

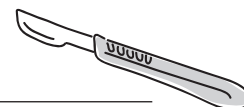
Diabetes 2009

From the 69th Annual Scientific Sessions of the
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BARI Interesting!

Important data on diabetes presented at the 69th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2009**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2009** will be followed by a **Diabetes 2009** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2009 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of β -cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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The long-anticipated results of the Bypass Angioplasty Revascularization in Type 2 Diabetes (BARI-2D) study were presented to a capacity crowd at this week's Scientific Sessions by Dr. Sheryl Kelsey of the University of Pittsburgh, Dr. Robert Frye of the Mayo Clinic, with commentary by Dr. Trevor Orchard, also of Pittsburgh. Dr. John Buse of the University of North Carolina chaired the symposium.

Because of the increased prevalence of coronary artery disease (CAD) in patients with diabetes, as well as their worse outcomes, the trial was set up to answer two important questions in patients with Type 2 diabetes and stable CAD:

- 1) whether elective coronary revascularization combined with aggressive medical therapy is better for patients compared to aggressive medical therapy with revascularization only if symptoms worsen, and
- 2) whether providing more insulin (sulfonylurea and/or insulin) is better for patients than giving medications that improve patients' insulin sensitivity (metformin and/or rosiglitazone). The target HbA1c level in each group was the same at <7.0%.

BARI-2D therefore combined both an 'ischemic control' study with a 'glucose control' study. It had a 2x2 factorial design, with 2,368 patients assigned to the prompt revascularization vs. medical therapy alone (with revascularization only if needed) and also to the two antihyperglycemic strategies. Notably, randomization occurred only *after* a cardiologist had made recommendations regarding coronary artery bypass grafting (CABG) vs. percutaneous coronary intervention (PCI). This approach ensured adequate balance between the groups.

Inclusion criteria were Type 2 diabetes, CAD suitable for elective revascularization, with at least one demonstrable coronary stenosis, and inducible ischemia. Exclusion criteria were CABG or PCI within the previous 12 months. All patients, irrespective of their treatment assignment, had intensive control of cardiovascular disease (CVD) risk factors. The primary endpoint was all-cause

mortality; a CV composite of mortality, myocardial infarction, and stroke served as the main secondary endpoint. The average follow-up was 5.3 years.

Baseline characteristics included a mean age of 62.4 years, 30% female, diabetes duration 10.4 years, HbA1c 7.7%, BMI 31.7 kg/m², insulin therapy in 28%, albuminuria in 33%, neuropathy in 50%, prior MI in 32%, and heart failure in 7% (18% had a left ventricular ejection fraction <50%.) CAD was equally divided between single, double, and triple vessel disease. Not surprisingly, those in whom CABG was advised over PCI had more extensive disease and were older. During the course of the trial, increasing adherence to CVD risk factor reduction strategies occurred, so that by the trial's end, 83% of participants had a LDL-cholesterol <100 mg/dl (95% on a statin), 71% had blood pressure <130/80 mm Hg, and only 11% continued to smoke. The use of CVD medications was also high by study end, with 92% taking an ACE inhibitor or ARB, and 94% on aspirin.

The vast majority (95%) of those randomized to prompt revascularization underwent such a procedure within 6 months. However, 42% of the "medical therapy" group also had revascularization by 5 years, as allowed by the protocol.

Using drugs from the opposing category was allowable to maintain glucose control. So, at the time of 3-year follow-up, 80% of the insulin sensitization patients were using sensitizers and 54% sulfonylureas/insulin. In the insulin provision group, 92% were on sulfonylureas/insulin and 18% on sensitizers. The specific breakdown in the insulin sensitization group was 75% metformin, 62% thiazolidinedione (TZD) (55% rosiglitazone), 18% sulfonylureas, and 28% insulin. Notably, patients assigned to insulin sensitizers over the course of the trial had an overall lower HbA1c (-0.5%) than those on an insulin provision regimen.

The main results of BARI-2D are seen in Figure 1. Essentially there were no overall differences in either mortality or major CV events based on randomization to prompt revascularization or medical therapy, nor based on assignment to a specific anti-hyperglycemic strategy.

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BARI Interesting!

Continued from page 1

In a pre-specified analysis of CABG vs. PCI strata, important differences in outcomes were noted based on randomized assignment, however. For the lower-risk patients advised PCI by their cardiologist, event-free survival was similar in the prompt revascularization and medical therapy groups. In the higher-risk patients advised CABG, though mortality was similar, major CVD events occurred more commonly in those assigned medical therapy (event-free survival: 69.5%, medical therapy vs. 77.6%, revascularization; $p=0.01$).

For the glucose control strategy study, in those undergoing revascularization, there was a trend toward benefit from insulin sensitizers, with major CV events occurring in 20.3% of this group and 25.2% of those assigned to insulin provision ($p=0.059$). In contrast, the event rates were identical at 24.1% in both glycemic strategy groups assigned to medical therapy. Also, in the CABG stratum, prompt revascularization had a greater benefit over medical therapy, especially in insulin sensitizer patients (event rate 18.7% vs. 32%, $p=0.002$) (Table 1).

As far as adverse events were concerned, the investigators saw no differences between the groups in bone fractures or heart failure. There were more hypoglycemia episodes in the insulin provision group (9.2% with at least one severe hypoglycemic

Figure 1. Rates of Survival and Freedom from Major CV Events

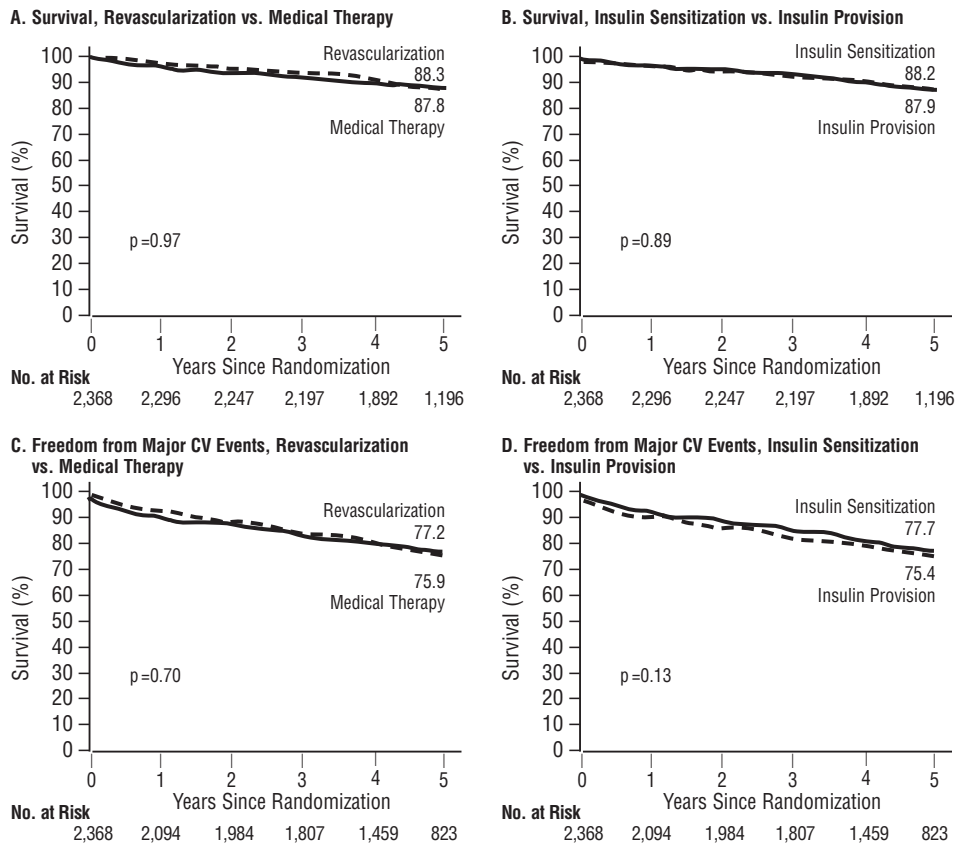


Table 1. Kaplan-Meier Estimates for Event Rates at 5 Years*

Variable	Death from Any Cause			Major Cardiovascular Events		
	Revascularization	Medical Therapy	p-value†	Revascularization	Medical Therapy	p-value‡
All patients						
Insulin sensitization, %	11.2	12.3	0.81	20.3	24.1	0.29
Insulin provision, %	12.2	12.0	0.85	25.2	24.1	0.63
p-value‡	0.75	0.90	0.78§	0.059	0.85	0.23§
PCI stratum						
Insulin sensitization, %	10.2	10.1	0.67	21.1	20.4	0.36
Insulin provision, %	11.4	10.3	0.56	24.9	21.7	0.28
p-value‡	0.79	0.94	0.92§	0.30	0.51	0.84§
CABG stratum¶						
Insulin sensitization, %	13.4	17.1	0.34	18.7	32.0	0.002
Insulin provision, %	13.9	15.6	0.67	26.0	29.0	0.58
p-value‡	0.83	0.71	0.72§	0.066	0.51	0.07§

* A total of 1,065 patients were in the percutaneous coronary intervention (PCI) stratum, and 763 were in the coronary-artery bypass grafting (CABG) stratum.

† Except where otherwise noted, the p-value is for the comparison between the revascularization group and the medical therapy group.

‡ Except where otherwise noted, p-value is for the comparison between insulin-sensitization group and the insulin-provision group.

§ The p-value is for the interaction between the cardiac study group and the glycemic study group.

¶ In the CABG stratum, the rate of major cardiovascular events differed significantly ($p=0.02$) among the four mutually exclusive randomized study groups.

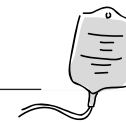
reaction vs. 5.9% with insulin sensitizer, $p=0.003$). There was no apparent additional risk from rosiglitazone, in keeping with the findings from the RECORD study (see Issue 2). Also, there was slightly more weight gain in the insulin provision group (BMI 32.5 vs. 31.7 kg/m² by study end, $p=0.003$).

The investigators concluded that in Type 2 diabetes patients with stable CAD, a strategy of aggressive medical therapy was equal to prompt revascularization in those whose disease was amenable to PCI. However, outcomes were better with prompt revascularization in those requiring CABG. These patients had similar outcomes irrespective of anti-hyperglycemic treatment assignment, with insulin sensitizers appearing to provide no distinct benefit overall. A trend toward a benefit was detected in those patients assigned to prompt revascularization, driven mainly by a reduction in major CV events in those receiving CABG.

We feel that BARI-2D indicates that the overall effects on CV outcomes from an insulin sensitizer strategy appear equal to those of an insulin provision strategy, although there may be trends favoring the sensitizers in promptly revascularized patients that require further study and analysis.



Glucose Control in the Hospital: How Tight is Too Tight?



There have been many changes this year in our approach to the hyperglycemic hospitalized patient. Data extending for more than a decade have associated inpatient hyperglycemia with adverse outcomes in both the critical and non-critical care settings. Whether glucose was serving as a true mediator of poor outcomes (wound healing, infection risk, altered myocardial energy dynamics) or simply an innocent marker of the sickest patients has always been a controversial question, with evidence pointing to either side of this argument.

Not quelling the controversy at all has been the fact that early intervention trials had major methodological flaws (such as the use of historical controls), which prevented their adequate interpretation and translation into clinical guidelines. In 2001, however, van den Berghe and Belgian colleagues presented their landmark paper in the *N Engl J Med* (345:1359-67), describing a 42% reduction in surgical ICU mortality in a group of over 1,600 patients assigned to intensive insulin infusion versus conventional care. The glucose target in the intensive group was radically lower than had ever previously been proposed: 80-110 mg/dl—essentially euglycemia. These data led to a great deal of interest in the field, as hospitals throughout the world implemented stringent insulin-based strategies to control hyperglycemia at their institutions, even in the non-critical care setting. These efforts were encouraged by medical societies and professional groups who published guidelines further endorsing strict inpatient glucose targets. Quality care efforts proved to be easier at some hospitals than others, as entrenched attitudes toward the relative importance of glucose in this setting often prevented change at the local level. Throughout these initiatives, the underlying fear of hypoglycemia, with its unknown implications in patients who are ill, frequently dominated the discussions.

Over the last two years, the pendulum appears to have swung in the opposite direction. Indeed, it has proven difficult to replicate the van den Berghe findings at other centers. First, in this group's own follow-up study, conducted in the medical ICU, no overall benefit on mortality could be demonstrated with intensive glucose control, despite an identical protocol as used in their surgical ICU. In the subgroup of patients requiring ICU care for at least 3 days, however, a reduction in mortality was seen. Two smaller, multicenter studies, VISEP (patients with sepsis) and Glucontrol (mixed medical-surgical ICUs), found no benefit and much more severe hypoglycemia in the intensive arms of their trials.

Most recently, the NICE-SUGAR study (Finfer *et al. N Engl J Med* 2009;360:1283) appeared to corroborate these latter findings and actually suggested a potential risk from aggressive insulin infusion therapy. In this multicenter mixed surgical-medical ICU trial, more than 6,100 patients were randomly assigned, within 24 hours after admission, to either intensive glucose control, with a target blood glucose range of 81 to 108 mg/dl, or conventional glucose management, with a target of ≤ 180 mg/dl. Insulin infusion therapy was used in both groups. The primary end point was 90-day all-cause mortality.

Because the treatment targets were closer than in prior trials, the mean glucose level between the two groups only differed by 29 mg/dl (time-weighted glucose, 115 [intensive] vs. 144 mg/dl [conventional]). Insulin was administered to 97% and 69% of patients, respectively. Fatal outcomes occurred in 829 patients (27.5%) in the intensive group and 751 (24.9%) in the conventional group (odds ratio [OR] for mortality with intensive control, 1.14 [95% CI, 1.02 to 1.28; $p=0.02$]). Moreover, there was no benefit from stringent glucose management demonstrated in any of the pre-specified subgroups. Specifically, the treatment effect did not differ significantly between surgical and medical patients (OR for death, intensive group, 1.31 and 1.07, respectively; $p=0.10$). As seen in other trials, severe hypoglycemia (<40 mg/dl) was encountered in 6.8% and 0.5% of the two groups, respectively (OR 14.7 [9.0-25.9]). There were no differences between groups in terms of hospital or ICU length of stay, renal function, organ failure rates, or the need for mechanical ventilatory support.

In light of these and other recent findings, a Consensus Statement by the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) has just advised less stringent targets than before. The final recommendations of the group are seen in Table 2.

A lively symposium was held on Monday, with members of the consensus committee presenting the recommendations and their rationale. Dr. Harold Lebowitz, chairman, began the program with a brief review of the NICE-SUGAR results. He then posed the following questions to the subsequent speakers:

- Should this trial change our management of acute hyperglycemia in critically ill hospitalized patients and, if so, how?
- What is the cause of the increased 90-day mortality?

Table 2. AACE/ADA Consensus Statement on Glucose Control for Inpatients

ICU Setting

- Insulin infusion preferred
- Starting threshold not higher than 180 mg/dl
- Maintain blood glucose 140-180 mg/dl (greater benefit likely at lower end of this range)
- Somewhat lower targets, while not evidence-based, may be appropriate in selected patients if already being successfully achieved by an institution
- Targets of < 110 mg/dl no longer recommended, due to safety concerns

Non-ICU Setting

- For most patients:
 - pre-meal blood glucose < 140 mg/dl
 - random blood glucose < 180 mg/dl
- More stringent targets may be appropriate in stable patients
- Less stringent targets may be appropriate in patients with severe comorbidities
- Scheduled subcutaneous insulin using the basal- nutritional-correction approach is preferred; avoid prolonged therapy with regular insulin sliding scales alone.

AACE= American Association of Clinical Endocrinologists.

- Is hypoglycemia implicated in the adverse outcome?
- Could the increased CV mortality be related to an effect of insulin?

Dr. Silvio Inzucchi from Yale first provided a critique of the NICE-SUGAR study. While generally complimentary of the trial, he outlined NICE-SUGAR's strengths and limitations (Table 3). Specifically, he wondered about the outcomes in the roughly 10% of patients assigned to intensive therapy who were withdrawn early from the study. They did not receive insulin infusion, but their outcomes were still assessed in the classical intent-to-treat analytical plan. A "per-protocol" analysis would shed light on this question. Despite these issues, NICE-SUGAR clearly shows no benefit from reducing glucose to < 110 mg/dl in critical care patients and some risk—at least hypoglycemia, if not a mortality risk.

Dr. Guillermo Umperierrez, Emory University, was the next speaker. He reviewed the frequency and implications of hypoglycemia in hospitalized patients. Dr. Umperierrez emphasized the need to minimize this complication whether the patient is

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Glucose Control in the Hospital...

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in the ICU or on a general hospital ward. He then reviewed his group's own data, confirming that basal-bolus insulin therapy with glargine-gulisine provided several advantages to traditional regular insulin sliding scales. He also noted, however, that in his studies, an older NPH-regular insulin regimen proved to be as effective in the hospital as one using the analogues, detemir and aspart.

Dr. Etie Moghissi, from U.S.C., co-chair of the Consensus Committee, then provided the historical background for the committee's work, emphasizing the changing landscape of clinical trial results in this arena. She underscored the charge given to the committee—to review the literature and assess its implications for clinical practice, and to recommend reasonable, achievable, and safe glycemic targets for hospitalized patients.

These comments provided a segue to the afternoon's final presentation by Dr. Mary Korytkowski, University of Pittsburgh, and co-chair of the Committee. Dr. Korytkowski reviewed the guidelines as listed in Table 2. Areas of future research were next described. These include physiological underpinnings of stress hyperglycemia, implications of severe hypoglycemia in the hospital setting, glycemic targets for non-critically ill patients and in pediatrics, and the effect of glycemic variability. Dr. Korytkowski then summarized the symposium by noting that an

Table 3. Strengths and Limitations of the NICE-SUGAR Study

Strengths

- Large study (N=6,104)
- Multicenter design
- Patient characteristics reflective of a general ICU population
- Uniformly applied, web-based IV insulin protocol
- Hard primary endpoint (90-day mortality)
- Robust analytical plan

Limitations

- Specified treatment targets and ultimate glycemic separation (27-29 mg/dl) not as large as in prior trials
- Treatment target not achieved in the intensive arm
- Variable methods for measuring blood glucose between hospitals
- More steroid therapy in the intensive arm
- More hypoglycemia in the intensive arm (15-fold higher)
- No explanation of increased mortality in the intensive arm (? hypoglycemia)
- ~10% early withdrawals in intensive arm; no 'per-protocol' (completers) analysis provided

appropriate level of glycemic control can be achieved in the majority of hospitalized patients who experience hyperglycemia, and that clinical judgment and ongoing assessment of a patient's clinical status must be incorporated into day-to-day decisions regarding glycemic management.

In the question and answer session that followed, several academic members expressed concern that the new guidelines would lead to a

setback in the gain that had been made over the past several years in hospital glucose control. Specifically, they wondered why the guidelines did not endorse a goal of 110-140 mg/dl. The committee members underscored the evidence-based approach they used in formulating the recommendation. They also advised that a somewhat tighter target may be acceptable in selected patients, especially if it can be safely achieved.



Update on Drug Development: Diabetes & Obesity



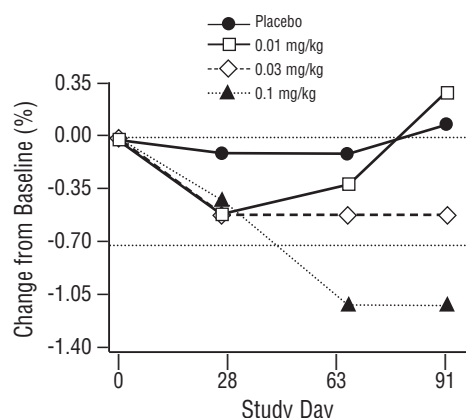
Despite an increasingly crowded field, investigators in academia and the pharmaceutical industry continue to explore new mechanisms of action for both anti-hyperglycemic and anti-obesity drugs.

Evidence suggests a role for elevated IL-1 β in β -cell failure of diabetes, and IL-1 receptor blockade has been shown to improve glycemic control and β -cell function, thus validating this pathway as a target for therapy. Donath *et al.* from Switzerland and the US administered a single IV infusion of placebo or the anti-IL-1 β antibody, XOMA 052, at doses of 0.03, 0.01, or 0.1 mg/kg to patients with inadequately controlled Type 2 diabetes (abstract 113-OR). HbA1c was reduced with study drug (0.1 mg/kg) by a median of 1.1% (Figure 2) and a maximum of 2.2% at 3 months, vs. being increased (0.1%) in placebo patients. XOMA 052 also continuously increased insulin production at 1 and 3 months compared to base-

line, while placebo-treated patients showed no improvement. Based on the promising HbA1c reduction with a single dose of XOMA 052, the investigators commented that once monthly or less frequent dosing will be assessed in future studies.

On the basis that chronic inflammation is mediated by NF- κ B and may be involved in the pathogenesis of Type 2 diabetes, Goldfine and US investigators evaluated salsalate, a non-acetylated prodrug of salicylate, in patients with Type 2 diabetes (mean age=56 years, BMI=34 kg/m², 58% male, HbA1c=7.7%) (abstract 115-OR). They conducted a multicenter, double-blind, dose-ranging study in which 108 patients were randomized to receive salsalate (3.0, 3.5, or 4.0 g/day divided in 3 daily doses) or placebo, as an add-on to their current therapy, for 14 weeks. A decrease in HbA1c ($\geq 0.5\%$, $p < 0.01$), mean fasting glucose (27-32 mg/dl), and triglycerides (31-49 mg/dl), and

Figure 2. Median HbA1c After a Single Dose of XOMA 052 or Placebo in Type 2 Diabetes Patients



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Update on Drug Development

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increase in mean adiponectin concentration (1.7-2.8 µg/ml) was observed with all doses of salsalate. Reductions in concomitant diabetes medications were required in the treatment groups, vs. increases in the placebo group. Tinnitus was more prevalent in the salsalate groups (20% vs. 11% placebo).

In a randomized, open-label, multicenter study, Karounos *et al.* from Kentucky and California randomized 112 patients with Type 2 diabetes (age 54 years, HbA1c 8.2%, BMI 36 kg/m²) to intensification of basal insulin therapy with prandial pramlintide (120 µg tid), rapid-acting insulin, or both agents (abstract 118-OR). This 36-week study consisted of 2 phases. Phase 1 (24 weeks) compared pramlintide with rapid insulin when added to basal insulin. Phase 2 (12 weeks) explored additional prandial therapy for patients failing to achieve HbA1c ≤6.5% at the end Phase 1. Compared to rapid insulin, pramlintide added to basal insulin therapy resulted in a similar improvement in glycemic control (HbA1c, -0.9%), a lower risk of hypoglycemia (55% vs. 82%), and no weight gain. Addition of the alternate prandial agent in Phase 2 resulted in maintenance of HbA1c and weight. Addition of pramlintide in Phase 2 for subjects on rapid insulin in Phase 1 allowed a decrease in daily insulin dosage (39 and 19 units/day at weeks 24 and 36, respectively).

Beysen *et al.* from California conducted a multicenter, randomized, double-blind study to investigate the potential glucose-lowering mechanism(s) of colesevelam, a bile-acid sequestrant (abstract 476-P). Patients with Type 2 diabetes were randomized to colesevelam 3.75 g/day (n=27) or placebo (n=28) added to their current antihyperglycemic regimen (number of colesevelam/placebo patients: metformin 16/20; sulfonylurea 4/2; metformin + sulfonylurea 5/5; diet 1/1) for 12 weeks. Colesevelam reduced fasting plasma glucose and HbA1C compared to placebo, without the increase in endogenous glucose production that occurred with placebo. These improvements in fasting glucose homeostasis were not associated with changes in insulin concentrations or insulin resistance. Further research is required to elucidate which tissues and what mechanisms account for the beneficial effects of colesevelam on fasting glucose homeostasis. Of note, this bile acid sequestrant, available for years as a lipid-lowering agent, was recently approved for use in Type 2 diabetes as an antihyperglycemic drug.

Animal data suggest that optimally timed delivery of bromocriptine to the central nervous

Table 4. Change from Baseline in HbA1c and Fasting Plasma Glucose at Week 52

Baseline HbA1c	HbA1c (%)		Fasting Plasma Glucose (mg/dl)	
	Cycloset	Placebo	Cycloset	Placebo
≥7.5%	-0.72*	-0.57*	-22*	-21
≥8.0%	-1.3*	-1.07*	-54*	-44*
≥8.5%	-1.6*	-1.21*	-58	-54

*p<0.05

system reduces hepatic glucose production by improving hypothalamic dopaminergic tone. Cycloset®, a quickly absorbed formulation of bromocriptine (n=53), was compared to placebo (n=68) for its impact on glycemic control by Scranton *et al.* from Rhode Island and Massachusetts in patients failing (HbA1c >7.5%) TZD therapy (abstract 481-P). Its central mechanism of action is thought to be potentially additive to other oral hypoglycemics. Concomitant oral hypoglycemic therapy was comparable in each group. Bromocriptine therapy produced sustained reductions in HbA1c over a 52-week treatment period in patients failing TZD therapy (Table 4). This is another agent, recently approved as a diabetes drug by the US Food and Drug Administration (FDA), which has been available in other formulations for years, used to treat hyperprolactinemia.

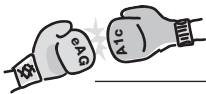
The efficacy of dapagliflozin (DAPA), a selective sodium-glucose co-transporter 2 inhibitor (a renal glucose reabsorption blocker) was evaluated in patients poorly controlled with insulin (at least 50 units/day) plus baseline oral agents (metformin and/or TZDs). Wilding *et al.* from Great Britain, Belgium, and the US randomized 71 patients to receive DAPA 20 mg, DAPA 10 mg, or placebo, comparing glycemic control parameters at baseline and at 12 weeks (abstract 482). The groups were maintained on oral agents taken before study entry and 50% of baseline insulin doses. In each DAPA arm, 65% of patients demonstrated a ≥0.5% decrease in HbA1c versus 16% of patients on placebo. Additionally, DAPA lowered postprandial glucose and weight more than placebo. The investigators concluded that DAPA can improve glycemic control in patients receiving concomitant oral agents in the setting of a 50% decrease in baseline insulin dose. This agent's mode of action involves the induction of glycosuria. Increased incidence of urinary tract infections has been reported, and more safety data are needed.

Smith *et al.* from the US reported the results of the BLOOM trial that evaluated the safety and efficacy of lorcaserin, a selective 5-HT_{2C} receptor agonist, an important modulator of food intake (abstract LB 96-P). In this placebo-controlled

trial, 3,182 subjects (84% women, weight 100 kg, BMI 36.2 kg/m²) were randomized to receive lorcaserin 10 mg twice daily or placebo for one year. After one year, the lorcaserin group was again randomized to receive placebo or active drug for an additional year. Echocardiograms were conducted at baseline and throughout the 2-year study. Average weight loss at year 1 was 5.8 kg with lorcaserin and 2.2 kg with placebo (p<0.0001; ITT-LOCF). At the end of year 2, there was less weight regain in the patients continued on lorcaserin than in those re-randomized to placebo. Cholesterol, triglycerides, and blood pressure significantly decreased in the lorcaserin versus placebo groups at year 1. There was no difference between groups with respect to FDA-defined cardiac valvulopathy, a concern with other serotonergic medications.

Wadden and US collaborators evaluated the effects of naltrexone/bupropion in conjunction with intensive behavioral modification on body weight (abstract 37-OR). Patients (n=793) with BMI ≥27 and ≤45 kg/m² were randomized (3:1) to receive sustained release naltrexone/bupropion (32 mg/360 mg) (n=482) or placebo (n=193) for 56 weeks along with 28 group sessions of behavioral modification (diet and exercise counseling). At 56 weeks, significantly greater weight loss occurred in the naltrexone/bupropion group (-9.3%) when compared to placebo (-5.1%, p<0.001). A higher percentage of patients in the active treatment group achieved body weight loss of ≥5%, ≥10%, and ≥15% (all p<0.001). Side effects occurred with greater frequency in the active treatment group. Nausea was the lead cause of discontinuation and occurred at a rate of 34% with naltrexone/bupropion vs. 11% with placebo. Two cases of serious cholecystitis also occurred in the active treatment group.

While we recognize that only a fraction of these anti-obesity compounds will actually become commercially available, we feel that keeping abreast of emerging drugs and drug targets is of significant interest to those involved in the care of diabetes patients.



Translating the A1c



Should laboratories report an “estimated average glucose” (eAG) along with their hemoglobin A1c (HbA1c) values?

Over the last two years, glycated hemoglobin assays have been standardized and are becoming a contender as the leading diagnostic test for diabetes (see Issue 2). A lively debate at this year’s meeting focused on the laboratory reporting of eAG alongside the A1c. In other words, does the A1c need a ‘translator?’

eAG is a number derived from the measured blood A1c value, and is meant to represent the mean blood glucose over the same 3-month time period. It would be presented using the same units as blood glucose values from glucometers or chemistry laboratories, ie, mg/dl or mmol/l. The eAG translates the percent of glycated hemoglobin, an established measure of chronic glycemic control, into an understood quantity—allegedly more patient-friendly than a percent value.

However, eAG is merely a calculated estimate, based on large correlative datasets, and its potential use brings up many concerns about the intricacies and shortcomings of the A1c test itself.

Dr. David Nathan of Massachusetts General Hospital kicked off the debate in support of eAG reporting from a clinical perspective. He reviewed how the A1c has a close association with a meaningful clinical outcome, mainly complications from diabetes. He also emphasized how the linear regression calculation of eAG was robustly determined from a clinical study of daily continuous glucose monitoring (CGM) in people of different populations.

Zachary Bloomgarden, MD, from Mt. Sinai in New York, presented the rebuttal, in which he listed the limitations of A1c in predicting eAG. Since it is a measure of the non-enzymatic reaction between glucose and hemoglobin, A1c is affected by any condition that might alter hemoglobin status,

including anemia, pregnancy, or uremia. Other factors such as age, ethnicity, and heritability also affect individuals’ A1c levels, independent of the chronic glucose exposure. For example, non-Hispanic blacks have a 2.4-fold increase in likelihood of an elevated HbA1c relative to Caucasians, even when corrected for glucose levels. Not only do different ethnicities have differing rates of glycation, but there is intra-patient variability in hemoglobin glycation. Dr. Bloomgarden stated that the eAG “dumbs down” the HbA1c because it does not take these intricacies into account.

This argument will likely continue into the foreseeable future. We’d agree that presenting an average glucose would be very meaningful for patients to better interpret the implications of their A1c. However, we are also concerned that the eAG calculation may not be truly reflective of the actual mean glucose during the prior 3 months in all patients.



So Many Posters, So Little Time...



Modulating RAS

Tauren *et al.* from Los Angeles carried out a randomized, controlled trial of aggressive vs. low dose inhibition of the renin-angiotensin system (RAS) for treatment of microalbuminuria in Type 2 diabetes patients (abstract 785-P). During a 1-3 month run-in period, HbA1c levels were brought to <8% and blood pressure to <130/80 mm Hg, with benazepril 10 mg daily and agents within other antihypertensive classes, as needed. Subsequently, patients were randomized to continue low dose or to escalating doses of benazepril (40 to 80 doses), followed by adding losartan (100 mg) to normalize microalbuminuria. In these patients already receiving low-dose inhibition of the RAS, intensification (with a higher dose of ACE-inhibitor combined with an angiotensin receptor blocker) did not favorably affect microalbuminuria, endothelial function (by post-hyperemia finger plethysmography), carotid intima medial thickness (CIMT), glomerular filtration rate, or inflammation (C-reactive protein levels), compared to continuation of low-dose inhibition over a mean treatment period of ~18 months.

Put Down that Beignet!

While it is known that early remission of Type 2 diabetes can occur in up to 80% of patients undergoing Roux-en-Y gastric bypass (RYGB) surgery, limited data are available on the durability of this remission. Improvement in glucose

dynamics often precedes substantial weight loss, and this may be the result of altered incretin biology when nutritional transit through the intestine is changed so dramatically. Leslie and colleagues from Minneapolis evaluated 584 patients with Type 2 diabetes who had RYGB surgery between January 2001 and December 2007 (abstract 1723-P). Remission, assessed at the last visit of pre-designated time intervals, was defined as no use of oral hypoglycemics or insulin and one of the following: HbA1c <6.0% or fasting plasma glucose <100 mg/dl. Rates of remission were 39.5% at 11-18 months, 35.7% at 19-30 months, 34.2% at 31-42 months, 28.6% at 43-54 months, and 27.0% at 55-66 months (all $p < 0.05$ vs. baseline). The researchers concluded that at 1 year post-RYGB, the Type 2 diabetes remission rate is approximately 40%, and that figure gradually decreases annually. The decrease in remission rate parallels regain of body weight (weight loss at the first and last intervals was 33.1 kg and 27.2 kg, respectively). These data suggest that RYGB may not permanently reverse diabetes in some patients.

Say What?

Evidence suggests an association between diabetes and hearing impairment among adults with diabetes. Bainbridge and Cowie from Maryland analyzed audiometry data from 472 participants,

aged 20-69 years, with diagnosed or undiagnosed diabetes as part of the National Health and Nutrition Examination Survey (NHANES) to determine if characteristics or complications of diabetes were associated with hearing impairment (abstract 957-P). Hearing was assessed from pure tone thresholds over low/mid frequency (500, 1000, 2000 Hz) and high frequency (3000, 4000, 6000, 8000 Hz) ranges. Suboptimal glycemic control (HbA1c $\geq 7\%$) was associated with more than a 2-fold increase in risk of high frequency hearing impairment (OR=2.73 [1.12, 6.66]). According to multiple logistic regression, after controlling for age, race, sex, socio-economic status, and marital status, there was a 6-fold increased risk of high frequency hearing impairment associated with peripheral neuropathy (OR=5.59 [1.62, 19.26]) and coronary heart disease (OR=5.84 [1.50, 22.71]). There was only weak evidence of an association between low/mid frequency hearing loss and coronary heart disease (OR=1.94 [0.95, 3.96]) and no association with either peripheral neuropathy or glycemic control. Diabetes duration and medication use were not associated with hearing impairment.

Similar results were reported by Ismail and Venkatesan from India (abstract 28LB-P). Taken together, these data provide support for offering audiometric examinations as part of routine diabetes care.

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