapy.

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