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Dear Colleague:

Time restraints prevented many of you from attending the 59th Annual Scientific Sessions of the American College of Cardiology (ACC) which was held during March in Atlanta, Georgia and the 70th Annual Scientific Sessions of the American Diabetes Association (ADA) which was held a few weeks ago in Orlando, Florida. Therefore, we developed Diabetes 2010 so that important information presented at the Conferences could be shared with you on a timely basis.

Diabetes 2010, a newsletter CME program, is being offered to you by Yale University School of Medicine with the support of educational grants from Takeda Pharmaceuticals North America, Inc., Amylin Pharmaceuticals, Inc. and Lilly USA, LLC, Bayer HealthCare Diabetes Care, Boehringer Ingelheim Pharmaceuticals, Inc., Medtronic MiniMed, Inc. d/b/a Medtronic Diabetes, Merck & Co., Inc., and Novo-Nordisk Inc. This booklet contains five Diabetes 2010 newsletters and a post-test. After successfully completing the test you will qualify for a maximum of 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

After successfully completing the program, you will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Describe the evolving cellular mechanisms associated with β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- 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.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- 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.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

Given the recent explosion of information on diabetes, as well as its relationship to cardiovascular diseases, we began publishing this newsletter series ten years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

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**Educational Needs**

This program seeks to provide physicians with the latest and most important information presented at scientific meetings this year. Unfortunately, despite the valuable information that can be gained at these conferences, the majority of practicing physicians are unable to attend them. And, given the size and scope of these meetings, attendees often miss data presentations of interest to them. Therefore, programs designed to disseminate information from these meetings on a timely basis to physicians who either cannot attend the conferences or who miss some of the presentations fulfill an educational need that would otherwise not be met.

**Learning Objectives**

At the conclusion of this program, the participant should be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Describe the evolving cellular mechanisms associated with β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- 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.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- 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.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

**Target Audience**

All endocrinologists and internal medicine and family practice physicians who have a special interest in and treat patients with diabetes.

**Educational Methods**

At the end of each conference day, a newsletter will be available on-line at www.cme.yale.edu or faxed or sent by e-mail to the office of participating physicians. Shortly after the ADA conference concludes, participants will receive a *Diabetes 2010* booklet containing all of the newsletters, a program highlights summary from the program co-editors, a course evaluation form, and a post-test. The *Diabetes 2010* booklet and post-test will also be available on-line at www.cme.yale.edu.

**Evaluation**

A course evaluation form will provide participants with the opportunity to review the program content and method of delivery and to identify future educational needs and possible bias in the presentation.

**Accreditation**

This program has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Yale University School of Medicine. Yale University School of Medicine is accredited by the ACCME to sponsor continuing medical education for physicians and takes responsibility for the content, quality, and scientific integrity of this CME program.

**Designation**

Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The American Medical Association has determined that physicians not licensed in the US who participate in the CME activity are eligible for AMA PRA Category 1 Credit™.
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Editors’ Summary

In this issue of the Diabetes 2010 monograph, we summarize important new diabetes information that was presented at the 59th Annual Scientific Sessions of the American College of Cardiology (ACC) and the 70th Annual Scientific Sessions of the American Diabetes Association (ADA).

Of particular interest to our readers are the results of lipid and blood pressure arms of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study that assessed the impact of treatment intervention on cardiovascular (CV) events. In the lipid arm of the study, the impact of open-label simvastatin with and without fenofibrate was assessed, and in the blood pressure arm of the study, intensive blood pressure control was compared to standard management (target systolic blood pressure <120 and <140 mm Hg, respectively). Data previously presented at the 2008 ADA Scientific Sessions indicated that intensive glucose therapy did not reduce overall risk for CV events after 5 years of total follow-up. Results of the lipid and blood pressure arms of ACCORD, as presented at the ACC meeting, showed that treatment targeted as lowering levels of triglycerides and blood pressure also did not reduce CV event rates, which stands in sharp contrast to the results of statin clinical trials involving LDL-cholesterol reduction. With regard to microvascular complications, intensive glycemic control (adjusted odds ratio [OR], 0.67; 95% CI, 0.51 to 0.87) and intensive combination treatment of dyslipidemia (adjusted OR, 0.60; 95% CI, 0.42 to 0.87) reduced the rate of progression of diabetic retinopathy, whereas intensive blood pressure control did not.

There was ongoing discussion of the optimal test(s) for diagnosing diabetes at the ADA meeting. By way of background, last summer the International Expert Committee recommended that HbA1c become the preferred test for the diagnosis of diabetes. In January of this year, the ADA added HbA1c (≥6.5% for diabetes, 5.7-6.4% for pre-diabetes) to then existing criteria for diabetes diagnosis (i.e., fasting plasma glucose [FPG] ≥126 mg/dl, 2-hour plasma glucose during an oral glucose tolerance test [OGTT] ≥200 mg/dl), but did not stipulate that one test is superior to another. It was noted that HbA1c is not a sensitive test (35 to 80% vs. FPG based on ethnic/age differences and other factors), the assay is variable, and many conditions affect its performance (hemoglobinopathies, anemia, renal failure). While there is substantial discordance between HbA1c and glucose-based tests, both measures show a strong relationship with the development of subsequent clinical outcomes. The optimal method for diagnosis remains hotly debated, and there remain advantages and disadvantages to both tests.

Results of the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes research) trial were presented during a Late-Breaking Clinical Trials session on the opening day of the ACC Scientific Sessions. In the study population of patients with impaired glucose tolerance and at increased CV disease risk, targeting insulin secretion with nateglinide was ineffective in preventing diabetes* (HR 1.07 vs. placebo at median of 5 years follow-up), and potentially harmful based on higher incidence of hypoglycemia. Additionally, the deleterious CV effects of postprandial glucose were called into question, given that nateglinide conferred no benefit compared to placebo on extended CV outcomes (death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina). Valsartan modestly decreased the incidence of new-onset diabetes*(33.1% vs. 36.8% for placebo, HR =0.86), but to a degree substantially less than drugs that target insulin resistance (metformin, thiazolidinediones). We reminds you that the DREAM trial conclusively demonstrated no diabetes preventative effect of the ACE inhibitor, ramipril (NEJM2006;355:1551-62). It would therefore seem unlikely that an angiotensin-receptor blocker (ARB) might have diabetes prevention properties not shared by ACE inhibitors.

During a “standing room only” symposium at the ADA meeting, experts presented the latest thinking on topics relating cancer with diabetes and its treatment. Results of observational studies were presented, supporting the association between Type 2 diabetes and increased incidence of selected cancers and documenting higher mortality rate from cancer in patients with Type 2 diabetes than the general population. Furthermore, in a soon-to-be published retrospective study, as presented during the symposium, mortality was directly associated with insulin use (HR 6.4 for ≥12 prescriptions/year vs. no insulin). While interesting, these data do not imply any causality. In this regard, speakers critiqued the observational study by Hemkens et al. (Diabetologia 2009), based on (retrospective) design and analysis shortcomings, and remarked that the totality of evidence, in contrast to the Hemkens study, shows no consistent signal between insulin glargine use and cancer incidence. Experiments conducted using a murine model suggest that endogenous hyperinsulinemia, as occurs in people years prior to their Type 2 diabetes diagnosis, may be the link between diabetes and cancer. It remains to be seen whether high-dose exogenous insulin, often required by today’s obese diabetic population, affects malignancy rates and/or growth.

Our appreciation for the impact of sleep apnea on glycaemia was furthered by a study of women with gestational diabetes mellitus (GDM), the majority of whom were found to meet the criteria for sleep disordered breathing based on overnight polysomnography (ADA abstract 11-OR). The link between obstructive sleep apnea and hyperglycemic states is probably stronger than initially considered and certainly deserving of more study across various patient populations.

Given the rising obesity epidemic, which is affecting younger age groups, and the known association between insulin resistance and CV disease, related perhaps to obesity, the results of a study by DeMarco et al., using the Strong Heart Study database (n=1,688 subjects 14-39 years old without known CV disease), were particularly troubling (ACC abstract 1183-92). In these younger individuals, including teens, insulin resistance was associated with not only multiple metabolic abnormalities, but also preclinical CV compensatory changes (e.g., larger left atrial dimension, left ventricular mass index, and stroke index).

Ongoing research continues to expand our understanding of currently available agents and uncover new agents of potential value in diabetes care. During a symposium on GLP-1 receptor agonists, their CV effects were discussed, including cardioprotective and vasodilatory actions in animals and favorable changes on surrogate markers in groups, although large-scale, prospective endpoint studies are needed to determine if these will translate into beneficial clinical outcomes. The future of insulin treatment may include one or more of the agents currently in development, among them agents that may mimic meal-time insulin secretion of a healthy pancreas following either subcutaneous injection (e.g., SC insulin co-injected with recombinant human hyaluronidase* [ADA abstract 353-OR; 387-PP]; VIAJet*, recombinant human insulin combined with an EDTA-containing diluent* [ADA abstract 36-OR]) or an alternative route of administration (e.g., intranasal insulin [Nasulins*; ADA abstract 520-P]; inhaled insulin [Technosphere**, ADA abstract 359-OR]) and longer-acting insulin with less glucose variability (e.g., ulindegude* [ADA abstracts 34-OR, 40-OR]). Other anti-hyperglycemia medications in development include: the renal sodium-glucose co-transporter-2 (SGLT-2) inhibitors (e.g., canagliflozin*; dapagliflozin*; ADA abstracts 21-LB, 77-OR); selective PPARγ modulators (SPPARMs; e.g., INT113*; ADA abstract 315-OR); protein tyrosine phosphatase 1B (PTP-1B) inhibitors that increase insulin sensitivity (e.g., ISIS 113715*; ADA abstract 316-OR); GPR (G-protein coupled receptor)-119 agonists (e.g., MBX-2982*, ADA abstract 603-P); and, longer-acting GLP-1 agonists (e.g., liraglutide*, ADA abstracts 591-P, 764-P). Which of these agents, if any, might eventually become commercially available to our patients remains to be seen.

More details on these and other topics are found in this volume of Diabetes 2010.

* The product is not labeled for the use under discussion or the product is still investigational.
In an opening session of “Late-Breaking Clinical Trials,” before a capacity audience, Drs. Henry Ginsberg, Columbia, NY and William Cushman, Duke, NC presented data from the lipid and blood pressure arms of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial. The overall ACCORD trial examined three general treatment interventions in patients with Type 2 diabetes and either cardiovascular disease (CVD) or cardiovascular risk factors to determine the impact on cardiovascular events: (1) glycemic control; (2) lipid management; and (3) blood pressure control. The impact of intensive glycemic control (target HbA1c <6.0%) versus standard therapy (target HbA1c 7.0% to 7.9%) has been previously published (NEJM 2008; 358(24):2545-59) and discussed in a prior edition of this newsletter (Diabetes 2008, Volume 17, pg. 26). That component of the ACCORD trial demonstrated that intensive glycemic control had no impact on the primary outcome of the trial, cardiovascular events, and, actually increased all-cause mortality (hazard ratio [HR] 1.22, 95% CI [1.01-1.46], p=0.04). The precise reason for the increased mortality remains nebulous—hypoglycemia, weight gain, and the complexities of polypharmacy have each been raised as possible contributing factors. Based on the ACCORD glycemic results, the American Diabetes Association (ADA) has maintained its overall treatment target for HbA1c (<7%), mainly to protect against microvascular diseases, although ‘individualization’ is now emphasized, especially in older patients and those with pre-existing CVD.

Lipid Arm

Of the 10,251 subjects examined in the ACCORD trial, a total of 5,518 were enrolled in the lipid arm, which examined the impact of open-label simvastatin with and without fenofibrate, a fibrate derivative that is known to reduce triglycerides and raise HDL-cholesterol (C). The underlying hypothesis that drove this aspect of the trial was that combating these two major components of diabetic dyslipidemia would result in additional reductions in cardiovascular event rates on top of standard statin therapy, which mainly addresses LDL-C. In addition to eligibility criteria for the glycemic arm of ACCORD, patient requirements for the lipid therapy component included: LDL 60-180 mg/dl; HDL <55 mg/dl (females, blacks) or HDL <50 mg/dl (all others); and, triglycerides <750 mg/dl (if not receiving lipid-lowering treatment) or triglycerides <400 mg/dl (if on current therapy). Subjects received open-label simvastatin (20-40 mg daily) and were randomized to additional therapy with blinded fenofibrate (160 mg daily, dose adjusted per eGFR) or placebo. The mean follow-up period was 4.7 and 5.0 years for the primary outcome and all-cause mortality, respectively.

Results of the study demonstrated no difference in the primary outcome of composite first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or death from cardiovascular causes (Figure 1a), which occurred at an annual rate of 2.24% (291 events) in the fenofibrate group and 2.41% (310 events) in the placebo group (HR 0.92; 95% CI [0.79-1.08]; p=0.32). There was also no significant difference between the groups with respect to annual mortality rate, which was 1.5% and 1.6% in the fenofibrate and placebo groups, respectively (HR 0.91; 95% CI [0.75-1.08]; p=0.33). Pre-specified sub-group analysis showed a benefit in men and potential harm in women (p=0.01) and a trend toward benefit in patients with high baseline triglycerides (≥204 mg/dl) and low HDL values (p=0.057).*

Ginsberg concluded his presentation stating that the ACCORD study does not support combination therapy with simvastatin and fenofibrate compared to simvastatin monotherapy to reduce cardiovascular risk in the majority of high-risk patients with Type 2 diabetes. In a subsequent commentary, Paul Thompson, MD (Hartford, CT) commented that it was not surprising that the addition of fenofibrate did not confer a benefit given the study population’s mean baseline triglyceride level was 162 mg/dl. In practice, it is likely patients with higher triglycerides and low HDL-C might be targeted for addition of fibrate therapy. He also commented that 4.7 years may not be a long enough time period to adequately assess impact.
Blood Pressure Arm

Dr. Cushman followed by presenting the results of the blood pressure arm of ACCORD. In this portion of the study, 4,733 patients were randomized to receive intensive blood pressure control or standard management. Intensive treatment was defined as a targeted systolic blood pressure (SBP) of <120 mm Hg and was achieved initially utilizing a two-drug regimen of a thiazide diuretic with an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) or a beta-blocker. Additional medications were used to maintain SBP <120 mm Hg. Medication regimens of those in the standard therapy group (target SBP <140 mm Hg) were intensified if patients demonstrated a reading of 160 mm Hg at one visit or >140 mm Hg at two visits. Down titration occurred when SBP was <130 mm Hg at one visit or <135 mg Hg at two visits. At one year, the mean SBP in the intensive and standard groups was 119.3 mm Hg and 133.5 mm Hg, respectively. Mirroring the results of the lipid portion of the study, there was no difference in the primary outcome (i.e., nonfatal MI, nonfatal stroke, or death from cardiovascular causes) between groups (Figure 1b): 1.87% per year (208 events) with intensive blood pressure treatment and 2.09% per year (237 events) with conventional treatment (HR 0.88; 95% CI [0.73-1.06]; p=0.20). There was also no difference in annual all-cause mortality rate, which was 1.28% in the intensive arm and 1.19% in the standard therapy group (HR 1.07; 95% CI [0.85-1.35]; p=0.55). However, in a pre-specified secondary outcome analysis, intensive blood pressure control was beneficial in decreasing the annual rate of stroke, occurring at a rate of 0.32% in the intensive arm versus 0.53% with standard therapy (HR 0.59; 95% CI [0.39-0.89]; p=0.010). The number needed to treat with intensive therapy was calculated at 89 to prevent one stroke over five years. As might be expected, serious adverse events, hypotension in particular, occurred with greater frequency in the intensive arm. In conclusion, Cushman stated that there is no conclusive evidence that intensive blood pressure control decreases the rate of composite major cardiovascular events in patients with Type 2 diabetes.

The third presenter at the session, Rhonda Cooper-Dehoff, MD, Gainesville, FL, shared further analysis of INVEST (International Verapamil SR—Trandolapril Study; JAMA 2003;290:2805-2816), a large (n=22,576) trial of hypertensive patients with coronary artery disease comparing initial therapy with a calcium channel blocker versus beta-blockade. For the entire study cohort and in the predefined subgroup of diabetic patients (Hypertension 2004;44:637-642), INVEST demonstrated no significant difference in the primary outcome (composite first occurrence of all-cause death, nonfatal MI, or nonfatal stroke) in patients whose blood pressure was managed initially with the non-dihydropyridine calcium blocker, verapamil SR, versus atenolol. If additional agents were required, the ARB, trandolapril was added to the calcium channel blocker, whereas hydrochlorothiazide (HCTZ) was added to the beta-blocker. (Subsequently, the opposite add-on drug [i.e., ARB or HCTZ] could then be used in each group, if required.) In this post-hoc analysis of the diabetes cohort, which accounted for approximately 28% of all patients, outcomes were segmented by the degree of SBP control: tight (<130 mm Hg), usual (131-139 mm Hg), and uncontrolled (≥140 mm Hg). The outcomes were minimally different between tight and usual control, yet the uncontrolled group had a significantly higher incidence of the composite cardiovascular endpoint (p<0.001). Of note, increased all-cause mortality was associated with the lowest SBP values in the tight control group (SBP 110-115 mm Hg), although there was no increased risk if the SBP was kept ≥115 mm Hg. These findings should not appreciably impact current blood pressure goals in diabetes, which remain at <130/80 mm Hg.

The results of each arm of the ACCORD trial along with the INVEST analysis have certainly answered some important questions regarding the optimal management of patients with diabetes and cardiovascular risk factors. In stark contrast to clinical trials involving LDL-reduction with statins, it appears that—at least as far as glucose, triglycerides, and blood pressure are concerned—lower is not necessarily better.

Results of the NAVIGATOR (NAteglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial were co-presented by Drs. Rury Holman from Oxford and Robert Califf of Duke in the Late-Breaking Clinical Trials session conducted on the opening day of the ACC Scientific Sessions. In this study, patients with impaired glucose tolerance (IGT) and at increased CVD risk (over CVD in patients ≥50 years or ≥1 CVD risk factor in patients >55 years) were randomized to receive the short-acting non-sulfonylurea insulin secretagogue, nateglinide (60 mg po tid before meals), and/or the ARB, valsartan (up to 160 mg) versus placebo using a double blind 2 x 2 factorial design. All patients received lifestyle modification instruction as well. A total of 4,631 patients received valsartan (2,316 valsartan + nateglinide; 2,315 valsartan and placebo), 4,645 received nateglinide (2,329 receiving nateglinide + placebo), and 4,661 were administered solely placebo. Three primary outcomes were assessed: (1) incident diabetes; (2) extended CVD outcomes that included composite death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization...
for heart failure, arterial revascularization, or hospitalization for unstable angina; and (3) core composite CVD outcomes that excluded unstable angina and revascularization.

Dr. Holman first reported the outcomes data for nateglinide. After a median of 5.0-years follow-up, there was no significant difference in the development of diabetes between the nateglinide (36.0%) and the placebo (33.9%) groups (HR 1.07, 95% CI [1.00-1.15], p = 0.05) (Figure 2a). Additionally, there was no difference between groups in the extended CVD outcomes (14.2% versus 15.2%; HR 0.93; 95% CI [0.83-1.03], p = 0.16) (Figure 2b) or in the composite core CVD outcomes (7.9% versus 8.3%; HR 0.94; 95% CI [0.82-1.09], p = 0.43). It was noted that hypoglycemia was significantly increased (p < 0.001) in the nateglinide group (19.6%, n = 911) versus placebo (11.3%, n = 527), although the vast majority of events were considered mild.

Dr. Califf then proceeded to present data from the valsartan arm of NAVIGATOR. Unlike nateglinide, the ARB did significantly, though modestly, decrease the incidence of diabetes in patients with IGT at 5 years*: 33.1% in the valsartan group versus 36.8% in the placebo arm (HR 0.86; 95% CI [0.8-0.92], p < 0.001) (Figure 2c). There were no significant differences between valsartan and placebo with respect to the extended (valsartan, 14.5% versus placebo, 14.8% [HR 0.96; 95% CI 0.86-1.07; p = 0.43]) and core (both groups, 8.1% [HR 0.99; 0.86-1.14; p = 0.85]) CVD composite outcomes. Dr. Califf further described an increase in hypertension (p < 0.001) in the valsartan group as well as a decrease in hypertension (p < 0.001).

Data were not presented for the combination treatment of valsartan and nateglinide. However, the investigators reported that there was no interaction between treatment groups. When asked for a hypothesis for the effect of valsartan, Holman suggested that the avoidance of routine first-line antihypertensive medications, thiazide diuretics and beta-blockers, which are frequently associated with metabolic abnormalities, and use of valsartan in their place, may have played a role.

Based on the NAVIGATOR results, targeting insulin secretion as a method to prevent diabetes is clearly not effective, and potentially harmful. Moreover, these data call into question the notion that postprandial hyperglycemia has deleterious cardiovascular effects, since addressing this defect with the rapid acting secretagogue, nateglinide, did not impact CVD outcomes. As for the valsartan aspect of the trial, we find the results somewhat difficult to interpret. The effect on diabetes prevention is very modest and much lower in comparison to the demonstrated effect of drugs that target insulin resistance (metformin, TZDs).* We agree that the results may have been driven by effects in the opposite direction (i.e., diabetogenic) from other anti-hypertensive drugs used in the placebo group. We recall that the DREAM trial conclusively demonstrated no diabetes prevention effect of the ACE-inhibitor, ramipril, in a similar group of pre-diabetic patients (NEJM 2006;355:1551-62). It would therefore seem unlikely that an ARB might have diabetes prevention properties not shared by ACE inhibitors. Similar to the ACCORD trial on p. 1, these results will likely have no effect on clinical practice.

Inpatient measures of hyperglycemia are associated with adverse clinical outcomes, especially in patients with CVD and undergoing cardiac surgery. Intervention trials to reduce blood glucose levels have had mixed results in these settings, however. Indeed, it remains less than clear whether glucose is an actual mediator of morbidity in acutely ill cardiovascular patients or is serving merely as an innocent marker of the sickest patients. Alternatively, glucose could also be an identifier of patients with the most profound metabolic derangements prior to their hospitalizations.

Despite more than two decades of study, whether therapy of hyperglycemia in the acute setting may impact peri-acute myocardial infarction/acute coronary syndrome (AMI/ACS) clinical outcomes remains unknown. An initial study conducted in the 1990s (DIGAMI) suggested a benefit on mortality following AMI, but the treatment target in the intensively controlled group was...
relatively modest (126-196 mg/dl) and a paired outpatient insulin treatment strategy made it difficult to ascertain any specific benefit from the inpatient component of the randomized therapeutic category. Since then, most studies have proven negative (DIGAMI 2, HI-5) but had methodological limitations. Clearly, larger studies will be needed before IV insulin therapy in hyperglycemic inpatients with ACS is considered part of routine care.

After synthesizing disparate views and conflicting data, the ADA, in conjunction with the American Association of Clinical Endocrinologists, proposed reasonable and achievable guidelines for the inpatient management of hyperglycemia. Specifically in the ICU, glucose levels should be reduced with intravenous (IV) insulin into the 140-180 mg/dl range. This response to amputating evidence base was a pull-back from earlier, more rigid recommendations.

**New Data**

As this proverbial “chicken versus egg” debate continues, many presentations this week continued to explore the relationship between glucose and outcomes following ACS. Ergelen and Turkish colleagues posed the provocative question, “Which is Worst in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction? Hyperglycemia, Diabetes Mellitus, or Both?” (abstract 1049-306). The investigators studied 2,482 patients with ST-elevation myocardial infarction (STEMI), mean age 56.5±11.9 years, almost 85% of whom were male. They defined hyperglycemia in the hospital as any admission plasma glucose ≥200 mg/dl and then classified the patients into 4 cohorts: non-diabetic/non-hyperglycemic (NDN, n=1,806); diabetic/non-hyperglycemic (DNH, n=271); non-diabetic/hyperglycemic (NDH, n=64); and diabetic/hyperglycemic (DH, n=341). Consistent with earlier reports, in-hospital mortality was higher in NDH patients (12.5%) compared to the other groups (DH 8.5%, DNH 6.3%, and NDNH 0.9%) (p<0.001). A composite endpoint of in-hospital major adverse cardiac events (MACE) was also higher in the NDH group (18.8% vs. DH 13.8%, DNH 10.3%, and NDNH 3.7%; p<0.001). In long-term (median, 21 months) follow-up, expressed using Kaplan-Meier plots, however, survival overall was lowest in DH patients (log rank p<0.001). After adjustment for potential confounders, both NDH (odds ratio [OR] 3.04, [95% CI 1.06-8.73]; p=0.03) and DH (OR 2.3, [1.29-4.09]; p=0.005) status—but not DNH (OR 1.22, [0.57-2.6]; p=0.6)—remained independent predictors of long-term cardiovascular mortality. The researchers concluded that in STEMI patients, non-diabetic but still hyperglycemic patients constituted the highest risk group for inpatient mortality and morbidity, but that in long-term follow-up, hyperglycemic patients with diabetes still had the worst outcomes.

Mulder and Dutch investigators wondered if the early data linking admission hyperglycemia to adverse outcomes in AMI patients has changed, now in the modern era of prompt reperfusion (abstract 1209-268). They studied 1,185 patients with AMI during two time periods, first in 1996-99 (pre-invasive era) and then in 2003-06 (invasive era). Follow-up over 5 years was assessed in light of the patients’ admission plasma glucose, with the two groups compared. After adjustment for multiple confounders, increased admission glucose was still associated with increased mortality irrespective of treatment era—with every 18 mg/dl rise in blood glucose associated with a 7% increased mortality (OR 1.07 [1.04-1.10]). The data were essentially indistinguishable between the two groups. Accordingly, the relationship between hyperglycemia and adverse clinical outcomes post-AMI persists even in the modern reperfusion era.

A similar observation was made by Magnuson et al. from the US, who focused on 3,805 patients with non-ST elevation ACS undergoing percutaneous coronary intervention (PCI) (abstract 1266-288). Of these, 957 were found to be hyperglycemic (defined as blood glucose >130 mg/dl), approximately two-thirds of which had pre-existing diabetes. Propensity-adjusted Cox regression models were used to compare adverse events between hyperglycemic and normoglycemic patients, with follow-up of up to 3 years following PCI. Patients with hyperglycemia experienced increased in-hospital mortality (1.4% vs. 0.3%, p<0.001) (Figure 3), non-elective bypass surgery (CABG) (2.4% vs. 1.3%, p<0.001), and in-hospital MACE (17.4% vs. 10.3%, p<0.010). The findings were irrespective of known diabetic status (2/3 of the hyperglycemic patients had preexisting diabetes).

**How Low Is Too Low?**

While there is a clear association between hyperglycemia and adverse outcomes in acute cardiovascular patients, what about hypoglycemia—often considered the ‘price of doing business’ when IV insulin is used? An Italian group led by Nusca addressed this question (abstract 2504-500). Their initial goal was to investigate the relationship between glucose and procedural myocardial damage in non-diabetic patients undergoing coronary stenting. 389 patients were enrolled and had blood glucose measured before PCI. They were then segmented into four groups based on their glycemic status: hypoglycemic (≤80 mg/dl), euglycemic (81-109 mg/dl), mildly hyperglycemic (110-125 mg/dl), and hyperglycemic (≥126 mg/dl). Creatinine kinase (CK) MB and troponin I levels were measured before as well as 8 and 24 hours post-PCI. A peri-procedural MI was defined as a post-PCI increase in CK MB and/or troponin I to greater than 3 times the upper normal limit. The investigators found that hypoglycemia was associated with increased incidence of peri-procedural MI (63% vs. 32% in the euglycemic group, p=0.006). Of note the hyperglycemic categories did not demonstrate any increase in MI rates compared with the euglycemic patients. The investigators proposed that previously demonstrated increases in inflammatory markers and platelet activation with hypoglycemia may explain their results, which is provocative. These data should lead all investigators and clinicians pursing aggressive glucose control measures in the ACS setting to proceed cautiously. Clearly, any protocols must compulsively attempt to minimize hypoglycemia.

**Glucose and AKI Risk Post-Angio**

In a related abstract presentation of a case-control study, Brott and US colleagues found a significant relationship between pre- and post-procedure blood glucose and the risk of acute kidney injury (AKI) following contrast angiography (abstract 2504-518). 116 patients with diabetes and contrast-induced AKI were identified and compared to a control group matched (1:2) for eGFR, diabetic status, contrast volume, and subsequent referral for CABG. Pre-procedural blood glucose and the change in...
blood glucose after the procedure were compared between the two groups. Risk (OR) for AKI was examined for each 20 mg/dl glucose increment above 100 mg/dl. The investigators found that a pre-procedure glucose of 180 mg/dl was associated with a significant increase in the OR for AKI (Figure 4). After adjustments using logistic regression models, the OR for AKI was 1.78 (1.22-2.59) for every 80 mg/dl increase in pre-procedure glucose >100 mg/dl (p=0.002). Moreover, the OR for AKI was 3.49 (2.04-5.98) for every 80 mg/dl increase in the post-procedure blood glucose over the pre-procedure level (p<0.001). So, hyperglycemia both before and after contrast studies appears to be strongly associated with adverse renal outcomes. These data suggest the need for a randomized clinical trial targeting a reduction in blood glucose before an angiographic procedure to <180 mg/dl in the intervention group, with subsequent maintenance of glycemic control after the conclusion of the test.

Mechanistically Speaking

If the relationship between acute hyperglycemia and adverse outcomes in ACS patients is cause-and-effect, several pathophysiological explanations have been proposed. These include the effects of glucose on inflammatory markers, coagulation factors, platelet reactivity, endothelial function, and microvascular flow, and deranged left ventricular (LV) remodeling. A Japanese group led by Yoshimori An studied 209 patients with anterior AMI who had undergone successful PCI and had coronary flow measured by Doppler guidewire (abstract 2501-494). Microvascular dysfunction was defined as diastolic deceleration of flow and systolic flow reversal. The patients were separated into two groups—those with (n=91) and without (n=118) hyperglycemia, using the cutpoint of an in-hospital blood glucose level >180 mg/dl. LV function was also assessed by ventriculogram during the PCI procedure and was repeated at 6 months (to assess post-AMI remodeling). The researchers found that both microvascular dysfunction (68.1% vs. 22.9%; p<0.001) and LV remodeling (46.4% vs. 17.2%; p<0.001) occurred more frequently in those patients with hyperglycemia. They proposed that their observations may explain the adverse outcomes reported in hyperglycemia patients with AMI.

A Spanish group led by Vivas, studied the effect of insulin control of hyperglycemia on platelet aggregation in patients with ACS (abstract 1219-340). In this prospective study, 115 patients with ACS and hyperglycemia were randomized to intensive glucose control (n=59) with IV insulin for 24 hours, followed by a basal bolus subcutaneous insulin regimen to control glucose to 80-120 mg/dl, or to the conventional arm (n=56) of the trial with subcutaneous insulin only when the glucose exceeded 180 mg/dl. Platelet aggregation was measured using light transmittance aggregometry after the addition of thrombin receptor activating peptide (TRAP). At baseline, there were no differences in platelet function between groups. At discharge, however, adjusted analysis showed a significant reduction in platelet aggregation in intensive patients compared with controls using all assays, on the order of 10-25% (all p<0.05). Whether attenuation of platelet reactivity with intensive glucose management will translate to improved clinical outcomes remains to be answered.

If there is a benefit from insulin infusion, another debate surrounds the question as to whether the benefit derives from insulin itself or from glucose reduction. A partial answer to this question may come from Heck et al., a group based in the UK (abstract 1262-252). They assessed the impact of IV insulin induced hyperinsulinemia in the context of euglycemia vs. hyperglycemia in 36 non-diabetic patients who had normal LV function but known coronary artery disease and were awaiting revascularization. The subjects underwent two dobutamine stress echocardiography tests, one at baseline and one during an IV insulin ‘clamp’ procedure. The patients were then randomized (2:1) to having their glucose levels clamped in the normal range with IV dextrose as insulin was being infused versus clamped at a hyperglycemic level (240 mg/dl). Both groups experienced a marked reduction in free fatty acids (FFA), which have themselves been linked to increased myocardial damage during ischemic coronary events. Stress echo, however, showed an augmentation in ejection fraction in the hyperinsulinemic-euglycemic group versus the hyperinsulinemic-hyperglycemic group (Table 1). The peak systolic velocity in both ischemic and non-ischemic myocardial segments was increased in the euglycemic patients. The investigators concluded that hyperinsulinemia improves LV function in those with significant coronary disease but only in the setting of euglycemia. They also proposed, based on their findings, that acute hyperglycemia may be detrimental to the ischemic myocardium. We don’t necessarily agree. While these data are interesting, our interpretation is that LV performance may be enhanced by the combination of hyperinsulinemia and euglycemia. A third group, perhaps rendered hyperglycemic but without any IV insulin, might have further elucidated the direct impact of glucose itself on the parameters measured.

**Table 1. Effects of Hyperinsulinemia on LV Performance**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Clamp</th>
<th>p-value</th>
<th>Control</th>
<th>Clamp</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-DSE Glucose (mg/dl)</td>
<td>99 (2.9)</td>
<td>96 (2.9)</td>
<td>NS</td>
<td>88 (2.9)</td>
<td>240 (8.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pre-DSE Insulin (pmol/l)</td>
<td>64 (8)</td>
<td>531 (34)</td>
<td>&lt;0.0001</td>
<td>86 (22)</td>
<td>378 (52)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Pre-DSE FFA (mcmol/l)</td>
<td>399 (49)</td>
<td>92 (14)</td>
<td>&lt;0.0001</td>
<td>429 (65)</td>
<td>77 (22)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Peak DSE LVEF (%)</td>
<td>65 (1.3)</td>
<td>72 (1.2)</td>
<td>&lt;0.0001</td>
<td>69 (2.4)</td>
<td>66 (3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic Segments</td>
<td></td>
<td></td>
<td>0.0001</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Peak Velocity (cm/sec)</td>
<td>7.1 (0.3)</td>
<td>7.9 (0.3)</td>
<td>0.06</td>
<td>8.4 (0.4)</td>
<td>8.6 (0.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

DSE = dobutamine stress echo, LVEF = LV ejection fraction.
We also wonder if enhancing LV contractility in this context might actually increase myocardial oxygen demand. The impact of such interventions on the overall myocardial ischemic burden would need to be carefully assessed.

**Treatment Trends**

Venkitachalam and American collaborators studied nearly 40,000 patients with AMI hospitalized between 2000 and 2008 at 55 US hospitals, using the HealthFacts database (abstract 1249-167). They sought to determine the temporal trends in blood glucose management during this period of time. Of the original cohort, 4,330 patients (11%) had a mean hospital blood glucose ≥200 mg/dl. This proportion decreased during the observation period, from 12% down to 8%. As far as treatment is concerned, overall, 61% of these patients with sustained hyperglycemia received any form of insulin—with only 16% being treated with IV insulin. Hierarchical multivariable models accounting for frequency of AMI admissions per site, showed that, although increasing insulin use was documented over time, about 1 in 3 significantly hyperglycemic AMI patients continued to receive no insulin. The investigators felt that their data likely reflected a lack of consensus in the cardiology community of the importance of addressing glucose during AMI. We would agree with this assessment—there certainly is substantial debate concerning how low the glycemic target should be in this setting. However, we would propose that untreated hyperglycemia to this degree may represent an opportunity for improving the quality of care provided in our hospitals.

**Insulin Resistance has been associated with CVD, particularly atherosclerosis, for decades. A cause and effect relationship remains uncertain, however, and is likely to remain so, since insulin resistance is itself related to many intermediaries of CVD. These include obesity, hyperglycemia, hypertension, dyslipidemia, inflammation, and endothelial dysfunction. Moreover, demonstrating a cardiovascular benefit from insulin sensitizing drugs has been mired in controversy. At this week's meeting, investigators continued to explore the nature of insulin resistance and its tie to heart disease.

Most of the data on insulin resistance and the heart stems from studies in middle-aged adults. There is relatively little information about this connection in younger individuals. Given the rising obesity epidemic in younger age groups, understanding the potential impact of such metabolic derangements on cardiovascular health is of some importance. With this in mind, De Marco and Italian colleagues studied the Strong Heart Study database, examining 1,688 individuals between the ages of 14 and 39 without known CVD (abstract 1183-92). The participants, 57% of whom were female, were divided into tertiles of insulin resistance, based on the homeostatic model assessment of insulin resistance (HOMA-IR), which is, essentially, a ratio between fasting glucose and insulin levels. The groups were compared using ANCOVA, with adjustments for major covariates. Not unexpectedly, increasing insulin resistance tertiles were associated with increasing age, BMI, waist-to-hip ratio (WHR), blood pressure, and dyslipidemia. After adjustment for these factors, patients in the upper HOMA-IR tertile had larger left atrial dimension, LV mass index, and stroke index (all p for trend <0.05). In multiple linear regression, logHOMA was independently related to age, female gender, WHR, triglycerides, HDL-cholesterol, systolic blood pressure, and LV mass index. The ORs for LV hypertrophy in those in the two top HOMA-IR tertiles were 3.15 (95% CI 1.15-6.51) and 4.24 (2.04-8.81), respectively, independent of age, gender, WHR, blood pressure, and lipids. The researchers argued that in younger individuals, including teens, insulin resistance is associated not only with multiple metabolic abnormalities, but also preclinical cardiovascular compensatory changes.

The link between insulin resistance and vascular disease is well established for coronary artery disease endpoints. There is less data on its relationship with cerebrovascular disease. Kim and US colleagues examined 9,230 adults from the National Health and Nutrition Examination Survey (NHANES) III database (1988-1994) to study this question (abstract 1053-324). The investigators also utilized a different HOMA method employing C-peptide levels. Multivariate logistic regression was used to calculate ORs for stroke according to the presence of insulin resistance, after adjustments for a variety of factors, including age, gender, race, obesity, diabetes, hypertension, dyslipidemia, obesity, C-reactive protein, and physical activity levels. Stroke had occurred in 1.8% of participants. Each quartile of insulin resistance had increasing percentage of participants with stroke (0.6%, 1.1%, 1.6%, and 4.3%). The mean HOMA score was 2.32 in those with stroke and 1.56 in those without (p<0.001). The unadjusted ORs (95% CI) for stroke in each of the top three quartiles compared to the lowest were 1.77 (0.90-3.48, p=0.094), 2.64 (1.34-5.20, p=0.006), and 7.25 (3.58-14.68, p<0.001). After adjustments for clinical and socioeconomic factors, ORs were 1.44 (0.76-2.74, p=0.26), 1.54 (0.82-2.91, p=0.18), and 2.76 (1.26-6.06, p=0.01) respectively.

**Linking Insulin Resistance to CVD**

Despite these associations, it remains unknown if targeting insulin resistance in patients with diabetes decreases atherosclerotic events. In a UKPDS substudy, metformin appeared to reduce MI as compared to diet therapy, with trends toward better outcomes as compared with sulfonylureas or insulin.* In the recently published BARI-2D study (NEJM 2009;360:2503-15), 2,368 patients with Type 2 diabetes and stable coronary artery disease, overall, experienced similar outcomes whether they were randomized to an anti-hyperglycemic strategy that employed insulin sensitizing drugs (metformin-rosiglitazone) versus one that focused on insulin provision (sulfonylurea-insulin). There was, however, a trend toward fewer major cardiovascular events with insulin sensitizers in the cohort of patients who were also randomized to the revascularization arm of the trial (as opposed to medical therapy alone) (20.3% vs. 25.2%, p=0.0059).* In the PROactive study, pioglitazone was associated with a 16% relative risk reduction in the secondary endpoint of mortality, MI, and stroke (p=0.03), as compared with placebo in 5,238 patients with Type 2 diabetes and pre-existing macrovascular disease.* (Dornandt et al., Lancet 2005;366:1279-89). The data surrounding rosiglitazone remains controversial with a randomized clinical trial, RECORD, showing no cardiovascular benefit or harm in a group of 4,447 patients with Type 2 diabetes failing either metformin or a sulfonylurea (Home et al., NEJM 2007;357:28-38). However, several, though not all, meta-analyses have found an increased risk of MI with this thiazolidinedione (TZD). At this time, therefore, there is simply not enough of an evidence base to know how important insulin resistance is as a therapeutic target. Clearly, more data are needed.

*References:

**Diabetes**

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**Atlanta, GA**

**Volume 21**

**March 16, 2010**
Data continue to accumulate evaluating the cardiovascular impact of various treatment regimens used in patients with Type 2 diabetes (Table 2). Although (one might even say ‘Because’) recent publications (ACCORD, ADVANCE, VADT) have been disappointing relative to anti-hyperglycemic therapy and macrovascular outcomes, much needs to be understood about the cardiovascular effects of the drugs we use to lower glucose.

A meta-analysis of studies evaluating intensive versus conventional glucose control was conducted by Athappan et al. from the US specifically looking at cardiovascular outcomes (abstract 1137-157). Eight trials representing 33,353 subjects were included. The primary endpoints were all-cause mortality and cardiac mortality. The secondary endpoints included: stroke, peripheral vascular disease (PVD), and major adverse cardiovascular events or MACE (composite of all-cause mortality, nonfatal MI, stroke, and PVD). The results, with a mean follow-up of 6 years and HbA1c differences between the groups of approximately 1% (7.2% vs. 8.2%), demonstrated lower cardiac mortality (OR 0.85; 95% CI, 0.76 to 0.96), but not all-cause mortality (OR 0.92; 95% CI, 0.79 to 1.07), with more intensive therapy. MACE showed a significant decrease (OR 0.85; 95% CI, 0.74 to 0.97) with intensive control, but there was no difference in stroke or PVD.

Investigators from Denmark assessed long-term outcomes of oral glucose-lowering medication in patients with diabetes and non-ST elevation myocardial infarction (NSTEMI). Jorgenson et al., through linkage of national registries, evaluated patients (≥30 years) admitted for NSTEMI receiving drug therapy for diabetes (abstract 1049-305). Controlling for confounding variables (i.e., age, gender, co-morbidities, and concomitant drugs), the investigators used multivariate Cox regression models to assess relationships between the composite endpoint of non-fatal MI and cardiovascular death with each glucose-lowering agent. With the exception of glinilide (HR 1.03; CI 0.87-1.21), monotherapy with any other sulfonylurea (n=3,649) such as glimepiride (HR 1.19; CI 1.07-1.33), glyburide (HR 1.38; CI 1.17-1.47), glipizide (HR 1.23; CI 1.11-1.42), or tolbutamide (HR 1.18; CI 1.04-1.35) was associated with an increased risk of the composite endpoint when compared to metformin monotherapy (n=711). These data and many others continue to buttress the widely held position that metformin is the best initial drug for most Type 2 patients.

Komiya and Japanese colleagues used intravascular ultrasound (IVUS) to assess vessel and plaque volume in 30 patients without and with early

**Table 2. Medical Therapies for Type 2 Diabetes and Their Cardiovascular Impact**

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
<th>CV Advantages</th>
<th>CV Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide, Glipizide, Glimepiride</td>
<td>• ↓ Microvascular risk</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May impair ischemic preconditioning</td>
</tr>
<tr>
<td>Glinides</td>
<td>Repaglinide, Nateglinide</td>
<td>• Reduces post-prandial glucose</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May impair ischemic preconditioning</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>• No hypoglycemia</td>
<td>• Lactic acidosis risk (very rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weight loss</td>
<td>• Contraindicated in severe heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Possible ↓ CVD events</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitzzone, Pioglitazone</td>
<td>• No hypoglycemia</td>
<td>• Weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Possible reduction in CVD events (pioglitazone)*</td>
<td>• Edema/heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↑ HDL-C</td>
<td>• ↑ LDL-C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Triglycerides</td>
<td>• Possible ↑ CVD events (rosiglitzzone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Blood pressure</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Acarbose, Miglitol</td>
<td>• No hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Post-prandial glucose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Possible ↓ CVD events</td>
<td></td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Exenatide, Liraglutide</td>
<td>• Weight loss</td>
<td>(No long-term CV safety data)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Post-prandial glucose</td>
<td></td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>Pramlintide</td>
<td>• Weight loss</td>
<td>(No long-term CV safety data)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Post-prandial glucose</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin, Saxagliptin</td>
<td>• No hypoglycemia</td>
<td>(No long-term CV safety data)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Post-prandial glucose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ND</td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam</td>
<td>• ↓ LDL-C</td>
<td>• ↑ Triglycerides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ CV events in lipid trials with this class*</td>
<td></td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>Bromocriptine</td>
<td>• No hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Microvascular risk</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Weight gain</td>
</tr>
<tr>
<td>Insulin</td>
<td>Human NPH, Human Regular, Glargine, Detemir, Lispro, Aspart, Glulisine, Premixed</td>
<td>• ↓ Microvascular risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Weight gain</td>
</tr>
</tbody>
</table>
Type 2 diabetes who were undergoing PCI (abstract 1018-93). Patients were assigned to two groups: the TZD, pioglitazone 30 mg daily or control. Volumetric and radiofrequency signal analysis in IVUS was completed for targeted plaques; baseline and 8-month serum lipid levels were assessed. Vessel and plaque volume significantly decreased (p<0.05) in the pioglitazone group, whereas lumen volume did not when compared with the control group with respect to change from baseline. There was no change in LDL-C levels at 8 months, yet HDL-C levels increased (p<0.05). Based on these findings, the researchers suggest that pioglitazone causes regression of coronary plaques with preservation of lumen volume or “reverse modeling” without alteration in LDL-C levels. Choi et al. of South Korea reported a similar benefit of pioglitazone (vs. placebo) on atherosclerosis progression and neointimal proliferation* in Type 2 diabetes patients who had received 8 months of therapy following the insertion of a drug-eluting stent (abstract 1169-373).

While few firm conclusions can be made at this point, it appears that various drug regimens may lead to different outcomes in at least selected patient populations. Research needs to continue so that we can fine tune our patient management strategies in order to achieve safe and effective glycemic control with, ideally, cardiovascular benefit—but at least with no cardiovascular harm.

**CV Effects of GLP-1**

GLP-1 receptor agonists (exenatide, liraglutide) are an emerging treatment strategy in patients with Type 2 diabetes. These agents, by mimicking native GLP-1, target the pancreatic islet to increase insulin secretion and decrease glucagon output, both in a glucose-dependent fashion. They also enhance satiety and delay gastric emptying. Their use is associated with moderate reductions in HbA1c, weight loss, and some improvement in cardiovascular risk factors (mostly related to weight loss). The discovery of GLP-1 receptors in the heart has raised interest in the precise role of this gut-derived hormone in cardiac tissues. Preliminary studies suggest potential roles in enhancing myocardial glucose uptake, in the protection from ischemic injury, and in reversing ventricular dysfunction. Read and British colleagues infused GLP-1 in 12 patients (mean age 65±9 years) with known coronary artery disease and normal LV function during dobutamine stress echocardiography (abstract 1159-304). Two studies were conducted in each patient, in randomized fashion, one with and one without GLP-1. Rate pressure product was similar between the GLP-1 and control scans (22,246 vs. 22,065; p=0.88). Plasma GLP-1 levels were increased by the infusion (185.9±1.8 vs. 6.6±3.7 pg/ml; p<0.0001) and glucose was modestly decreased (81±20 vs. 95±18 mg/dl; p=0.0001) at peak stress. GLP-1 infusion improved global LV function (i.e. mitral annular systolic tissue velocity) and regional wall function (peak systolic tissue velocity, strain, strain rate) at peak stress.* Also, myocardial “stunning”—a reduction in function in recovery compared to baseline—occurred in the control scan, but was not observed with GLP-1 infusion.* The implications of these findings in patients with diabetes and heart disease are unclear but deserving of further study.

**Pre-DM in Seniors**

Insulin resistance has been linked to CVD, particularly atherosclerosis, for decades. Pre-diabetes, according to the 2010 ADA guidelines, includes fasting plasma glucose (FPG) of 100-125 mg/dl, 2-hour plasma glucose during an oral glucose tolerance test (OGTT) of 140-199 mg/dl (IGT), or an HbA1c of 5.7%-6.4%. Deedwania et al. from the US studied 5,795 patients 65 years of age or older in the Cardiovascular Health Study (abstract 1140-174). Of 4,786 subjects without diabetes and with baseline FPG data, 2,239 had prediabetes based on FPG criteria. Propensity scores for prediabetes were calculated for each patient and 1,476 pairs (normal FPG/IFG) were matched on their baseline characteristics. Cox regression models were constructed to estimate the effects of prediabetes on all-cause mortality (Figure 5) and cardiovascular morbidity over a 13-year follow-up period. Overall, there was no difference in either mortality or in the incidence of acute MI, angina pectoris, heart failure, stroke, or peripheral artery disease. The investigators concluded that, among ambulatory community-dwelling older individuals, prediabetes by FPG carried with it no independent risk of mortality or cardiovascular morbidity, suggesting lack of any major intrinsic effect of mildly elevated FPG in these patients.

**PREVENTing Contrast Nephropathy**

Results from the PREVENT Trial (Preventive Strategies of Renal Insufficiency in Patients with Diabetes Undergoing IntraVEnTion or Arteriography) were presented by Won-Jang Kim of South Korea (abstract 3014-8). It is well known that hydration is an effective strategy to minimize the incidence of contrast induced nephropathy in predisposed patients (e.g., diabetics with renal insufficiency). There are also some mixed data suggesting that volume expansion with a solution of sodium bicarbonate (NaHCO₃) may be superior to normal saline (NaCl). The PREVENT trial randomized diabetes patients with mild to moderate chronic kidney disease to receive either NaCl (n=189) or NaHCO₃ (n=193) infusions. Patients were similar with respect to baseline characteristics and each received N-acetylcysteine (1200 mg po bid x 2 doses pre-procedure) as well as the same iodinated contrast, ioxaglate, at comparable volumes. The primary endpoint was development of AKI within 48 hours defined as increase in serum creatinine by greater than 25% or absolute increase of 0.5 mg/dl from baseline. Overall, the incidence of AKI was 7.2% and not statistically significant between the two treatment arms (5.3% with saline, 9.0% with sodium bicarbonate, p<0.17). Thus, Kim concluded that in patients with diabetic nephropathy undergoing coronary or endovascular angiography, intervention with bicarbonate was not superior to saline hydration for the prevention of contrast-induced nephropathy. Based on these results, it appears that either hydration regimen is acceptable (in addition to N-acetylcysteine).

* The product is not labeled for the use under discussion or the product is still investigational.

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**So Many Posters, So Little Time....**

**Pre-Diabetes in Older Adults**

<table>
<thead>
<tr>
<th>Follow-up in Years</th>
<th>Pre-diabetes</th>
<th>Normal fasting glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>2.5</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>5.0</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>7.5</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>10</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>12.5</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>0.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**HR: 1.08; (95% CI, 0.95-1.22) p=0.256**

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**Editors, Yale University, New Haven, Connecticut**

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Silvio E. Inzucchi, MD
Robert S. Sherwin, MD
The cardiovascular complications and implications of diabetes continue to attract much attention from both the scientific and clinical communities. At a symposium on Saturday chaired by Dr. Ted Mazzone from the University of Illinois, speakers convened to weigh in on the following question: Does Diabetes Affect the Approach to Diagnosis or Management of Cardiovascular Disease?

Dr. Silvio Inzucchi from Yale University first presented “Screening for Cardiovascular Disease in Asymptomatic Patients—Lessons from DIAD.” The Detection of Ischemia in Asymptomatic Diabetics study is a randomized prospective investigation that sought to determine the prevalence of silent myocardial ischemia in patients with Type 2 diabetes over age 50. The DIAD investigators screened 522 patients with a nuclear pharmacological stress test (adenosine-sestamibi SPECT). Abnormal findings were detected in 22%, much lower than prior studies, (up to 50-60%) which had analyzed mainly referral populations. In contrast, DIAD patients were carefully screened to be entirely asymptomatic from a cardiovascular standpoint and had normal baseline ECGs. Of the abnormal SPECT studies, nearly three in four (73%) involved perfusion defects, 40% of which were graded as either moderate or large. In all, these markedly abnormal scans constituted 6% of the originally screened cohort. (The remainder of the abnormal studies [27%] were non-perfusion abnormalities, including low ejection fraction, transient ischemic dilation, lung uptake of radiopharmaceutical, and ECG changes during adenosine infusion.) Other than male gender, diabetes duration, and the presence of cardiac autonomic neuropathy, no other clinical predictors of myocardial ischemia could be identified. The lessons learned from “DIAD-1” are that silent ischemia is present in fewer diabetes patients than had been previously proposed and that few clinical predictors were helpful in identifying which patients might benefit from screening.

A subsequent aspect of DIAD involved the retesting of patients with nuclear stress imaging 3 years after their baseline study. For “DIAD-2,” 358 still asymptomatic patients from the original cohort were reimaged. (Those with interval cardiac events or interventions were not retested.) Much to the investigators’ surprise, the overall silent ischemia rate actually declined to 12%. Indeed, 79% of originally abnormal studies had reverted to normal. Although 10% of the normal studies showed new defects, the general trend was for less ischemia over time. A post-hoc analysis suggested that patients with resolution of ischemia were more apt to have been treated with risk factor modifying drugs, such as statins and ACE inhibitors. The lesson from DIAD-2 was that, in contrast to what had been anticipated, myocardial perfusion defects often improve over time.

The final segment of DIAD consisted of an analysis of clinical outcomes after 5 years, comparing the screened group to the unscreened control group (n=562). Overall, the cardiac event rate was extremely low in the study (0.6% per year for the primary endpoint of cardiovascular death + non-fatal myocardial infarction). Abnormal stress tests did actually identify patients at the highest risk, with the event rate with moderate-large defects being ~12% over 5 years. In spite of this, however, the overall event rates between the screened and unscreened participants were essentially identical, including both primary and secondary outcomes. Thus, and somewhat counter-intuitively, the final lesson from “DIAD-3” is that routine screening for coronary artery disease (CAD) in this population does not improve clinical outcomes. Accordingly, routine CAD screening in otherwise asymptomatic patients cannot be endorsed at this time.

Admittedly, DIAD has several limitations. First, specific treatment directed at the CAD discovered was not stipulated by the study. Instead, any further investigations or interventions were deferred to the patients’ personal physicians. It is therefore conceivable that a more goal-directed therapy trial may have resulted in better (or worse) outcomes in the screened group. Second, there were few data available beyond the baseline visit as to the trends in the patients’ cardiovascular risk factors. Finally, with event rates so low, the study was likely underpowered in certain areas,
especially in its ability to identify risk predictors for abnormal myocardial perfusion imaging.

In the morning’s second talk, Dr. Darren McGuire from the University of Texas/Southwestern in Dallas addressed “Revascularization vs. Medical Treatment for Coronary Disease in Diabetes.” He began by underscoring the important links between these two conditions. In the UK Prospective Diabetes Study (UKPDS), the cardiovascular event rates were approximately 25% over 12 years, some 3-fold higher than in the general population. Additionally, diabetic patients—either diagnosed or undiagnosed—constitute up to 50% of patients undergoing cardiovascular procedures. Accordingly, it is of critical importance to understand the optimal management strategies for treating CAD in this population.

In the original Bypass Angioplasty Revascularization Study (BARI) trial almost 20 years ago, survival in the diabetic patients after coronary artery bypass surgery (CABG) proved to be much higher than after percutaneous coronary intervention (PCI), which at the time did not involve coronary stenting. However, survival was still markedly reduced in the diabetic patients irrespective of their revascularization strategy. Since BARI, there have been major advances in the comprehensive therapy of CAD. In addition to tighter metabolic targets and an increasing array of pharmacological strategies to ameliorate risk factors, the tools of the invasive cardiologist have greatly expanded. These now include intracoronary stents, more recently including drug-eluting stents, as well as the use of insulin sensitizers (metformin, rosiglitazone) and the other, insulin provision treatment. Howeve r, in the drug-eluting stent era, as20-25% in those with diabetes, a substantial proportion of those randomized to medical therapy, with an event ‘cross over’ rate of 42%. This would obviously tend to mitigate any differences between the two groups.

For the primary composite cardiovascular endpoint, there were no differences in either aspect of the trial. That is, the event rates were statistically indistinguishable between those assigned revascularization or medical therapy, as well as in those receiving insulin sensitization vs. insulin provision treatment. However, in the prespecified CABG stratum (which, of course, tended to include the sicker patients), major benefits were observed in those randomized to urgent revascularization. For example, the composite cardiovascular primary outcome rate was reduced from 29.9% to 20.9% (p<0.01) in the revascularization arm. Myocardial infarctions were impressively almost cut in half (14.6 to 7.4% [p<0.01]). (Not reviewed by Dr. McGuire, but worth mentioning, there were some trends toward better clinical outcomes in CABG patients who were randomized to insulin sensitizers.)

Dr. McGuire mentioned that the event rates in BARI-2D remained excessive at 2% - 5% per year, depending on the revascularization stratum chosen. In fact, even in the drug-eluting stent era, in clinical practice restenosis rates remain as high as 20-25% in those with diabetes, several fold higher than in non-diabetic CAD patients. Also, in-stent acute thrombosis is 3-fold more common when diabetes is present. This observation has led to follow-up investigations that have ascribed the phenomenon to platelet resistance to clopidogrel therapy in patients with diabetes. He also stated that despite a systematic attempt within BARI-2D to optimize medical management in all participants, HbA1c, blood pressure, and lipid control each remained short of target in a substantial proportion.

In the question and answer session, one audience member cautioned that all diabetic patients may not behave similarly as far as their CAD is concerned. Specifically, it was noted that in many trials there is no attempt to distinguish patients with Type 1 from those with Type 2 diabetes. Dr. McGuire agreed and mentioned that an American Heart Association task force is about to tackle this very issue.

In the symposium’s final presentation, Dr. Peter Reaven from the Phoenix Veterans Administration Hospital was posed the question, “Should the Presence of Cardiovascular Disease Affect Glycemic Targets”—a hotly contested issue. The approach to lowering glucose has changed somewhat over the past 1-2 years, with results from large cardiovascular trials suggesting a lack of benefit and perhaps some risk to overly stringent glucose control in high-risk, older patients. These publications have stimulated more attention on the issue of hypoglycemia and how it may be related to cardiovascular complications. Accordingly, it is now quite clear that the clinician should balance the advantages of glucose control with the potential for harm (Figure 1).

Early diabetes treatment trials were generally disappointing in demonstrating any cardiovascular benefit from tighter vs. more conventional glucose control. Studies like the Diabetes Control and Complications Trial (DCCT), the Kumamoto Trial, and the UKPDS each showed a significant advantage for microvascular complications, especially
retinopathy and albuminuria, but the data on myocardial infarction, stroke, and all-cause mortality were unconvincing. More recently, however, well-publicized follow-up studies from the DCCT (a/k/a, EDIC, Epidemiology of Diabetes Interventions and Complications) and the UKPDS suggest that, over time, a cardiovascular benefit indeed emerges—but it might take some 15-20 years to become statistically manifest. In EDIC, for example, despite the fact that during most of the post-randomized study follow-up period, the HbA1c levels between the two groups essentially converged, a nearly 50% reduction in the composite cardiovascular event endpoint was realized in the cohort assigned to intensive therapy in the original DCCT.

In the UKPDS follow-up, tighter control with sulfonylureas and insulin was eventually associated with a 15% relative risk reduction in myocardial infarction, again despite similar HbA1c trends between the initially randomized groups. These provocative data have led to theoretical concepts of ‘metabolic memory’ or the ‘legacy effect’ of glycemic control—i.e., that any prolonged period of better control has a long-term payoff. Of note, however, the opposite concept has also recently emerged—that there may be a ‘bad legacy’ effect on the arterial tree from prior periods of poor control—that a vascular price is paid for previous prolonged hyperglycemia. Admittedly, both concepts are hypothetical constructs and not based on hard science.

Recent trials have focused on whether near-normalization of blood glucose (i.e., HbA1c target of <6-6.5%) could reduce cardiovascular complications vs. conventional therapy targeting standard control (HbA1c ~7.5%). These large investigations—ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation), and the VADT (Veterans Affairs Diabetes Trial)—each came to the same conclusion, almost simultaneously as presented two years ago at this very meeting. In each, the primary endpoint was not achieved—that is, tighter glucose control did not reduce cardiovascular complications overall. Several subset analyses from the trials, however, suggest that those patients with shorter disease duration, better glycemic control, and no established cardiovascular disease at baseline might actually benefit from more intensive glucose control. In one such analysis from the VADT, benefit was detectable when diabetes duration was <15 years, whereas event rates increased exponentially beyond this point.

Dr. Reaven noted that subsequent meta-analyses involving more than 27,000 patients from these trials have suggested a very modest ~10% relative risk reduction in cardiovascular events from intensive glucose lowering. Moreover, a recent retrospective database analysis by Greenfield et al. (Ann Intern Med 2009) indicates no benefit from tight glucose control when many comorbidities are present, whereas outcomes are much better (HR = 0.58 for cardiovascular events) in otherwise healthy diabetic patients.

These data are now buttressed by Dr. Reaven’s own RACED substudy from the VADT. Selected participants underwent coronary artery calcium (CAC) scoring by electron beam computed tomography (EBCT) at baseline. Those with baseline CAC scores of >400 Agaston units had worse outcomes with tighter glucose control, whereas the opposite was true in those with scores <100.

Finally, based on these new data, revised rational HbA1c targets were proposed, incorporating both the known benefits and emerging risks of intensive glycemic management (Figure 2). We feel these are reasonable and represent a thoughtful synthesis of the growing evidence base. They also, in part, answer the need for more individualization of our treatments and patient-centeredness of our care.

The approaches to treatment of CAD in patients with diabetes and the treatment of diabetes in patients with CAD are obviously rapidly evolving. We look forward to more discussions on these critically important topics at this week’s Scientific Sessions of the American Diabetes Association.

**Figure 2. Proposed Individualized Glycemic Targets Based on Patient Comorbidities**

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Target HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High risk for hypoglycemic event(s)</td>
<td>&lt;6.5-7%</td>
</tr>
<tr>
<td>2. Likely low benefit from HbA1c reduction (e.g., age, comorbid conditions, advanced disease)</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>3. Glycemia difficult to control despite efforts</td>
<td>7.5-8.0%</td>
</tr>
<tr>
<td>4. Increased ‘vascular age’ (e.g., known cardiovascular disease)</td>
<td></td>
</tr>
</tbody>
</table>

**A 1-2 Punch**

Early intervention with multiple medications to manage diabetes from diagnosis was the subject of the symposium entitled, “Combination Therapy for Type 2 Diabetes from the Get Go: Are We There Yet?” Each of the three presenters made a case for specific drug classes targeting the different defects in diabetes: insulin resistance (thiazolidinediones), an impaired incretin system (GLP-1 receptor agonists/DPP-4 inhibitors), and relative insulin deficiency (insulin). Baseline assumptions and themes common to each presentation were: (1) data clearly support the use of metformin as a standard component of combination therapy; (2) early intervention is desirable to prevent metabolic decline and preserve endogenous insulin secretion; and (3) “clinical inertia” or lack of treatment intensification based on individual patient factors (e.g., HbA1c, weight, glycemic variability, etc.) is, unfortunately, a well-documented trend in clinical practice.

Dr. Bernard Zinman, University of Toronto, began the session providing specific rationale for early combination therapy in general:

- An early and robust decrease in HbA1c;
- The avoidance of the traditional step-wise approach (i.e., diet/exercise → drug monotherapy → drug combination therapy → insulin injections), inevitably leaving a patient with uncontrolled hyperglycemia for many years;
- Complementary mechanisms of action (Table 1), which properly address the multi-faceted and complex pathophysiology of diabetes; and,
- The potential for synergy leading to use of less than maximal doses of each medication, thereby minimizing drug-related adverse effects.

Given the currently available 11 classes of medications to manage diabetes, the optimal add-on choice to a foundation that typically consists of metformin is not entirely clear. Metformin and sulfonylureas (SU) are frequently used in combination, given their complementary mechanisms (i.e., enhancing insulin action as well as insulin secretion). Disadvantages of the SU class include...
hypoglycemia and weight gain, with no evidence of durable effectiveness over the long term. The primary advantage of the combination is cost: each component available generically and at a nominal price. The early role in the disease course of a thiazolidinedione with metformin was examined by Dr. Zinman's Canadian Normoglycemia Outcomes Evaluation or CANOE study (e-pub, Lancet, 6/3/10). This randomized, placebo-controlled trial compared a combination of rosiglitazone 2 mg and metformin 500 mg twice daily (n=103) versus placebo (n=104) in patients with impaired glucose tolerance over a median time span of 3.9 years. The primary outcome measured was new onset of Type 2 diabetes; secondary outcomes were measures of cardiovascular risk (e.g., blood pressure, weight, CRP, etc.). Fourteen patients (13.6%) progressed to Type 2 diabetes in the treatment arm, whereas 41 (39.4%) were so diagnosed with placebo (p<0.0001). Additionally, regression to normal glucose tolerance was significantly more common with combination therapy (79.6%) versus placebo (53.1%, p=0.0002). No significant differences in side effect profiles were detected, with the exception of diarrhea (16% with treatment, 6% placebo, p=0.025). Secondary outcomes such as weight, BMI, beta-cell function, and lipid parameters did not differ between groups. However, CRP and insulin sensitivity (measured by OGTT) were significantly improved in the active treatment arm.

Zinman remarked that initial combination therapy in patients with IGT shows great promise, recognizing further studies assessing benefits and risks are needed. Certainly, the cost implications would be considerable. We would remind our readers that no specific pharmacological therapy for any pre-diabetic state has been approved by the US Food and Drug Administration (FDA). The American Diabetes Association has, however, endorsed at least the consideration of metformin in patients felt to be at very high risk for diabetes, who also have specific features that predict a favorable response to this drug (age <60 years, BMI >35 kg/m², fasting plasma glucose >110 mg/dl).

Robert Cuddihy, MD, from the International Diabetes Center in Minnesota, followed and echoed the need and rationale for early intervention in patients with diabetes and, more controversially, perhaps even pre-diabetes. He reinforced that treatment is often initiated too late, limiting efficacy and impact, as patients have already established a “bad” metabolic memory (See “Getting to the Heart of Diabetes” page 1 of this issue). Dr. Cuddihy then defended the choice of incretin therapies as the ideal modality to use in combination with metformin for early intervention. He stated that agents leading to weight gain (e.g., sulfonloylureas, insulin), although initially improving glycemic control, may exacerbate long-term metabolic profiles. Secondly, choice of therapy should address the risks of hypoglycemia. A related point is that the need for self-monitoring of blood glucose may be diminished with incretin-based treatments, leading to decreased costs.

The speaker further emphasized the importance of a “lipocentric” view of diabetes as opposed to traditional ‘glucocentricity,’ suggesting that drug-induced weight gain and fat deposition into muscle, liver, and beta-cells exacerbate the underlying disease process. The inverse association between weight and insulin sensitivity is well documented. Therefore, drugs that are weight neutral may be the ideal choice for initial treatment. Dr. Cuddihy recognized, however, that clinical outcomes data are lacking to support either DPP-4 inhibitors or GLP-1 receptor agonists for early treatment. He went on to share several case presentations, however, utilizing combination therapies with these agents in which patients demonstrated decreases in HbA1c, weight loss, low glycemic variability, and no hypoglycemia. He closed his presentation with a proposal for diabetes prevention trials that focus on patients with pre-diabetes at greatest risk who might ultimately benefit from very early treatment with medications that modulate the incretin axis.

Lastly, Dr. Hannele Yki-Jarvinen, MD, Kuopio University Hospital, Finland, reviewed multiple studies evaluating insulins in combination with a variety of other therapies to manage Type 2 diabetes. Dr. Yki-Jarvinen emphasized several points. First, in insulin-treated patients, the dose of the hormone must be adequate to achieve glycemic targets. To a large degree, hepatic fat content dictates insulin requirements, and as a result, modalities that decrease liver fat are likely to have the greatest potential for use in combination with insulin. Secondly, the choice of insulin formulation does not really impact the magnitude of HbA1c lowering. However, basal insulin therapy (versus mixed or intermediate insulins) generally does decrease the risk of hypoglycemia. Dr. Yki-Jarvinen concluded her presentation with the question “Is insulin the real

Table 1. Pharmacological Therapies for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide, Glipizide, Glimepiride</td>
<td>Closes K&lt;sub&gt;ATP&lt;/sub&gt; channels</td>
<td>↑ Pancreatic insulin secretion</td>
</tr>
<tr>
<td>GLIs</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>Activates PPAR-γ mainly in adipocytes</td>
<td>↑ Peripheral insulin sensitivity</td>
</tr>
<tr>
<td>Metformin</td>
<td>Activates AMP-kinase in the liver</td>
<td>↓ Hepatic glucose production</td>
<td></td>
</tr>
</tbody>
</table>

| α-Glucosidase inhibitors | Acarbose, Miglitol | Blocks small intestinal alpha-glucosidase | ↓ Intestinal carbohydrate absorption |
| GLP-1 agonists | Exenatide, Liseglcuditide | Activates GLP-1 receptors | ↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion; delays gastric emptying; ↑ satiety |
| Amylinomimetics | Pramlintide | Activates amylin receptors | ↓ Pancreatic glucagon secretion; delays gastric emptying; ↑ satiety |
| DPP-4 inhibitors | Sitagliptin, Saxagliptin | Inhibits dipeptidyl peptidase-4 | ↑ Endogenous incretin levels |
| Bile acid sequestrants | Colesevelam | Binds bile acid cholesterol | unknown |
| D2 agonists | Bromocriptine | Activates dopaminergic receptors | Alters hypothalamic control of insulin sensitivity |
| Insulin | NPH, Regular, Glargine, Detemir, Lispro, Aspart, Glulisine | Activates insulin receptors | ↑ Glucose disposal; ↓ hepatic glucose production; ↓ proteolysis, lipolysis, ketogenesis |
solution?" She answered positively, as it is the only agent proven to reduce both micro- and macrovascular disease. Moreover, when properly used, it is associated with a low risk of hypoglycemia and only minimal to modest weight gain.

Based on these presentations, along with audience response during question and answer sessions, there appears to be significant interest in earlier, aggressive treatment with combination therapy, not only in early Type 2 diabetes but also in those with pre-diabetes (the latter involving agents that do not result in hypoglycemia).* Clearly, however, expertly designed prospective clinical trials are needed to adequately assess the long-term impact of such an aggressive strategy and also to identify the best combination regimens.

**Monitoring Continuously**

**Table 2. Impact of CGM vs. SMBG on HbA1c and Glucose Excursions**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All CGM vs. SMBG</th>
<th>‘Real Time’ CGM vs. SMBG</th>
<th>‘Retrospective’ CGM vs. SMBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (relative % Δ from baseline):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-8 wks</td>
<td>-4.7*</td>
<td>-4.7*</td>
<td>N/A</td>
</tr>
<tr>
<td>12-16 wks</td>
<td>-8.4*</td>
<td>-9.3*</td>
<td>-4.6*</td>
</tr>
<tr>
<td>24-26 wks</td>
<td>-2.7*</td>
<td>-2.7*</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration BG (min/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤55 mg/dl</td>
<td>-4.3*</td>
<td>-9.3*</td>
<td>-9.3*</td>
</tr>
<tr>
<td>≤80 mg/dl</td>
<td>-11.3*</td>
<td>-10.4*</td>
<td>-10.4*</td>
</tr>
<tr>
<td>71-180 mg/dl</td>
<td>59.5*</td>
<td>69.8*</td>
<td>69.8*</td>
</tr>
<tr>
<td>≥240 mg/dl</td>
<td>-49.3*</td>
<td>-49.3*</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypoglycemic events/day (BG &lt;70 mg/dl)</td>
<td>0.1*</td>
<td>0.0</td>
<td>0.3*</td>
</tr>
</tbody>
</table>

*BG = blood glucose, CGM = continuous glucose monitoring, SMBG = self-monitoring of capillary blood glucose.  
*p<0.0001; †p<0.001; ‡p=NS

As CGM emerges as a tool in selected intensively-managed patients, it remains unclear if the devices will gain more widespread acceptance. Concerns persist regarding accuracy and cost.
**Exenatide and Islet Function After Transplant**

The GLP-1 receptor agonist, exenatide, has been shown to improve insulin secretion in response to glucose in addition to protecting beta cells from apoptosis and promoting beta-cell regeneration in animals. Furthermore, exenatide pretreatment of non-human primates before islet transplantation has been associated with long-term normoglycemia and robust insulin secretory responses for up to 2 years after transplantation. The results of a study by Buss et al. from Ohio, suggest that exenatide pre-treatment alone may be sufficient to maintain islet graft survival in non-human primates, relative to post-transplant treatment alone (141-OR). Beta-cell function of pancreatectomized cynomolgous monkeys that underwent islet allotransplantation improved post-transplant in the animals that were pre-treated with exenatide (53.3% vs. 94.9%), while a marked decrease was noted in untreated animals (20.2% vs. 1.8%), as well as in animals treated only post-transplant (28.8% vs. 13.8%). IV glucose tolerance tests showed normal glucose and insulin curves in the pre-treated group only.

**Decline in Lower Extremity Amputations**

Levels of preventive care services, cardiovascular risk factor management, and glycemic control have all improved during the last decade among US adults with diabetes. In line with these advances, Li et al. from Georgia (CDC) determined there was a decline in age-adjusted rate of hospitalizations for non-traumatic lower extremity amputation from 1988-2006 among American patients with diabetes, with these encouraging findings observed in all demographic groups examined (188-OR). Declines since 2000 were particularly strong (annual percentage change > -11.0%) among those aged 75 and older, women, and whites.

**A Lifetime with Diabetes?: Priceless**

Zhuo et al. from Georgia (CDC) and North Carolina developed and validated a diabetes mellitus simulation model, which they used to calculate the lifetime direct and indirect costs since diagnosis associated with Type 2 diabetes (434-PP). The costs were in 2009 US dollars, and future charges were discounted at 3%. The lifetime cost was estimated at $172,000 for a person diagnosed at age 50. The expenditures were substantial and varied by age at diagnosis and gender (Table 3). Indirect costs (productivity loss) were the primary drivers of the age- and gender-variation. More than half of the total direct medical expenses was attributed to macrovascular complications, based on both high incidence and high cost per event. Over 60% of the medical charges were incurred within 10 years after the diagnosis. These incidence-based estimates of Type 2 diabetes costs may be useful in evaluating the financial benefits of programs designed to prevent Type 2 diabetes.

**Glucose Variability and Autonomic Dysfunction**

Heart rate variability and baroreflex sensitivity—markers of autonomic nervous system integrity—are known to be impaired in patients with diabetes. Moreover, these have been associated with increased cardiovascular events and mortality. Thomakos and colleagues from Greece assessed the relationship between glucose variability (as measured by CGM) and autonomic nervous system function in 22 patients with Type 2 diabetes (15 male, mean age ±SD 55.7±9.6 years, diabetes duration 5.8±4.7 years) on oral agents (abstract 516-P). Glucose variability was assessed by the standard deviation of all obtained 48-hour mean glucose values (SDG). After adjustment for age, SDG was negatively correlated with baroreflex effectiveness index and indices of heart rate variability (with greater variability indicating a more functional autonomic system). After adjustment for 48-hour mean glucose value, the correlation with the baroreflex index remained statistically significant (r = -0.572, p = 0.008). HbA1c, in contrast, was not correlated with any of the autonomic measures. Thus, glucose variability, as assessed by CGM, was associated with autonomic dysfunction, whereas HbA1c was not. These data give support to the notion that it is the variability in blood glucose that has a greater impact on end organs than does mean blood glucose.

* The product is not labeled for the use under discussion or the product is still investigational.

**Table 3. Incidence-Based Lifetime Cost Estimates of Type 2 Diabetes ($1,000)**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Age at Diagnosis (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Total Medical Cost</td>
<td>67</td>
<td>61</td>
</tr>
<tr>
<td>Diabetes Care</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Total Complication</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>CHD</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Indirect Productivity Loss</td>
<td>113</td>
<td>191</td>
</tr>
<tr>
<td>Absenteeism</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Presenteeism</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>Disability</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Premature Death</td>
<td>76</td>
<td>126</td>
</tr>
<tr>
<td>Total Lifetime Cost</td>
<td>180</td>
<td>251</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease

NOTE: The analytical sample came from NHANES 2005, and the cost parameters were obtained from published literature.
The evidence establishing an association between Type 2 diabetes and cancer is building in both the epidemiological and basic science literature (Figure 1). The American Diabetes Association and American Cancer Society recently published online *Diabetes and Cancer: A Consensus Report* (*CA Cancer J Clin* 2010; 60), reviewing this data and providing a united front in the collection and dissemination of information on this topic. Meanwhile, last years’ four publications of observational studies regarding exogenous insulin use and cancer risk have undergone appropriate scrutiny. In a packed symposium, experts presented the latest thinking about topics relating cancer with diabetes and its therapy.

From a scientific standpoint, insulin has clear mitogenic (growth-promoting) activities, which may actually be enhanced in the setting of insulin resistance with its resultant hyperinsulinemia—as seen in patients with obesity and Type 2 diabetes. Clinically, two common skin findings in obese and diabetic patients, namely acanthosis nigricans and acrochordons (‘skin tags’), are likely a direct manifestation of these properties. Certain tumors like breast cancer are known to have increased levels of insulin receptor (IR)-type A (IR-A), which is thought to have greater mitogenic potential than its isomer cousin, IR-B, upon activation by insulin. A further concern is that exogenous insulin analogues may also activate the insulin-like growth factor 1 (IGF-1) receptor to a greater degree than human insulin. IGF-1 translates many of the mitogenic effects of growth hormone itself.

Jeffrey Johnson, PhD, an epidemiologist from Alberta, Canada, launched the forum by stating that cancer is a close contender to cardiovascular disease as the leading cause of death in Type 2 diabetes (29% vs. 31% in a population study by the US Centers for Disease Control [CDC]), and may indeed soon overtake it. He reviewed many observational studies highlighting two strong and consistent findings. First, people with Type 2 diabetes have an increased risk of certain cancers, predominantly those of the endometrium (OR 2.10), liver (OR 2.50), breast (OR 1.20), and pancreas (OR 1.82). Second, people with Type 2 diabetes have a higher mortality rate from cancer as compared to the general population. For example, diabetic women were found to have a ~40% increased risk of mortality in a large retrospective study of over 6,100 women with breast cancer aged 55-79 years old from Ontario, Canada (HR 1.39, 95% CI 1.22-1.59). Although they can be difficult to tease apart in observational cohort studies, many factors such as obesity, hyperinsulinemia, hyperglycemia, or delayed screening may contribute to this increased mortality rate. For example, women with Type 2 diabetes require more complex medical care, and physicians may simply miss opportunities for general cancer screening. In support of this notion, Dr. Johnson quoted Maruthur et al. who demonstrated that women with obesity have a reduced likelihood of receiving a Papanicolaou smear (*Obesity* 2009;17, 375-81). Dr. Johnson also addressed the use of exogenous insulin and cancer. He referred to a soon-to-be published retrospective study of a cohort of 10,309 individuals with Type 2 diabetes followed for a mean of 5.4 years. The mortality risk increased for those with a higher number of prescriptions for insulin when compared to those
who had never taken insulin. For less than 3 prescriptions a year, the hazard ratio (HR) for any cancer was 2.22; 3-11 prescriptions, HR 3.33; and ≥12 prescriptions, HR 6.40. Of note, metformin use attenuated the mortality rates, with HR of 0.80 when used as a single agent.* While these associations are of interest, they do not necessarily imply any causality. The need for insulin therapy may simply be serving as a marker of a group of patients (e.g., longer diabetes duration) that may be predisposed to the development of malignancy. Or, perhaps, the ability to take and be controlled with oral agents may identify a healthier group of individuals.

Dr. Derek LeRoith from Mt. Sinai in New York provided murine evidence that hyperinsulinemia may be the main driver behind the increased growth of breast cancer in women with Type 2 diabetes. He demonstrated that non-obese, hyperinsulinemic mice have an increased tumor volume and more aggressive metastatic spread than occurs in wild-type mice with normal insulin levels. Also, blocking the insulin receptor in these mice prevents this excess tumor growth. He pointed out that his model mimics the endogenous hyperinsulinemia that occurs in people for years prior to their diagnosis of Type 2 diabetes, but excludes the confounding variable of obesity.

John Lachin, ScD from George Washington University in Washington, D.C. critiqued the statistics used in the controversial retrospective German study that reported an association between insulin glargine and cancer (Hemkens, et al. Diabetologia 2009; 52:1732-44). The article was published alongside other observational studies that did not find a consistent signal between this insulin analogue and cancer incidence. Dr. Lachin emphasized that observational studies are for the purpose of hypothesis generation, and only randomized control trials can determine a causal association. The Hemkens study was retrospective from an insurance company database, including 127,031 patients exposed for an average of 1.63 years to glargine. Important covariates such as type of diabetes, duration of diabetes, degree of glucose control, and body mass index were not available. In fact, the patients requiring glargine were different in their baseline characteristics than the patients using NPH, and it is statistically difficult, if not impossible, to adjust for these differences. Also, the researchers computed an average insulin dose for each subject over the entire follow-up period, which introduced bias in the results interpretation. When the analysis was repeated and not adjusted for dose, the study did not demonstrate any increased risk for cancer.

In the final presentation, Jay S. Skyler, MD from the University of Miami reiterated the weaknesses of the Hemkens study. He remarked on the disconnect between the cautiously worded articles and editorials in Diabetologia, and the ensuing press releases that intimated a clear relationship between glargine and cancer. He argued for a more measured and scientific approach to such issues. To date, there is no clear-cut evidence that glargine is associated with an increased risk of cancer. However, there is a strong association between Type 2 diabetes itself and an increased risk of certain malignancies as well as higher cancer-related mortality. Long-standing elevation in endogenous insulin levels are a possible culprit. It remains to be seen whether high dose exogenous insulin, often required in today’s very obese diabetic population, affects malignancy rates and/or growth.

In the late 1990’s, the thiazolidinediones (TZDs) were touted as the edge of the new frontier of anti-hyperglycemic therapy, focusing on insulin resistance. The opening session of the ADA, provocatively entitled “The Good, The Bad, and the Ugly,” addressed the impact of these drugs on diabetes care since then, with a focus on both their purported benefits and an increasing array of concerns. Although these PPAR-γ agonists decrease insulin resistance and likely preserve beta-cell function, they also increase the risk for heart failure and bone fractures, the latter at least in women. One member of the class, rosiglitazone, may also increase cardiovascular events, although the data here are conflicting. Four speakers discussed old and emerging issues with this drug class.

Dr. Tom Buchanan from the University of Southern California highlighted the benefits of TZDs on beta-cell preservation with resultant slowing of disease progression. Metabolically normal individuals compensate for changes in insulin sensitivity by increasing insulin secretion and thus maintain glucose concentrations in the normal range. Type 2 diabetes results from the combination of defects in both insulin sensitivity and insulin secretion— which are, notably, present long before hyperglycemia ensues. Several studies have shown that TZDs decrease diabetes incidence in individuals at high risk.* Importantly, Dr. Buchanan argued, they do so not by merely decreasing glucose and delaying the onset of the disease, but by actually modifying the progression of the disease.* Support for this comes from multiple trials, including TRIPOD (Troglitazone in the Prevention of Diabetes), PIPOD (Pioglitazone in the Prevention of Diabetes), DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), and most recently ACT Now (Actos Now for the Prevention of Diabetes). Diabetes incidence over time for individuals treated with TZDs is not only lower than for controls, but, when plotted, the incidence lines appear to diverge and never meet, even after pharmacological intervention is ceased. Furthermore, the early trials with troglitazone (since then removed from the market) in Hispanic women with a history of gestational diabetes (TRIPOD) showed that protection from diabetes was strongly linked to the degree of improvement of beta-cell function. This appeared to be mediated by a reduction in the secretory demands placed on beta cells.

These beneficial beta-cell effects also extend to those with already established Type 2 diabetes. The ADOPT (A Diabetes Outcome Progression Trial) trial compared metformin, glyburide, and rosiglitazone treatment in patients with diabetes. Although sulfonylureas achieved the most rapid reduction in fasting glucose and HbA1c levels, TZDs were associated with the most durable effect over time. The recent RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial similarly showed stability of HbA1c over time in patients treated with rosiglitazone as compared to those on sulfonylureas and metformin. Therefore, Dr. Buchanan argued, TZDs are highly attractive agents early in the disease process once lifestyle interventions fail. However, he cautioned, not everyone responds to these drugs (in his studies, ~1/3 of patients don’t respond and have no change in fasting insulin levels even after 3 months). Also, data for TZD use is not available for all ethnic groups, information on long-term effects on microvascular disease is lacking, and other factors (such as weight gain, risk of fractures, edema) need to be considered carefully.

Much recent attention has been focused on the deleterious effects of TZDs on bone health. Dr. Andrew Grey from the University of Auckland reminded the audience that bone loss results
from an imbalance in the normal process of bone remodeling, during which osteoclast recruitment/activation are tightly coupled to bone formation by osteoblasts. PPAR-γ activation appears to disrupt this delicate balance by inhibiting the differentiation of mesenchymal cells into osteoblasts and, instead, diverting these progenitor cells to adipocyte lineage (Figure 2). In addition, PPAR-γ activation may also stimulate the development of osteoclasts.

Multiple pre-clinical studies confirm that PPAR-γ agonists promote adipogenesis and inhibit osteoblastogenesis with resultant decreases in bone formation and increases in bone resorption. In animal studies, the mechanism by which these agents affect bones appears to differ based on age. In younger animals, PPAR-γ activation primarily decreases bone formation while in older animals, it primarily increases bone resorption. Whether similar age-related differences apply to humans remains unclear.

To elucidate the mechanisms of PPAR-γ in human studies, markers of bone formation and resorption were examined by Grey’s lab in 50 postmenopausal women randomized to rosiglitazone or placebo for 14 weeks. The osteoblast markers (procollagen type I N-terminal propeptide and osteocalcin) declined in the rosiglitazone group, but there was no change in a bone resorption marker (C-terminal telopeptide of type I collagen) in this short-term study. Bone mineral density was significantly reduced at the hip in the rosiglitazone group compared to placebo (spine bone density fell but was not significantly different between the groups). More recently, analysis of the ADOPT trial comparing longer-term therapy with rosiglitazone, metformin, or glyburide showed that a marker of osteoclast activity (C-terminal telopeptide) was increased in women (but not men) on rosiglitazone, while it decreased on the other two agents. In this study, markers of osteoblast activity were reduced for both men and women in almost all treatment groups (greatest in metformin, intermediate in rosiglitazone, and smallest in the glyburide group). Therefore, both bone formation and bone resorption may be influenced by TZD therapy.

Although biomarkers and bone density help elucidate the mechanisms of TZD's effects on bone health, it is the rate of fractures that is the most relevant patient outcome. In the 2008 analysis of the ADOPT trial, rosiglitazone therapy for 4 years resulted in fractures in 60 (9.3%) women, compared to 30 (5.1%) on metformin, and 21 (3.5%) on glyburide. Fractures were seen predominantly in the lower and upper limbs, but this may not be surprising since these fractures are more common in general. Subsequent meta-analysis of 10 randomized trials and 2 observational studies by Loke et al. showed that pioglitazone and rosiglitazone doubled the risk for fractures among women, but not among men.

The next question raised was whether classical osteoporotic fractures occur more commonly in TZD users and whether the risk is really only increased in women. Based on the analysis of a large UK primary care database, hip and femur fractures were more common in users of TZDs, suggesting that the risk may not be limited to distal fractures. In addition, a recent large prospective cohort study in British Columbia comparing treatment with a TZD or a sulfonylurea reported that the risk of fractures may be indeed increased in both men and women. Finally, the Scottish Diabetes Research Network group examined national data and showed that TZD exposure was associated with hip fractures in both men (age-adjusted incidence rate-ratio 2.23, 95% CI 1.16-4.28) and women (1.90, 95% CI 1.29-2.81) (74-OR).

The totality of evidence suggests that TZDs are, in fact, detrimental to skeletal health. Dr. Grey recommended a careful assessment of the risk for fractures for patients considering treatment with TZDs and felt that if the estimated risk exceeds 10%, TZDs should be avoided or used with caution in concert with therapies aimed at protecting bone. He conceded, however, that the efficacy of bone protective therapies (e.g., bisphosphonates) has not been evaluated for patients treated with TZDs.

Next, Dr. Philip Home took the podium to talk about cardiovascular effects of these agents. Rosiglitazone and pioglitazone were approved by the FDA in 1999, when both fluid retention and probable heart failure were recognized as potential adverse side effects. However, early on, TZDs appeared to have a beneficial effect on cardiovascular events. In 2005, PROactive, a secondary prevention trial of pioglitazone, showed a 10% relative risk reduction in the primary endpoint (a composite of cardiovascular events and procedures), which did not achieve statistical significance, but a 16% relative risk reduction in the secondary, more conventional, endpoint of all-cause mortality, MI, and stroke was significant.

The tide began to turn in 2006 when the sponsor of rosiglitazone, GSK, performed a meta-analysis suggesting increased risk of MI with an odds ratio of 1.31 (95% CI 1.01-1.70). In 2007, Nissen and Wolski published their meta-analysis again showing increased risk signal for rosiglitazone (OR 1.43, 95% CI 1.03-1.98). Dr. Home reported that recently GSK performed an additional meta-analysis (including RECORD and ADOPT studies) that actually showed a lower OR of 1.10, which was not statistically significant (95% CI 0.89-1.35). These meta-analyses are partly based on studies with small numbers of events, not designed for assessment of cardiovascular outcomes. He concluded that meta-analyses are generally less convincing than a large prospective controlled trial specifically designed to assess the outcome of interest. Meta-analyses can only be hypothesis-generating.

To that point, he turned our attention to the RECORD trial, for which he served as principal investigator. In this large (n=4,447) randomized controlled study, with an average follow up of 5.5 years, addition of rosiglitazone to metformin or sulfonylurea was compared to the combination of the latter two agents with the primary outcome of cardiovascular death or hospitalization for cardiovascular events. The hazard ratio for this primary endpoint was 0.99 (95% CI 0.85-1.16), meeting the criterion of ‘non-inferiority’ and, Dr. Home argued, gave no suggestion at all for cardiovascular harm. Dr. Home showed various analyses performed (per protocol, for each secondary outcome, for atherosclerotic events only, for cardiovascular deaths only, subgroup analyses of background metformin and background sulfonylurea) as well as a variety of individual secondary endpoints (MI, acute coronary syndrome [ACS], angina, revascularization, etc.), none of which showed any increased cardiovascular risk with rosiglitazone therapy, except for the known risk of heart failure (HR 2.19, 95% CI 1.35-3.27).

The RECORD trial has been heavily criticized for several methodological flaws. It was an open-label trial and, due to the concurrent TZD controversy, many patients stopped taking the study
Diabetes and depression are highly prevalent in US adults, and their coexistence has been reported by many. Anderson RJ, Diabetes Care 2001. Pan et al. from Massachusetts and the United Kingdom evaluated the diabetes-depression association using data from the Nurses’ Health Study (n=52,745 women, aged 50-75 years in 1996 who were followed until 2006) (abstract 1985-P). Clinical depression was defined as having diagnosed depression or using antidepressants; depressed mood was defined as clinical depression or severe depressive symptoms based on Mental Health Index (MHI-5) score ≤52. During a 10-year follow-up (473,233 person-years), 2,521 incident cases of Type 2 diabetes were documented. After adjustment for BMI, physical activity, and other covariates, there was a 16% increased risk of developing Type 2 diabetes among individuals with depressed mood (RR, 1.16; 95% CI, 1.04-1.30). In a parallel analysis, 5,327 incident cases of clinical depression were documented over the 10-year follow-up (407,746 person-years). Compared to subjects without diabetes, the risk of developing clinical depression was substantially increased among patients with diabetes: multivariate-adjusted RR=1.32 (95% CI, 1.20-1.46) for all diabetes patients, 1.24 (95% CI, 1.06-1.43) for those not treated with medication, 1.37 (95% CI, 1.18-1.59) for those treated with oral antihyperglycemic agents, and 1.45 (95% CI, 1.14-1.84) for those treated with insulin. These associations remained significant after adjustment for comorbidities. These results support the bi-directional association between diabetes and depression and underscore the importance of simultaneous prevention and management of both conditions.

The connection from diabetes to depression is not difficult to understand, as any chronic condition may unmask an underlying predisposition to affective symptoms. That from depression to diabetes is more difficult to comprehend, however. If it is indeed cause-and-effect, perhaps activation of counter-regulatory factors, such as catecholamines and/or cortisol may be to blame. Another fascinating consideration is a link through inflammation. Doyle et al. from the US and Italy studied the possibility that inflammatory factors may mediate the relationship between diabetes and depression (123-LB). The hypothesis for their study was formed on the basis of up-regulated levels of interleukin-6 (IL-6), TNF-α (TNF), and C-reactive protein (CRP) being common to both Type 2 diabetes and depression. The study cohort included 3,014 adults, aged 70-79 years, who participated in the Health ABC Study. Presence of Type 2 diabetes was assessed per self-report, medication use, fasting glucose, and/or glucose tolerance test results. Depressed mood was categorized using the Center for Epidemiologic Studies Depression scale. IL-6 (pg/ml) was significantly higher (p<0.05) among patients with Type 2 diabetes and depression compared to the other groups analyzed (4.4 versus 2.7 for diabetes only, 2.6 for depression only, and 2.3 for healthy controls). Similarly, CRP (mg/l) was significantly higher among those with Type 2 diabetes and depression (5.3) compared to depression only (2.9, p<0.05) or healthy controls (2.8, p<0.05), and approached the level of statistical significance for diabetes only (3.6, p=0.07). After adjustments for potential confounding factors, the interaction between Type 2 diabetes and depressed mood status with levels of IL-6 and CRP was significant. A graded relationship was not observed for TNF after adjustment for covariates. These findings support the hypothetical model that links inflammation, Type 2 diabetes, and depressed mood. Further study of these relationships will enhance our understanding of the biological pathways driving the relationship between these two common conditions.
On the horizon for treating Type 2 diabetes are potential new groups of oral agents, including sodium glucose co-transporter 2 (SGLT-2) inhibitors, non-thiazolidinedione (TZD) selective PPARy modulators (SPPARMs), protein tyrosine phosphatase 1B (PTP-1B) inhibitors, and GPR (G-protein coupled receptor)-119 agonists.* Reports of developmental studies for compounds within these classes were presented this week at the ADA Scientific Sessions.

**SGLT-2 Inhibitors**

Sodium-glucose cotransporter (SGLT)-2 inhibitors block glucose reuptake in the proximal nephron, allowing hyperglycemia to be corrected by glycosuria, particularly in the postprandial period. While modest efficacy and some weight loss have been shown in early clinical trials of SGLT-2 inhibitors, concern has been raised about their potential for increasing urinary tract infections and candidal vaginitis/balanitis.

Rosenstock et al. from Texas and New Jersey conducted a double-blind, dose-ranging study in which they randomized 451 Type 2 diabetes patients who were suboptimally controlled on metformin (mean age 53 yrs, weight 87 kg, HbA1c 7.7%, fasting plasma glucose 162 mg/dl) to the SGLT-2 inhibitor, canagliflozin* 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, or 300 mg bid, to the DPP-4 inhibitor, sitagliptin 100 mg qd, or to placebo (abstract 77-OR). Statistically significant improvements from baseline in fasting plasma glucose and HbA1c, relative to placebo, were observed at week 12 for all active treatment groups, with maximum and similar decreases for each in the canagliflozin 300 mg qd and 300 mg bid groups. Dose-related weight reduction was seen with canagliflozin, compared to a small mean increase with sitagliptin (Table 1). Treatment-emergent adverse events were generally similar in type and incidence across the treatment groups, with the exception of slightly higher rates of asymptomatic genital infections with canagliflozin (3.8% vs. 2% with both placebo and sitagliptin). Of note, the incidence of urinary tract infections ranged from 3-9% across the canagliflozin dose groups, with the rate not related to dose, was 6% for placebo, and 2% for sitagliptin. The incidence of hypoglycemia with canagliflozin (0-6%) was not related to dose, and compared to rates of 2% and 5% for placebo and sitagliptin, respectively.

Wilding et al. from North America and Europe reported the results of a 48-week study of another SGLT-2 inhibitor, dapagliflozin* 2.5 mg, 5 mg, or 10 mg daily, compared to placebo, in 808 Type 2 diabetes patients (mean HbA1c 8.5%) poorly controlled with insulin (mean 77 units/day) ± oral antihyperglycemic agents (abstract 21-LB). Insulin was up-titrated if HbA1c was >8% or fasting plasma glucose was >178 mg/dl from weeks 24-48. Reduction in HbA1c at week 24 (primary endpoint) was maintained at week 48 (-0.43% for placebo, -0.74%, -0.94%, and -0.93% for 2.5 mg, 5 mg, and 10 mg dapagliflozin, respectively), as was weight reduction, even when including data after insulin up-titration (+0.9 kg for placebo vs. -1.5 kg for dapagliflozin 10 mg). Insulin dose increased over the study period in the placebo group and was stable for patients treated with dapagliflozin. Consistent with the findings from the Rosenstock study, urinary tract infections (7.9-10.8% vs. 5.1% with placebo) and genital infections (6.4-10.7% vs. 2.5% with placebo) were reported more commonly with dapagliflozin, with most events reported during the first 24 weeks and responsive to treatment.

The SGLT-2 inhibitors appear to be modestly effective antihyperglycemic agents with an unusual mechanism of action. More information is needed on their safety profiles, particularly involving the urogenital tracts.

**SPPARMs**

While PPAR-γ activation leads to improvements in insulin resistance, hyperglycemia, endothelial function, and markers of inflammation, it is also associated with unwanted side effects such as weight gain, fluid retention, and increased risks of heart failure and bone fractures. Research is under-way to determine if actions through the PPAR-γ receptor can be selectively modulated to separate insulin-sensitizing actions from the less desirable effects. Early evidence from clinical studies suggests favorable metabolic effects and potentially fewer adverse effects with the SPPARM, INT131. DePaoli and American coworkers reported the results of a 24-week, double-blind study of INT131* (0.5, 1, 2, or 3 mg qd), pioglitazone 45 mg qd, or placebo in 366 patients with Type 2 diabetes who were on a stable dose of sulfonylurea with or without metformin (mean age 55.9±9.5 yrs, duration of diabetes 8.4±6.1 years, 47% women, BMI 32.0±5.5 kg/m², HbA1c 8.3±0.7%) (315-OR). Improvement in HbA1c at endpoint was directly related to INT131 dose, and comparable to TZD at the higher doses studied. Incidence of edema (feet, ankles, mid-pretibial) with INT131 was not different from baseline or placebo, and was less than that with pioglitazone (Figure 3). These findings suggest the potential for fewer edema-related adverse effects with this SPPARM than with currently available PPAR-γ agonists, although trials of longer duration are clearly needed. More information will be needed regarding weight and bone changes.

**PTP-1B Antisense Inhibitor**

Protein tyrosine phosphatase 1B (PTP-1B) is a negative regulator of insulin action. In preclinical models, reduction of PTP-1B activity enhances insulin sensitivity. Brandt et al. of California conducted a multicenter, double-blind study of patients with Type 2 diabetes (duration ≤12 yrs, HbA1c 8.7%, fasting plasma glucose ~100 mg/dl), poorly controlled by maximal doses of sulfonylureas, who they randomized to 100 mg or 200 mg (n=26) weekly injections of ISIS 113715,* a novel PTP-1B antisense inhibitor, or placebo (n=26) for 13 weeks (316-OR).
The 200 mg dose was superior to placebo based on improvements in fasting plasma glucose and self-monitored plasma glucose (≤25 mg/dL, p = 0.026), fructosamine (≤25 µmol/L, p = 0.009), glycated albumin (p = 0.03), LDL-cholesterol (≤11 mg/dL, p = 0.005), apoB, and HDL-cholesterol, indicating favorable effects on glycemia and metabolic dyslipidemia. Consistent, but less robust, glycemic effects were seen with the 100 mg dose. Additionally, placebo-subtracted weight loss of >0.5 kg was recorded after 13 weeks in the 200 mg group, preceded by an improvement in adiponectin (an adipocytokine that increases with insulin sensitization), which increased by 65% by the end of the study (p = 0.023). Injection site erythema was the most common adverse event. PTP-1B inhibition may be promising as a novel target for treating Type 2 diabetes patients.

**GPR-119 Agonist**

GPR-119 is a G-protein coupled receptor that regulates glucose by enhancing glucose-sensitive insulin secretion while simultaneously stimulating incretin hormone release from the intestines. Suppressive effects on food intake and GI motility have also been described. Roberts et al. from California conducted a phase 1, dose-ranging pharmacokinetic/pharmacodynamic study of MBX-2982,* an oral GPP-119 agonist, at once daily doses of 25 mg, 100 mg, 300 mg, and 600 mg (n = 8 per dose) vs. placebo (n = 12), in subjects who fulfilled impaired fasting glucose or impaired glucose tolerance criteria, or had an HbA1c ≥5.8% (abstract 603-P). A significant reduction in glucose was observed with all doses of active study drug during a mixed meal tolerance test performed on Day 4; there was a pooled 48% reduction in glucose AUC (p < 0.001 vs. placebo). Glucose lowering was best in subjects with the greatest derangements in glucose tolerance: -76% in subjects with postprandial glucose >180 mg/dl (n = 3), -61% in those with postprandial glucose >160 mg/dl (n = 6), and -49% in those with postprandial glucose >140 mg/dl (n = 13).

In an increasingly crowded anti-hyperglycemic drug space, it remains unclear which of these agents, if any, will eventually be approved by the FDA and be available for clinical use. Safety is a focus of the agency these days, and new agents must now demonstrate convincing cardiovascular safety before approval.

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**So Many Posters, So Little Time....**

As mentioned in our review of the cardiovascular symposium in yesterday’s edition (Getting to the Heart of Diabetes, pg 3), although intensive glucose lowering strategies did not improve cardiovascular outcomes in patients in the VADT trial, they did appear to lower the risk for patients with lower coronary calcium (by EBCT) at baseline. Saremi et al. from the US examined 197 subjects participating in a sub-study of VADT to examine whether intensive glucose therapy reduced the progression of coronary and abdominal aortic artery calcium (CAC and AAC, respectively) (405-PP). Baseline and follow-up scans (average 4.6 years) were performed and CAC and AAC were categorized into none, low (<100 for CAC; ≤1,000 for AAC), and high (>100 for CAC; >1,000 for AAC). Treatment assignment to intensive or standard therapy was not associated with annual changes in calcium or in progression of atherosclerosis, irrespective of baseline CAC and AAC category in these patients with long-standing Type 2 diabetes. These data support the current notion that once substantial atherosclerosis has become manifest, glucose control may have little impact on its further evolution.

Patients with diabetes not only have a higher rate of coronary disease, but also of heart failure. In another abstract presentation, Eurich et al. from Canada and the United Kingdom performed a nested case control study using the United Kingdom General Practice Research Database to determine the effects of various treatments on mortality in patients with co-existent Type 2 diabetes and heart failure (731-PP). There were 1,633 cases (≥35 years of age, newly diagnosed with diabetes and heart failure after January 1988 who had died before October 2007) and 1633 controls matched on age, sex, site, year, and duration of follow-up. The mean age was 78 years, 53% were male, and one-fifth had a HbA1c ≥8%.

In multivariate analyses, as may be expected, the use of beta blockers, ACE inhibitors, and angiotensin receptor blockers was associated with reduced mortality. The use of metformin was also associated with lower mortality compared to patients who were diet- or lifestyle-controlled for their diabetes (OR 0.66, 95% CI 0.49-0.89), but the use of other anti-hyperglycemic agents or insulin appeared not to influence outcomes. We note that metformin is no longer contraindicated in patients with stable, compensated heart failure, but should obviously still be avoided in those with unstable status, acute decompensation, or superimposed renal disease. Prospective studies will be needed to demonstrate whether this biguanide medication may actually improve outcomes in the growing population of patients with both diabetes and ventricular dysfunction.*

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* The product is not labeled for the use under discussion or the product is still investigational.

**Silvio E. Inzucchi, MD**  
**Robert S. Sherwin, MD**  
Editors, Yale University, New Haven, Connecticut
The inpatient management of hyperglycemia continues to draw intense interest at the American Diabetes Association (ADA) Scientific Sessions, and this year was no exception. A well-attended symposium on Sunday brought together experts from around the country to discuss the implications of both hyper- and hypoglycemia in the hospital setting, review current guidelines, and discuss implementation strategies.

To lead off the session, Dr. Mary Korytkowski from the University of Pittsburgh went over the evidence from observational data sets linking hyperglycemia to morbidity and mortality in hospitalized patients. A cause-and-effect relationship is suggested but remains not entirely proven. The results from clinical trials, most conducted in the ICU in which intensive insulin therapy was used to reduce glucose levels into the normal range, have been conflicting. Initial enthusiasm about attaining euglycemia has since been attenuated, after the realization that any such intervention markedly increased the hypoglycemia risk. The latest, large randomized clinical trials have shown no benefit from glucose targets in the 80-110 mg/dl range, as opposed to a more reasonable and achievable goal of 140-180 mg/dl. Accordingly, the ADA with the American College of Clinical Endocrinologists last year relaxed their recommendations, advising IV insulin to achieve blood glucose levels of 140-180 mg/dl range in the critical care setting (Table 1).

Dr. Mikhail Kosiborod next discussed the important issue of hypoglycemia. Like hyperglycemia, hypoglycemia is also associated with increased mortality. In elegant retrospective studies, Dr. Kosiborod’s group has found evidence that insulin-induced hypoglycemia (i.e., iatrogenic) is not associated with adverse outcomes, whereas spontaneous hypoglycemia is. This suggests that underlying patient comorbidities, such as sepsis, liver and renal disease, and malnutrition may actually be driving the increased mortality. Nonetheless, hypoglycemia in the hospital setting, especially when severe, should be avoided for obvious reasons.

### Table 1. AACE-ADA Consensus Guidelines for Inpatient Hyperglycemia

**ICU Patient**
- Use IV insulin by validated protocol
- Need frequent BG monitoring
- Begin IV insulin at BG no higher than 180 mg/dl
- BG target: 140-180 mg/dl
- Lower target (110-140 mg/dl) acceptable
- Targets <110 mg/dl no longer considered safe

**Non-ICU Patient**
- Maintain BG <140 mg/dl pre-meal
- Maintain all post-meal BG <180 mg/dl
- More stringent targets in selected, stable patients with prior tight control
- Less stringent targets in patients with severe comorbidities
- Consider adjusting regimen once BG <100 mg/dl
- Basal-bolus insulin therapy preferred approach
- Avoid prolonged use of RISS
- Oral agents usually not appropriate.
- Use clinical judgment to optimize control and avoid hypoglycemia

BG = blood glucose, RISS = regular insulin sliding scale.

Methods to do so were introduced and explored further by Dr. Mercedes Falciglia from the University of Cincinnati who reported that IV insulin is the optimal strategy in the ICU to minimize the risk of hypoglycemia, given the very short half life of insulin. Dozens of IV protocols are available, including several computerized versions, but without head-to-head studies, it is difficult to recommend one over another. The best protocols tend to be ‘dynamic’ ones, responding with different algorithmic instructions based not only on the blood glucose level, but also on its rate of change. Good protocols also have specific targets, are easily implemented by the nursing staff in response to a single physician order, and incorporate orders for hypoglycemia and transition to subcutaneous insulin after the patient has stabilized.
The sessions’ final speaker, Dr. Steve Clement from Georgetown University took a case-based approach and highlighted the complexity of managing glycemia outside of the ICU, where frequent interruptions, dietary indiscretions, and changes in the patient’s condition can greatly impact control. He endorsed basal-bolus therapy in most patients requiring insulin in this setting, but emphasized the need to individualize approaches in all patients.

In a related session earlier in the week, Dr. Guillermo Umpierrez from Emory reported on his RABBIT 2-Surgery study in which basal-bolus therapy with glargine and glulisine was compared to traditional regular insulin sliding scale (RISS). 211 patients with a blood glucose between 140-400 mg/dl and a history of Type 2 diabetes for more than 3 months who were undergoing general surgery were randomized to one of the two treatment arms (33-OR). Mean age was 58±11 years, admission glucose 190±92 mg/dl, and HbA1c 7.7±2.2%. According to the study protocol, the total daily dose of the basal-bolus regimen was started at 0.5 U/kg, given half as glargine once daily and half as glulisine before meals. RISS was given 4 times per day for glucose >140 mg/dl. The mean daily glucose levels after the first day were 145±32 mg/dl and 172±47 mg/dl, respectively (p<0.01), and the percentages of glucose readings <140 mg/dl were higher with basal-bolus (53±30% vs. 31±28%, p<0.001). There was no difference in mortality (1% each). There were numerical reductions with basal-bolus in wound infection (2.9% vs. 10.3%, p=0.05), pneumonia (0% vs. 2.8%; p=0.24), and acute renal failure (3.8% vs. 10.3%; p=0.10), which at most trended toward significance. However, the prespecified primary endpoint, a composite of these adverse outcomes was significantly and dramatically reduced with the more aggressive regimen (8.6% vs. 24.3%; p=0.003). In those requiring critical care transfer, ICU length of stay was also reduced (1.2±0.6 vs. 3.2±2 days, p=0.003). Hypoglycemia was more common with glargine-glulisine: <70 mg/dl in 23.1% of patients (1.9% of blood glucose readings) vs. 4.7% of RISS patients (0.3% of blood glucose readings), p<0.001. Readings <40 mg/dl occurred in 3.8% and 0%, respectively.

The investigators concluded that a basal/bolus insulin regimen is preferable to RISS in the hospital management of general surgery patients with Type 2 diabetes. These data have been long awaited. Those of us who manage hospitalized patients can now say that more aggressive control of post-operative glucose will result in better clinical outcomes, but at the expense of some hypoglycemia. These data should be replicated in a larger, multicenter trial.

In a session entitled, Key Issues in the Management of Dyslipidemia, the optimal LDL-cholesterol (C) goal for diabetes patients and the current roles, if any, for fibrates and niacin were discussed. The morning began with a debate between Dr. Sergio Fazio from Tennessee, who defended an LDL-C target of <70 mg/dl, and Dr. Lawrence Leiter from Toronto who took the opposing view.

Dr. Fazio began by noting that up to 80% all diabetes mortality is related to atherosclerosis (75% of this from coronary and 25% from cerebral and peripheral) and 75% of hospitalizations for diabetes are related to cardiovascular disease (CVD). He next reviewed multiple randomized controlled clinical trials providing evidence that lowering LDL-C using HMG-CoA reductase inhibitors (statins) significantly reduces the risk of events. He reminded the audience that no other drugs for dyslipidemia, other than statins, have been validated with such robust outcomes data.

Dr. Fazio recognized that the goal LDL-C in each of the trials was not specifically <70 mg/dl, however, it is clear that “lower is better.” While the specific number, 70, was never the target, several studies brought their mean LDL-C close to this, conferring a significant benefit vs. standard therapy/placebo arms, which maintained LDL-C in the low 100’s mg/dl. For example, in the treatment arm of the Collaborative Atorvastatin Diabetes Study (CARDS, Lancet 2004; 364:685-96), the mean LDL-C was 82 mg/dl vs. 121 mg/dl in the placebo group. Similarly, in the Treat to New Targets (TNT) trial (Diabetes Care 2006; 29:1220-26), the high-dose atorvastatin group (80 mg) achieved a mean LDL-C of 77 mg/dl versus the low-dose group (10 mg), which resulted in a mean LDL-C of 99 mg/dl. In each of these investigations, active therapy patients experienced major reductions in their cardiovascular events.

Dr. Fazio therefore was in full accord with the current lipid guidelines as recommended by the ADA (Table 2). He also noted that for individuals without overt CVD the suggested target is LDL-C <100 mg/dl, but that he suggested lowering it with statins by 30 to 40%, regardless of the baseline value.

Table 2. ADA 2010 Lipid Guidelines

<table>
<thead>
<tr>
<th>Parameter and Patient Characteristics Target</th>
<th>LDL cholesterol in patients with CVD</th>
<th>LDL cholesterol in patient without CVD</th>
<th>HDL cholesterol in men</th>
<th>HDL cholesterol in women</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD=cardiovascular disease.</td>
<td>&lt;70 mg/dl</td>
<td>&lt;100 mg/dl</td>
<td>&gt;40 mg/dl</td>
<td>&gt;50 mg/dl</td>
<td>&lt;150 mg/dl</td>
</tr>
</tbody>
</table>

Dr. Leiter assumed the opposing view and began with two brief cases. The first patient was a 22 year-old female, diabetes duration of 1 year, with an active, healthy lifestyle and laboratory values (e.g., HbA1c, blood pressure, etc.) well within desired ranges. The second individual was a 54 year-old male smoker with hypertension, sedentary lifestyle, diabetes duration of 15 years, and an HbA1c of 9.4%. He pointed out that these two individuals do not have similar risks despite lack of overt CVD. He then reviewed several studies (e.g., OASIS, HOPE, MR FIT) that have demonstrated that diabetes confers a lower risk of CV events in those without prior cardiac history than in those with overt CVD but without diabetes. Alexander et al. (Diabetes 2003; 52:1210-14) used the NHANES III database to identify age-adjusted prevalence of CVD in patients over 50 years categorized by diabetes and metabolic syndrome. Those with highest risk had both diabetes and metabolic syndrome (19.2%), and those with the lowest risk had diabetes, but not metabolic syndrome (7.5%). The other two categories, no diabetes/no metabolic syndrome and no diabetes/with metabolic syndrome had risks of 8.7% and 13.9%, respectively. Therefore, at least in this cohort, diabetes did not confer additional risk unless other metabolic risk factors were also present.

He then questioned the target of <70 mg/dl, restating that most of the study results identified by Dr. Fazio had not actually achieved...
that specific goal. Leiter also shared the Canadian, Joint European, and Joint British Societies guidelines, which target LDL-C values of <80 mg/dl, <100 mg/dl, and <77 mg/dl, respectively. In his closing remarks, Leiter concluded that although the data are mixed, diabetes is not a coronary risk equivalent, as is often stated. There is significant heterogeneity in risk among patients and, thus, LDL-C target should not be simplified for all. In addition, the current LDL-C targets are not as evidence based as many believe.

Beyond Statins

Henry Ginsberg, MD from Columbia in New York addressed the issue of identifying patients in whom fibrates may be beneficial. Reviewing their pharmacology and clinical trial data, fibrates generally decrease triglycerides by 25% to 40%, increase HDL-C by 5% to 20%, with a variable impact on LDL-C. Other than the Helsinki Heart Study from the 1980’s, which demonstrated a 34% reduction in event rates in the gemfibrozil 600 mg twice daily arm, fibrates have failed to achieve statistically significant reduction in CV events for patients with diabetes in recent clinical trials, such as FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes). However, in a subgroup analysis of FIELD (Diabetes Care 2009; 32:4938), the relative reduction in CVD was 27% (95% CI, 9-42%, p=0.005) for patients with elevated triglycerides (≥200 mg/dl) and low HDL-C (<40 mg/dl). Similarly, in a pre-specified subgroup analysis of ACCORD (NEJM 2010; 362:1563-74), patients with the combination of high triglycerides (>204 mg/dl) and low HDL-C (<34 mg/dl) treated with fenofibrate experienced a primary outcome rate of 12.4% versus 17.3% in the placebo group, approaching statistical significance (p=0.057). For all other patients, outcome rates were 10.1%. Despite these generally disappointing trial results, he suggested that fibrates may still be worth adding to the often complex medication regimens in patients with diabetes, in particular, those with high triglycerides (≥200 mg/dl) and low HDL-C values (<35-40 mg/dl).

John Guyton, MD, from the University of North Carolina closed the symposium with the presentation, The Case for Add-On Niacin Therapy in Diabetes. He described HDL-C as critically important in the removal of cholesterol from atherosclerotic plaque. In epidemiologic studies, HDL-C is typically far superior to LDL-C with respect to predictive value for atherosclerosis. Although there are some non-pharmacologic means of increasing HDL-C (e.g., weight loss, exercise, smoking cessation, ethanol ingestion), drug therapy may be more efficient. In terms of increasing HDL-C, niacin has the greatest impact, with an average increase of 25%. Pioglitazone, fenofibrates, and statins increase it by approximately 15%, 3-15%, and 2-14%, respectively.

Guyton recognized that primary prevention data supporting the use of niacin are lacking. However, there are secondary prevention and anatomic endpoint studies that support its use.* For example, Lee et al. conducted an MRI study in patients with CVD (n=71, 68% diabetes) and determined that extended-release niacin 2000 mg/day significantly decreased carotid atherosclerosis (p=0.003) and increased HDL-C by 23% after 12 months of treatment (JACC 2009; 54:1787-94).

Insulin: New and Improved?

The emerging global diabetes pandemic, associated with rising prevalences of obesity and metabolic syndrome, has created the need for better insulins, especially so in developing countries where there are unique challenges relating to storage and use. To this point was a symposium at the ADA Scientific Sessions entitled, “Newer Insulins—As They Approach Availability What Should We Know?”

Warp-Speed Insulins

The first speaker, Michael Weiss, MD, PhD, from Case Western Reserve University, Cleveland Ohio reviewed the status of “warp-speed insulins” in development. With the objective of mimicking meal-time insulin secretion of a healthy pancreas, Weiss mentioned that new ultra-fast insulins must improve upon currently available rapid insulin analogues, by reducing early postprandial hyperglycemia and late-phase postprandial hypoglycemia. He reviewed in detail various development pathways being taken. The first was co-injection of rapid-acting insulin with hyaluronidase, which depolymerizes the subcutaneous site and enhances insulin absorption. Results of several studies presented in posters this week showed that hyaluronidase co-injection of rapid insulin analogs accelerates the pharmacokinetics and glucodynamics of rapid insulin analogs.

Aspirin is commonly used in the US to reduce flushing, as this continues to be a significant side effect associated with niacin. For best results, Guyton specifically recommends a 325 mg dose, administered 30 minutes prior to niacin. An agent currently available only in Europe, laropiprant,* inhibits prostaglandin release and has been used in combination with niacin to reduce flushing.

He advised that niacin ‘extended-release’ is the preferred product and should be taken twice daily in the middle of the breakfast and dinner meals. The extended release formulation is associated with the most extensive outcomes data and appears to be better tolerated than ordinary formulations. In contrast, so-called, ‘slow-release’ niacin should be avoided due to an increased potential for hepatic toxicity.

Reports of niacin-induced hyperglycemia have recently been corroborated (Am J Card 2010; 105:487-94). Guyton explained that the majority of data suggest that elevated blood glucose is a short-term phenomenon (within first 12 to 24 weeks of therapy), generally returning to baseline over the course of a year. While each presenter made valid points, we remain skeptical concerning additional lipid-lowering therapy beyond the aggressive use of statins in our patients with diabetes, unless the triglyceride or HDL-C levels are markedly abnormal, in which case adjuvant therapy may be considered. (Extremely high triglycerides (>500-1000 mg/dl) are associated with pancreatitis.) Certainly, the evidence base for the use of fibrates or niacin remains unconvincing. We also continue to be concerned about the potential diabetogenic effects of niacin, as well as potential drug interactions with statins, although admittedly this appears to be mainly an issue with the older fibrate, gemfibrozil.
California found that co-injection of rhHuPH20 with lispro significantly reduced postprandial hyperglycemia following a liquid meal (mean 2-hour level from 159 to 138 mg/dl; p=0.019) and reduced hypoglycemia (66% reduction in excursion area <70 mg/dl; p=0.03) in patients with Type 2 diabetes (abstract 387-PP).

Another platform mentioned by Weiss for improving the kinetics of rapid insulin is the combination of recombinant human insulin with an EDTA-containing diluent, which removes zinc (thereby destabilizing insulin’s zinc-mediated hexamer assembly). This results in a rapidly absorbed monomeric insulin. One such formulation in development is VIAject™. Rodbard et al. from the US and Germany conducted a 6-month, open-label, multicenter study in which they treated 471 patients with Type 2 diabetes with either VIAject™ or regular human insulin (RHI) in combination with previously prescribed insulin glargine, metformin, and/or thiazolidinediones (abstract 36-OR). HbA1c was 8.2% at baseline and decreased by -0.6% in the VIAject group and -0.7% in the RHI group (95% CI -0.05, 0.32) at study endpoint. In addition to comparable glycaemia control, study patients receiving VIAject achieved a 2-fold reduction in rate of non-severe hypoglycemia (0.33 vs. 0.66 events/month with RHI, p<0.02) and significantly less weight gain (0.46 vs. 1.35 kg, p<0.05), as compared to patients in the RHI group. There has been little data, however, comparing this new insulin with currently available rapid analogues.

Weiss also described very early protein engineering projects, for instance halogenation of insulin with currently available rapid analogues. In closing, Weiss noted that “smart insulins”, which combine insulin with a built-in glucose sensor, are in development, with Phase 1 studies imminent. Should these products be successful, they may revolutionize future insulin therapy.

### Alternative Delivery of Insulin

**The final speaker, Dr. William Cefalu from LSU School of Medicine, Baton Rouge summarized the status of insulins administered by alternate (to SC injection) delivery methods (Table 3), which are being developed with the goals of increasing compliance and quality of life, providing more physiologic insulin delivery, and perhaps achieving better metabolic control. The over 2,000 literature citations for alternative insulin delivery routes speak to their substantial scientific interest. Yet only one, inhaled insulin, came to market, to market, namely Exubera, but this was quickly removed mainly due to poor sales, although concerns persisted regarding pulmonary safety.**

While intranasal delivery of insulin results in rapid onset of action, challenges include low bioavailability without a permeability enhancer, as well as nasal irritation. Stote et al. from the US presented study results for Nasulin™,* a human insulin in pill form *would be ideal, however, enzymatic degradation in the GI tract, binding by the mucosal barrier, and first-pass hepatic clearance have converged to thwart all attempts to date at developing a clinically viable p.o. formulation. Several lines of investigation suggest that tenacity may pay off, however. An oral insulin candidate, IN-105 (Biocon), is a human insulin molecule conjugated on position B29 with polyethylene glycol via an acyl chain to reduce degradation. In phase 1 studies, a “second-generation” tablet is absorbed rapidly and has shown dose-dependent glucose lowering, with maximum effect when taken -20 minutes before a meal. In a recently published proof-of-concept study, Kapita et al. demonstrated that absorption of oral insulin (combined with a delivery agent) under fasting conditions was feasible, leading to greater maximum insulin concentration and faster onset compared to RHI. However, between-subject variability in absorption was high (Diabetes Care 2010; 33:1288-90).

Inhaled insulin leverages the large (size of tennis court) surface area of the alveolar tree for absorption. As noted, one such product passed all efficacy and safety approval hurdles of the FDA, but was subsequently removed from the US.

### Table 3. Alternative Delivery of Insulin*

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
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<tbody>
<tr>
<td>Nasal</td>
<td>Zimman and worldwide coworkers randomized insulin-naive Type 2 diabetes patients (mean: 54.2 years, HbA1c 8.7%, fasting plasma glucose 184 mg/dl, BMI 29.5 kg/m²) to insulin degludec SC 3-times weekly (n=62) or once daily (n=60) or insulin glargine once daily (n=62), all in combination with metformin (abstract 40-OR). All insulins were titrated to achieve fasting plasma glucose of 72-108 mg/dl. Insulin degludec administered 3-times weekly or once daily provided similar glycemic control to glargine (final mean HbA1c at week 16 = 7.3, 7.4, and 7.2%, respectively) following similar insulin doses (3.4, 3.1, and 3.3 U/kg/wk, respectively). The rate of confirmed hypoglycemia (&lt;56 mg/dl or requiring assistance) was lower for once daily insulin degludec than 3-times weekly or daily glargine (0.6, 2.3, 1.1 events/patient/yr, respectively; p=NS). A formulation combining insulin degludec with insulin aspart in a mix (70%/30%) is also under study (34-OR).</td>
</tr>
<tr>
<td>Sublingual</td>
<td>The over 2,000 literature citations for alternative insulin delivery routes speak to their substantial scientific interest. Yet only one, inhaled insulin, came to market, namely Exubera, but this was quickly removed mainly due to poor sales, although concerns persisted regarding pulmonary safety. While intranasal delivery of insulin results in rapid onset of action, challenges include low bioavailability without a permeability enhancer, as well as nasal irritation. Stote et al. from the US presented study results for Nasulin™,* a human insulin in pill form *would be ideal, however, enzymatic degradation in the GI tract, binding by the mucosal barrier, and first-pass hepatic clearance have converged to thwart all attempts to date at developing a clinically viable p.o. formulation. Several lines of investigation suggest that tenacity may pay off, however. An oral insulin candidate, IN-105 (Biocon), is a human insulin molecule conjugated on position B29 with polyethylene glycol via an acyl chain to reduce degradation. In phase 1 studies, a “second-generation” tablet is absorbed rapidly and has shown dose-dependent glucose lowering, with maximum effect when taken -20 minutes before a meal. In a recently published proof-of-concept study, Kapita et al. demonstrated that absorption of oral insulin (combined with a delivery agent) under fasting conditions was feasible, leading to greater maximum insulin concentration and faster onset compared to RHI. However, between-subject variability in absorption was high (Diabetes Care 2010; 33:1288-90).</td>
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<tr>
<td>Buccal</td>
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</tr>
<tr>
<td>Oral</td>
<td>After war years, Symptomatichypoglycemia occurred less frequently in the Nasulin™ group. As for sublingual administration of insulin, Cefalu briefly mentioned Viatab technology,* Data from pre-clinical laboratory models have demonstrated rapid onset of insulin effects, improved shelf-life of the insulin, and pharmacodynamic activity. The thin, highly permeable mucosa of the sublingual area lends itself to drug absorption. Buccal delivery of insulin has undergone study for decades. Oral-lyn™ RapidMist™,* a liquid formulation of RHI with a spray propellant for oral administration, results in a more rapid increase in insulin action compared to SC regular insulin administered at mealtimes (Heinemann L. J Diabetes Sci Technol 2009; 3:568-84).</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Inhaled insulin leverages the large (size of tennis court) surface area of the alveolar tree for absorption. As noted, one such product passed all efficacy and safety approval hurdles of the FDA, but was subsequently removed from the US.</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Shorter with Nasulin™ (mean±SD, 18.7±2.73 minutes) than for lispro 10 IU (43.1±3.46 minutes) or lispro 20 IU (44.1±3.5 minutes) (both, p&lt;0.001), with a smaller counterregulatory glucagon response afterwards. Symptomatic hypoglycemia occurred less frequently in the Nasulin™ group.</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td><strong>Table 3. Alternative Delivery of Insulin</strong></td>
</tr>
</tbody>
</table>
market by its developer. Another currently under review by the FDA is Technosphere®, an ultra rapid-acting inhaled insulin with a pharmacokinetic profile that suggests earlier control of post-prandial plasma glucose may be possible. Rosenstock et al. recently showed that prandial Technosphere® insulin plus bedtime insulin glargine led to comparable reduction in HbA1c compared to premixed bipart insulin 70/30 (-0.68% vs. -0.76%, respectively), and attenuated weight gain after 1 year of treatment of Type 2 diabetes patients (Lancet 2010; 375:2244-53). Consistent with the Exubera experience, Cefalu mentioned that FEV1 decreases slightly with this inhaled formulation, although not progressive, with apparent remission with long-term administration.

At this week’s sessions, Raskin et al. from Dallas and California presented the results of a study in which Type 2 diabetic patients with inadequately glycemic control (HbA1c > 6.6%, ≤12.0%) had prandial Technosphere® inhaled insulin incorporated into the usual antihyperglycemic regimen (n = 656; mean ± SD dose = 141.7 ± 62.9 U) or continued on their baseline program (i.e., insulin, oral hypoglycemics, and/or diet and exercise; n = 678) (abstract 359-OR). At 2 years, there was comparable reduction from baseline in HbA1c between the 2 groups (Figure 1, p = 0.30) and less hypoglycemia among patients who received inhaled insulin (0.15 vs. 0.24 events per patient-month for usual-care patients treated with insulin injections (p = 0.03 overall). Weight gain was observed in both groups (+1.56 kg vs. +1.75 kg, respectively; p = 0.67).

We remain wary about these insulins on several fronts. First is cost — these products are bound to be appreciably more expensive than current insulins. Second, potential safety issues for inhaled products will need to be resolved. Finally, the bioavailability of some agents may be unreliable, especially the oral products.

In a symposium devoted to renal disease in diabetes, Dr. Mark Molitch of Northwestern University addressed “Controlling Glycemia in CKD—What Are the Targets and How to Achieve Them?” Dr. Molitch began the session by reminding the audience that diabetes continues to be the leading cause of renal failure in the US. In addition, once dialysis is initiated, overall and specifically cardiovascular mortality is much worse in diabetic patients vs. their non-diabetic peers. He summarized the main goals of diabetes care as they relate to the kidneys to be to:

1) Reduce the total number of patients with diabetes;
2) Reduce the number of patients with diabetes who develop nephropathy; and
3) Slow the rates of progression once nephropathy is present.

Focusing on the second and third goals, a multifaceted approach to care is important. This involves, in addition to diabetic management, meticulous blood pressure control, judicious use of drugs that block the renin-angiotensin axis, and the avoidance of acute renal injury (Table 4). Next, Dr. Molitch reviewed what is known about glucose control and the development and progression of kidney disease. From the DCCT to the Kumamoto study to the UKPDS, it is quite clear that tight glycemic control prevents renal microvascular complications. The relationship between HbA1c and albuminuria is curvilinear, with much of the benefit occurring when HbA1c is dropped from the 11-12% range down to 9%, less so—but still demonstrable—when reduced further to 7%, and negligible additional improvement as 6% is approached. In the follow up to the DCCT, past more intensive glucose control continued to benefit renal outcomes, even after 20 years. For example, by the end of the follow-up period, the development of serum creatinine (Scr) levels >2 mg/dl was reduced by more than 60% and the need for dialysis or transplantation by more than 70%. Based on these data, the widely accepted HbA1c target of <7% appears to be a reasonable goal in most patients.

Dr. Molitch next turned to the metabolic changes in diabetic patients with decreasing glomerular filtration rate (GFR). There are notable changes in the renal contribution to gluconeogenesis and in the renal clearance of both insulin and several oral antihyperglycemic agents. Accordingly, patients with failing renal health are often predisposed to hypoglycemia. As renal failure develops, some of these changes are blunted by increased insulin resistance but may be aggravated further by decreased nutritional intake due to nausea in frank uremia as well as a deficient catecholamine response to hypoglycemia. Clearly, managing glucose in those with progressive loss of GFR is a great challenge.

With regard to specific drug therapies, there are many considerations. The longer-acting sulfonylureas are dangerous due to renal clearance of active metabolites, especially glyburide. Thiazolidinediones may be problematic because of fluid retention in chronic kidney disease (CKD) patients whose renal function has deteriorated to the point of not being able to fully excrete sodium. The recent concerns of bone loss may tend to exacerbate renal osteodystrophy as well. The incretin mimetic, exenatide, is not be used in those with creatinine clearance <30 ml/minute, and the DPP-4 inhibitors, which are excreted in the urine, require dose adjustments as renal function falter.

Nateglinide and acarbose should be avoided when Scr exceeds 2 mg/dl.

Metformin’s contraindications in renal failure are well known, although, as Dr. Molitch pointed out, the prescribing guidelines in Europe are more liberal than in the US. The concern is lactic acidosis due to decreased metformin clearance. American physicians are instructed to...
stop metformin when the SCR reaches 1.5 mg/dl in men and 1.4 mg/dl in women. Protocols in the UK, however, suggest stopping the drug only if the estimated GFR falls below 50 ml/minute. Others have suggested continued therapy but progressive dose reductions when SCR levels rise, but only stopping the drug if the estimated GFR falls below 30 ml/minute. Clearly, more evidence-based guidelines would be helpful.

Dr. Molitch concluded his presentation by reminding the audience that the leading cause of death in patients with diabetes and CKD is cardiovascular disease, a much more frequent occurrence than the need for dialysis. As a result, stringent control of other cardiovascular risk factors, especially lipids and blood pressure, are of utmost importance. There is early evidence of potential benefits on the cardiovascular system from treatment of secondary hyperparathyroidism with vitamin D analogues as well as addressing anemia with erythropoietin analogues.*

### Insulin Therapy in Extreme Insulin Resistance

The obesity epidemic is shaping the landscape of Type 2 diabetes both in its prevalence as well as its therapeutic challenges. Obesity often confers severe insulin resistance, with resulting endogenous hyperinsulinemia. As the beta cell fails and Type 2 diabetes becomes apparent, obese patients tend to require larger amounts of insulin to maintain glycemic control. It is no longer uncommon in clinical practice to have patients with severe resistance, defined as the requirement of more than 200 units of insulin per day. A vicious cycle of weight gain and up-regulation of insulin dosing is not only frustrating, but also may be counter-productive to promoting health. Hyperinsulinemia is implicated in cardiovascular disease and cancer (see "Diabetes and Cancer: Making the Link," page 1). Therapeutic means of reducing the total daily insulin dose needed to achieve glycemic control may be beneficial. A symposium on Monday addressed managing insulin therapy in the obese, extremely insulin-resistant patient.

Wendy Lane, MD an Endocrinologist from Asheville, North Carolina spoke about the use of U-500 in this population. U-500 is a regular human insulin formulation that is five times more concentrated than regular insulin, and has a pharmacodynamic profile between that of regular insulin and NPH. It is administered by injection two to three times daily, and may be infused from an insulin pump, although this is still off-label.* U-500 is generally initiated in order to decrease the volume and frequency of injections as well as to improve insulin absorption. Another important advantage is significant cost savings as compared with U-100 insulins, and especially vs. newer insulin analogues. Despite the growing need for concentrated insulin, there are fewer than 10 published studies on the use of U-500 in practice, and half of them are uncontrolled, retrospective reports. However, their take-home messages are improved glycemic control with fewer injections, better compliance, and typically a reduced total dose of insulin over 24 hours. Changes in weight were not consistent across the studies, with some reporting weight loss and others reporting mild weight gain. In general, the number of hypoglycemic episodes was unchanged, although it is noted that close monitoring is required since U-500 has a longer period of action and may produce late hypoglycemia. We would advise extreme caution in using this type of insulin. In particular, careful prescribing instructions are mandatory since the term ‘units’ may be misinterpreted by patients and pharmacists when this type of insulin is employed.

Another therapeutic option to achieve glycemic goals with less insulin is to add oral agents. Candis Morello, PharmD from University of San Diego, California, compared the relative pros and cons of oral agents in achieving improved glycemic control when insulin therapy is insufficient (Table 5).

And finally, Francesco Rubino, MD of Cornell University, New York addressed why bariatric surgery is now being termed “metabolic surgery.” Many studies have demonstrated a rapid reduction in insulin resistance and normalization of glycemia after gastric bypass surgery, even before there is significant weight loss. The mechanism for this is still not understood, but may involve intestinal proteins such as GLP-1.

Since its inception, the safety record of bariatric surgery has improved. In a recent NIH study, the mortality rate for laparoscopic gastric bypass was 0.3%, similar to hip replacement (0.3%) or laparoscopic cholecystectomy (0.35-0.6%). The overall complication rate was 15% in 2006, down from 24% in 2002. While surgical expertise in this procedure has improved, complications that have remained unchanged in their rates include ulcers, hemorrhage, deep vein thrombosis, and pulmonary embolism (Fleins et al. NEJM 2009). Recent ADA Standard of Care guidelines recommend considering bariatric surgery for anyone with diabetes and a BMI ≥35 kg/m².

Since obesity rates are increasing, particularly in childhood, the options for managing severe insulin resistance will become more important. Therapeutic outcome studies for this subset of our population with diabetes are needed to make informed choices about how to optimize their care.

### Table 5. Profile of Oral Agents when Added to Insulin

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>TZDs</th>
<th>α-Glucosidase Inhibitors</th>
<th>DPP-4 Inhibitors</th>
<th>Bile Acid Sequestrants</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ HbA1c</td>
<td>0.9-2%</td>
<td>0.5-2.4%</td>
<td>-0.6%</td>
<td>-0.6%</td>
<td>-0.4%</td>
</tr>
<tr>
<td>↓ FPG</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>↓ PPG</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Weight effect</td>
<td>Loss</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Other concerns</td>
<td>Lactic acidosis (rare)</td>
<td>Edema, heart failure, bone fractures</td>
<td>GI</td>
<td>—</td>
<td>GI</td>
</tr>
</tbody>
</table>

FPG=fasting plasma glucose, PPG=postprandial glucose, TZD=thiazolidinedione.

* The product is not labeled for the use under discussion or the product is still investigational.
In January of 2010, the American Diabetes Association (ADA) endorsed new criteria for the identification of glycemic disorders, based upon glycated hemoglobin (HbA1c) cut-points: ≥6.5% for diabetes and 5.7-6.4% for pre-diabetes (Table 1). The original criteria based on fasting plasma glucose (FPG) and 2-hour glucose after an oral glucose tolerance test (OGTT) remain valid tests as well—the ADA did not stipulate that one test is superior to another. Multiple presentations this week noted something that many clinicians across the country have observed—that HbA1c and FPG may not always necessarily agree. Furthermore, interesting differences in the characteristics of persons identified by the two tests are emerging.

In a symposium dedicated to the diagnosis of diabetes by HbA1c, Dr. Ed Gregg from the CDC addressed the challenges inherent in defining cut-points for pre-diabetes, given that the risk for subsequent diabetes lies along a continuum of FPG, 2-hour plasma glucose during an OGTT, as well as HbA1c. These cut-points are, therefore, driven by the choice of intervention and resources available since the ‘optimal’ thresholds remain ambiguous. Dr. Gregg asked several questions: “What HbA1c levels correspond to prior FPG/OGTT criteria?”; “At what HbA1c levels are prevention efforts effective?”; “What is the relationship between HbA1c and future diabetes incidence?”; and “What cut-points provide potential for the greatest health impact?”

First, Dr. Gregg shared data from the 2003-2006 NHANES examination in which 14% of individuals were identified with pre-diabetes by HbA1c and 26.2% by FPG (i.e., having impaired fasting glucose). However, 6% of individuals were identified by HbA1c but not by FPG (favoring non-Hispanic blacks, women, and older persons) and 17% by FPG but not by HbA1c. He underscored that significant discordance exists between the two tests. Secondly, in the successful Diabetes Prevention Program (DPP), the largest lifestyle intervention trial, the mean HbA1c was 5.9%. A recent analysis from this trial suggests that effectiveness of diet and exercise was similar in those with higher and lower HbA1c levels. Accordingly, patients with HbA1c’s in the range denoted by the ADA for pre-diabetes are reasonable. Third, a systematic review (Zhang et al., in press) evaluating HbA1c at baseline and subsequent diabetes risk showed no distinct threshold, with increases in relative risk of ~10-20 fold at HbA1c of 5.5-5.9% and of ~20-40 fold at HbA1c of 6.0-6.4% (as compared to those in the lowest HbA1c range of <4.5%). Of note, FPG and HbA1c together were more predictive than each one alone. Lastly, the decision for particular cut-points depends to some degree upon the intent of intervention. In a hypothetical example using the DPP as a model, a HbA1c cut-point of 5.7% would require 24 persons thus identified to undergo lifestyle intervention in order to prevent one case of diabetes. The higher the HbA1c, the more cost effective the strategy, and vice versa. Dr. Gregg concluded that HbA1c is a strong and continuous risk factor for diabetes. However, discordance between HbA1c and glucose-based tests suggests that neither can be viewed as ideal.

Dr. Robert Cohen from the University of Cincinnati next reviewed biological aspects of HbA1c and the basis of the frequent disagreement between glucose- and HbA1c-based testing. HbA1c is an indirect measure of glycemia based upon the glycation of hemoglobin within red blood cells. Therefore, HbA1c depends upon how much glucose enters the red blood cell, the rate of glycation, and the red blood cell life span. Seminal work showing how well glucose and HbA1c relate comes from the A1c Derived Average Glucose (ADAG) study by Nathan et al. (Diabetes Care 2008;31:1473-8). Dr. Cohen pointed out that when glucose is plotted against HbA1c, one can easily see that an HbA1c of 7.0% corresponds to an average glucose ranging between 130 and 200 mg/dl and, likewise, an average glucose of 150 mg/dl corresponds to an HbA1c anywhere between 5.9 and 7.5%. The term “glycation gap” has been applied to this phenomenon of imperfect representation of glucose by HbA1c. In elegant experiments, Dr. Cohen and others have shown...
that glucose does not penetrate the red cell in the same way in all people, and although glycation appears to be constant over the red blood cell lifespan, the lifespan itself varies considerably. He emphasized the racial and ethnic differences in HbA1c and concluded that confirmation of diabetes requires consistency among tests and a single cut-point is not sufficient for all individuals.

In a counter-argument, Dr. Jonathan Shaw from the University of Melbourne stated that HbA1c and glucose are actually equally valid tests for diagnosing dysglycemic states. He acknowledged that there are problems with HbA1c—it is not a sensitive test and estimations of prevalent diabetes based on it may not be correct; the assay is variable; ethnic/age differences exist in its relationship to glucose; and many conditions may interfere in the performance of the assay (hemoglobinopathies, anemia, renal failure). However, fasting glucose has its own set of limitations: specimens need to be processed promptly; day-to-day variability is in the range of 12-15% (compared to <2% for HbA1c); and, fasting is required. Therefore, each test has its own conceptual challenges, and neither exactly and reliably matches the concept of chronic glycaemia. The sensitivity of HbA1c as compared FPG is being reported in the range of 35-80% depending on the population studied. The discordance, Dr. Shaw noted, is now well-established—but is it important? He argued that it would be if we knew which test was the ‘gold standard’, but we don’t.

Dr. Shaw showed that each test for diabetes predicted the diabetes complication of retinopathy very well. In the DETECT-2 project pooling 47,000 people from 13 studies, moderate non-proliferative diabetic retinopathy (as assessed by retinal photography) was extremely rare below HbA1c ∼6.5%, FPG ∼126 mg/dl, and 2-hour OGTT ∼200 mg/dl, but rose sharply with increasing values. The discriminatory value of these tests was almost identical. Therefore, while the choice of the test might depend on many factors, including availability, reliability, cost, and the prevalence of underlying hemoglobinopathies, in general, each one is intrinsically valid. In related presentations this week, several investigators noted the differences in diagnosis of diabetes and pre-diabetes based upon HbA1c and the more traditional, glucose-based measures. In the Insulin Resistance Atherosclerosis Study (IRAS), Haffner et al. from Texas found that 15.9% of individuals had diabetes based upon the new ADA criteria, but out of these individuals, only one-third were identified by HbA1c, about one-half by FPG, and the vast majority by OGTT (424-PP). Discordance was also noted in those at risk for diabetes, with men, African Americans, and non-Hispanic whites more frequently identified by FPG, women or Mexican-Americans more frequently identified by OGTT, and very few whites being identified by HbA1c. Similarly, Lipska et al. from Connecticut (1136-P) noted poor sensitivity of HbA1c compared to FPG (57%) for diabetes diagnosis in a cohort of older Americans (mean age 76.5 years) in the Health ABC study. Differences between the two tests were accentuated by race and gender. The white/black differences were further evaluated by Selvin et al. from Hopkins based on the Atherosclerosis Risk In Communities (ARIC) study (1135-P). Interestingly, levels of HbA1c, fructosamine, and glycated albumin were all higher in blacks than whites, with and without diabetes, at similar FPG levels. However, 1,5-anhydroglucitol (which is reduced with postprandial hyperglycaemia) trended lower in blacks. This study suggests that ambient glycaemia, rather than alterations in glycation or other genetic factors, may explain black/white disparities in HbA1c levels.

Despite this controversy, support for the strong relationship between HbA1c and clinical outcomes was confirmed in several late-breaking presentations. Selvin's group analyzed data from 11,092 participants in the ARIC study who did not have cardiovascular disease or diabetes at baseline (44-LB). Over 15 years of follow-up, in adjusted analyses, HbA1c 5.7-6.4% was associated with increased risk for subsequent diagnosed diabetes (HR 3.0), coronary artery disease (HR 1.6), ischemic stroke (HR 1.6), and all-cause mortality (HR 1.4). Notably, HbA1c predicted risk of these clinical outcomes even after adjustment for FPG. In summary, while there appears to be significant discordance between HbA1c and glucose measures for the diagnosis of dysglycemic states, both glucose and HbA1c measures show a strong relationship with subsequent clinical outcomes. The optimal method for diagnosis remains hotly debated, and this controversy may not soon be reconciled.

### ACCORD Update

ACCORD (Action to Control Cardiovascular Risk in Diabetes) is a multi-center, randomized, controlled trial with a factorial design evaluating intensive glycemic, lipid, and blood pressure strategies in 10,251 individuals with Type 2 diabetes at high risk for cardiovascular disease. The primary outcome was a composite of first occurrence of nonfatal MI, nonfatal stroke, or cardiovascular (CV) death. The trial was halted due to the higher risk for CV death and all-cause mortality in the intensive glucose arm. During the closing symposium of the 2010 ADA Scientific Sessions, investigators of the trial presented updated findings. Dr. William Cushman from the University of Tennessee addressed whether targeting systolic blood pressure (SBP) <120 mmHg compared to <140 mmHg reduces CV events. Based on data from 4,733 eligible participants followed for 4.7 years (baseline mean age 62 years, BP 139/76 mmHg, Cr 0.9 mg/dl, HbA1c 8.3%, BMI 32 kg/m², 34% with prior CV disease, diabetes duration 10 years), intensive therapy did not significantly reduce the primary outcome (HR 0.88, 95% CI 0.73-1.06) with resultant mean SBP of 134 mmHg (2.1 medications)
in the standard and SBP 119 mmHg (3.4 medications) in the intensive groups (NEJM 2010;362:1575-85). In a subgroup analysis, stroke risk was reduced (HR 0.59, 95% CI 0.39-0.89) in the intensive group, but this effect needs to be confirmed in future trials. Overall, there was no evidence that targeting SBP <120 mmHg compared to <140 mmHg reduced CV events.

Dr. Henry Ginsberg from Columbia University reported on the main results of the lipid trial (NEJM 2010;362:1563-74). There were 5,518 eligible participants (LDL-cholesterol [C] 60-180 mg/dl, HDL-C <55 mg/dl for women/blacks and <50 mg/dl otherwise, triglycerides [TG] <750 mg/dl if no on therapy and TG <400 mg/dl otherwise). Randomization was to open-label simvastatin (20-40 mg/day) with addition of fenofibrate (54-160 mg/day based on renal function) vs. placebo. Participants (similar characteristics to that in the blood pressure study above, with mean LDL-C 101, HDL-C 38, TG 162 mg/dl) were followed for an average of 4.7 years. Addition of fenofibrate was not associated with reduced risk for the primary outcome (HR 0.92, 95% CI 0.79-1.08) compared to statin therapy alone. In subgroup analyses, there was heterogeneity in treatment effect according to sex, with a benefit for men, but possible harm for women (p = 0.01 for interaction). Although much has been made of apparent benefit in the prespecified lipid subgroup with both high TG (>204 mg/dl) and low HDL-C (<34 mg/dl) (see Cholesterol Chronicles, Issue 4, page 2), the interaction here was of only borderline significance (p = 0.057 for interaction).*

Dr. Mertz Gerstein from MacMaster University in Canada reported on the effects of 3.7 years of intensive glycemic control on CV outcomes after 5 years of total follow-up, providing additional information about the participants after the intensive glycemic strategy was halted. The median HbA1c was 7.5% at the end of intervention and increased to 7.6% at the end of follow-up in the standard group, and was 6.4% increasing to 7.2% in the intensive glycemic group. Rates of severe hypoglycemia (requiring assistance) decreased from 3% of participants/year in the intensive and 1%/year in the standard groups to 0.8%/year in both groups at the end of follow-up. The primary outcome at the end of follow-up was not significantly reduced, but CV death risk continued to be higher in the intensive arm (HR 1.29), with non-fatal MI risk reduced (HR 0.82). These findings are very similar to those observed when the intensive glycemic strategy was abandoned and show no reduction in the overall risk for CV events with intensive glucose therapy.

Dr. Faramaz Ismaeil-Beigi from Case Western Reserve University discussed the effect of intensive glycemia treatment on development and progression of microvascular outcomes (Lancet, June 29, 2010). In this analysis, several pre-specified secondary composite outcomes were assessed: 1) dialysis or renal transplantation, high serum Cr (>3.3 mg/dl), or retinal photocoagulation or vitrectomy; 2) peripheral neuropathy and the first composite outcome; and 3) 13 other pre-specified outcomes relating to kidney, eye, and nerve function. (Although not mentioned in this presentation, it is important to note that investigators and participants were aware of treatment group assignment.) The first and second outcomes were not significantly different between treatment groups (first outcome: HR 1.00, 95% CI 0.88-1.14; second outcome: HR 0.96, 95% CI 0.89-1.02). There were also no differences in individual outcomes for these renal or retinal complications between the groups. Intensive therapy was, however, associated with reduced rates of microalbuminuria, macroalbuminuria, fall in eGFR, fall in visual acuity measures, and loss of pressure sensation.

Notably, with so many comparisons, the probability of finding a positive association is greatly increased. In summary, intensive glycemic strategy did not improve advanced measures of microvascular disease. Whether improvements in some of the surrogates (such as microalbuminuria) translate to clinically meaningful outcomes is not clear in this older group of patients.

Dr. Emily Chew from the National Institutes of Health presented results of intensive glycemic, blood pressure, and lipid control on progression of diabetic retinopathy in a sub-study of the ACCORD trial (NEJM June 29, 2010). Out of 3,472 participants enrolled in the eye study (no history of photocoagulation or vitrectomy), 2,856 (82%) completed baseline and year 4 follow-up. The primary endpoint here was progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale (ETDRS) or progression of retinopathy necessitating photocoagulation or vitrectomy. Intensive glycemic control was associated with reduced odds for the primary endpoint (OR 0.67, 95% CI 0.51-0.87), as was intensive lipid therapy with addition of fenofibrate* (OR 0.60, 95% CI 0.42-0.86), but not intensive blood pressure control (OR 1.23, 95% CI 0.84-1.79).

In summary, intensive glycemic control in the ACCORD trial did not significantly reduce the primary outcome, significantly increased all-cause mortality, and reduced nonfatal MI, did not delay composite microvascular outcome measures, but did delay several measures of microvascular disease and reduced retinopathy progression. Blood pressure control to the normal range did not significantly reduce the primary outcome, significantly reduced stroke in a subgroup analysis, and did not affect retinopathy progression. Lipid treatment did not significantly reduce the primary outcome, showed some heterogeneity of effect in a few subgroups, and reduced retinopathy progression.
GLP-1 added to standard therapy in patients (n=12) with NYHA Class III/IV heart failure, comparing LVEF to a control group (n=9) who received standard therapy (J Card Fail 2006; 12:694-99). The GLP-1 arm significantly improved LVEF (21±3% to 27±3%, p<0.01), independent of a diagnosis of diabetes. Long-term, large-scale prospective trials are needed to truly assess any potential role in this area.

Dr. Carol Wysham of the University of Washington led the next presentation that reviewed the newer, long-acting GLP-1 agonists. As compared to exenatide, newer GLP-1 agonists, including liraglutide,* exenatide LAR,* taspoglutide,* and albiglutide,* have better glycemic effects (an additional 0.3-0.4% decrease of HbA1c), and some (e.g., liraglutide, exenatide LAR, albiglutide) have been shown to have fewer GI side effects, perhaps due to lesser effects on gastric emptying (GE).

Wysham also discussed that the longer acting agents appear to have a decreased impact on postprandial glucose excursions in comparison with twice-daily exenatide. While not specifically known, it may be related to a lack of continued effect on GE. This was demonstrated in a study by Knudsen and Danish investigators who assessed the impact of acute and chronic exposure of liraglutide and exenatide twice daily on GE, food intake, and body weight in rats (591-P). GE was quantified using a standard acetalaminophen release assay. Area under the curve (AUC) measurements were assessed after a single IV injection and after 14 days of twice-daily doses of exenatide, liraglutide, or placebo. Both compounds decreased AUC acutely versus placebo (p<0.001), suggesting an immediate impact on GE. After two weeks, AUCs were lower for placebo and liraglutide (9362±429 and 8135±380, p=0.022), yet exenatide continued with a profound decrease in GE (591±137, p<0.001). Each active treatment continued to have comparable effect on body weight at 14 days versus placebo (p<0.0001). From these data, the researchers suggested that slowed GE is not the primary mechanism for weight loss due to GLP-1 agonists, rather regulation of appetite signals in the brain may be responsible. Accordingly, the difference in long-term GE may explain the lesser impact on postprandial glucose excursions with the longer acting agents.

Wysham concluded her presentation noting that it is likely the GLP-1 agonists will be used with one to two concomitant oral agents. Sulfonylureas enhance the likelihood of hypoglycemia when used concomitantly, which may be solely a function of the sulfonylurea. In a related poster, a meta-analysis was presented at this week’s meeting comparing hypoglycemia rates between glimepiride and liraglutide. Gough, along with UK and Danish colleagues, evaluated the rates of hypoglycemia of liraglutide alone and in combination with other oral agents using data from six Phase 3 randomized, controlled trials (n=3,967) (764-P). At 26-weeks, liraglutide 1.8 mg and 1.2 mg was associated with a 91% reduced risk of hypoglycemia compared with glimepiride at HbA1c of 7% (p<0.0001). A reduced risk of ~95% of hypoglycemia was observed for 1.8 mg and 1.2 mg doses when the HbA1c reached 6.5% (Figure 2).

The third presenter, Dr. Kathleen Dungan from Ohio State University, discussed recent concerns of acute pancreatitis and C-cell hyperplasia that have been attributed to incretin mimetic drugs. The FDA issued safety alerts in 2007 for exenatide (and in 2009 for the DPP-4 inhibitor, sitagliptin), metformin, sulfonylurea and/or thiazolidinedione (n=24,255) and a non-diabetic control group (n=1,113,392) were identified. They were followed until the earliest of the following: development of pancreatitis, discontinuation of index medication, or the end of the observation period (6-18 months). According to Cox proportion hazards model of time to first acute pancreatitis adjusted for baseline risk factors, there was no increased risk of pancreatitis with either exenatide (adjusted HR, 0.86; CI: 0.60-1.24, p=0.42) or sitagliptin (adjusted HR, 1.01; CI: 0.77-1.31, p=0.97), compared to the diabetes control group. The researchers concluded that their analysis does not support an increased risk with incretin mimetics. Dungan echoed the conclusions of the poster presentation.

The FDA recommends a conservative approach to this issue: maintain a low threshold of suspicion for acute pancreatitis in patients receiving GLP-1 agonists or DPP-4 inhibitors and avoid rechallenging patients with the medications in whom the condition is confirmed.

With respect to C-cell hyperplasia and the risk for medullary thyroid cancer, Dungan shared that the relationship between rodent and human data is unknown. More research will be needed.

Among the most heavily studied of the antihyperglycemic drug classes, GLP-1 receptor agonists’ role continues to evolve. Potential CV benefits are now proposed but more data are needed. The availability of longer-acting compounds on the market will likely expand their use, but any emerging concerns about potential toxicities will require careful consideration.
Both sulfonylureas (SUs) and dipeptidyl peptidase 4 (DPP-4) inhibitors work within the pancreatic beta cell to stimulate insulin release, albeit through very different mechanisms. Although the SUs may be more potent across the range of HbA1c, both drugs are comparable in Type 2 diabetes patients with milder hyperglycemia. Given the increasing popularity of the latter class, the question posed in a debate on Sunday was “Will the DPP-4 Inhibitors Replace the Sulfonylureas?”

Dr. Michael Nauck of Germany began by extolling the virtues of the DPP-4 inhibitors as the preferred class of oral anti-hyperglycemic agents. DPP-4 inhibitors have the mechanistic advantage of prolonging the half-life of GLP-1, which has insulinotropic activity only upon glucose stimulation. These drugs have, accordingly, low rates of hypoglycemia, and are weight neutral in contrast to the more traditional insulin secretagogues. In addition, there is early data suggesting that DPP-4 inhibitors may protect beta cells from apoptosis, and possibly even protect cardiac myocytes from ischemia during vascular occlusion. He concluded that DPP-4 inhibitors are a safer alternative to SUs. In an era of increasing CV vigilance, the side effect profile of SUs, which includes hypoglycemia, weight gain, and potential effects on ischemic preconditioning, make them a less attractive oral agent class.

Dr. David Matthews from Oxford, England gave an entertaining defense of the tried and true SUs. He was forthright in stating that SUs are not necessarily better medications than DPP-4 inhibitors, but they have over 40 years of use in clinical settings and have demonstrated safety and efficacy in lowering blood glucose. He reviewed more than five large, longitudinal randomized control trials, including the UGDP (University Group Diabetes Program), UKPDPS (UK Prospective Diabetes Study), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation), and ADOPT (A Diabetes Outcome Progression Trial). SUs have demonstrated their abilities in head-to-head trials with other drugs, as well as their role in preventing microvascular disease. Dr. Matthews agreed that hypoglycemia is the main problem with these agents, and it is clear that DPP-4 inhibitors have significantly lower rates. However, he felt that the risk is acceptable, and clinicians may adjust the dosing to prevent the likelihood of this adverse effect. He concluded that SUs are well validated and cost a small fraction of the newer agents. In the global pandemic of Type 2 diabetes, we need a safe and cheap treatment strategy, so SUs will remain one of this disease’s core agents.

Defining “Normal” in GDM

Since the third trimester of pregnancy is associated with increased insulin resistance, placing metabolic stress on pancreatic beta cells, it can serve as a unique window into future diabetes risk. Retnakaran et al. from Toronto reported that women with glucose intolerance in pregnancy experienced beta-cell function decline, even within the first year postpartum (13-OR). They assessed 392 women with a glucose challenge test (GCT) and oral glucose tolerance test (OGTT) during pregnancy, and then a repeat OGTT at 3 and 12 months postpartum. The women were divided based on initial OGTT into four groups: GDM (n=107), gestational impaired glucose tolerance (GIGT, n=75), abnormal GCT with normal glucose tolerance (NGT) (n=137), and normal GCT with NGT (n=73). The prevalence of abnormal glycaemia at 3 months and then again at 12 months postpartum increased progressively across the baseline defined groups from GCT/NGT (2.7% and 2.7%, respectively) to abnormal GCT/NGT (10.2% and 11.7%), GIGT (18.7% and 17.3%), and GDM (34.6% and 32.7%) (p<0.0001 for comparisons across groups at both time intervals). Between 3 and 12 months postpartum, the subgroups showed significant differences in beta-cell function, as calculated by the Insulin Secretion Sensitivity Index-2 (ISSI-2) (Figure 3, p=0.0036), with ISSI-2 declining in both the GDM and GIGT groups. Notably, this occurred without any changes in insulin sensitivity.

These results indicate a continuous relationship between abnormal glucose metabolism in pregnancy and future beta-cell decline. The concerning feature of this study is how quickly beta-cell abnormalities become manifest in otherwise young, healthy women.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study also found a continuous, linear association of abnormal glucose metabolism in pregnancy and adverse neonatal and maternal outcomes. In particular, the association was strongest with fasting plasma glucose (FPG). At this meeting Metzger et al. reported on a subgroup analysis of women with a FPG ≤79 mg/dl, which represented the cohort mean (160-OR). They sought to determine whether this fasting glucose level could serve as a cut-point in excluding gravidas from undergoing an OGTT. They divided the women into non-GDM and GDM based on their 1- and 2-hour OGTT values. They then compared the prevalence of adverse neonatal and maternal outcomes in each group. In the GDM subgroup with FPG ≤79 mg/dl, frequencies of outcomes tended to be similar to those of the HAPO cohort overall and substantially lower than found in the all HAPO GDM group. However, the results did not provide enough evidence for the investigators to recommend not performing an OGTT in pregnant women with such a low FPG. More research is required to better elucidate an appropriate cut-off, which is difficult given the linear and continuous relationship between glucose and adverse outcomes in this population.

Lastly, Reutrakul, et al. from Chicago evaluated the relationship of sleep disturbances to abnormal glucose tolerance in pregnancy (11-OR). They administered three different measures of sleep quality to 157 pregnant women on the same occasion as their screening 50g OGTT. No significant differences were found in reported sleep quality between women with normal glucose metabolism and those with impaired glucose metabolism.

Figure 3. Change in Beta-Cell Function Between Months 3 and 12 Postpartum by Glycemia Status
However, nine women with GDM and one woman with one abnormal value on OGTT were further assessed with an overnight polysomnography. Of these, seven (70%) women met criteria for sleep-disordered breathing. These findings suggest that impaired sleep is under-recognized by patients, and may contribute to the risk of abnormal glucose metabolism in pregnant women, as has been shown in other populations. We would add that the link between obstructive sleep apnea and hyperglycemic states is probably stronger than initially considered and certainly deserving of more study across various patient populations.

Feeling Low

Hypoglycemia continues to be the most frequent adverse event in the management of diabetes. But what are the long-term consequences of hypoglycemia? Two studies examined this in a Type 1 and 2 diabetes population.

Asvoid, et al. from Norway presented a 16-year follow-up study on cognitive function in people with Type 1 diabetes and exposure to severe hypoglycemia before the age of 10 years (29-OR). Twenty-seven children with Type 1 diabetes were matched with a control of the same sex, age, and social background, and followed into adulthood. Nine of the children had been exposed to severe hypoglycemia, and 16 had not. Cognitive assessment was performed and reported as a standard deviation (SD) from the control subjects. Diabetic patients with early severe hypoglycemia were found to have reduced cognitive ability, with an overall score of -1.0 SD (95% CI -0.5 to -1.5), whereas diabetic patients without severe hypoglycemia were similar to controls (-0.1SD, 95% CI -0.4 to 0.2). Specifically, they scored lower in problem solving (-2.2 SD), verbal function (-1.5 SD), and psychomotor efficiency (-1.3 SD). In addition, cognition scores were lowest in those who were exposed to hypoglycemia before 6 years of age (overall -1.3 SD). The researchers concluded that early severe hypoglycemia was associated with reduced cognitive function across several domains in adulthood.

In another study, hypoglycemia was found to be independently associated with an increased risk of acute CV events in people with Type 2 diabetes. Johnston et al. from the US did a retrospective analysis of 860,845 people with Type 2 diabetes within a large healthcare claims database, examining the association between ICD-9-CM coded hypoglycemic events and acute CV events (30-OR). The CV events included acute myocardial infarction, coronary artery bypass grafting, revascularization, percutaneous transluminal coronary angioplasty, and new unstable angina. Using a multiple logistic regression model with adjustment for confounding variables, they found that people with hypoglycemic events had a 79% greater risk of CV sequelae (OR 1.79, 95% CI 1.69-1.89) than people without hypoglycemia. Only two other variables, age (OR 13.25 for age 85+) and prior CV disease (OR 2.87) held a greater risk for acute CV events than hypoglycemia.

Both of these studies underscore the importance of avoiding hypoglycemia as much as possible in our treatment of diabetic patients, particularly those on insulin therapy.

So Many Posters, So Little Time....

Bariatric Surgery

Roux-en-Y gastric bypass surgery (RYGB) has been associated with a hypoglycemic syndrome characterized by postprandial hypoglycemia and hyperinsulinemia. To assess the etiology, Kim et al. from California compared glucose-stimulated insulin secretion rate in 8 RYGB patients who developed post-operative hypoglycemia to that in 34 nondiabetic, nonsurgical individuals (54-OR). The investigators observed that patients with hypoglycemia post-RYGB appeared to have appropriate insulin secretion rates in response to intravenous glucose (similar to the insulin-sensitive control subjects). They concluded that the hyperinsulinemic/hypoglycemic episodes in these patients are likely secondary to the bypass surgery, per se, without any intrinsic change in pancreatic β-cells. These data do not rule out a possible derangement of incretin physiology, as others have proposed.

Hirsch et al. from Brazil conducted a study to characterize the underlying mechanisms related to non-resolution of Type 2 diabetes after RYGB, despite significant postoperative weight loss. This occurs in ~20% of patients undergoing the bariatric procedure (379-OR). At a mean of 41 months following RYGB, 28 diabetics patients underwent mixed meal tolerance testing. The subjects whose diabetes resolved post-operatively appeared identical to those whose diabetes did not with regards to age, disease duration, degree of weight loss, fat distribution, and underlying beta-cell function. The investigators, however, observed a combination of greater insulin resistance, chronic subclinical inflammation, and impaired incretin response to meals in the patients whose diabetes persisted.

Fiber Facts

Johansen and Sørensen from Norway conducted a case-control study of 362 subjects without a diagnosis of diabetes mellitus or impaired glucose tolerance (IGT) to determine the prevalence of idiopathic reactive hypoglycemia (IRH) (abstract 1761-P). IRH was defined by 1h- or 2h- post-load (oral glucose tolerance test, OGTT) glucose <70 mg/dl or 1h or 2h glucose < fasting glucose and no evidence of Type 2 diabetes or IGT. IRH was found in 12.4% of subjects, who had higher fasting but lower 2h-glucose, but were similar to controls based on age and BMI. In a second part of their investigation, 12 subjects with documented IRH participated in a four-week crossover study—two weeks each with and without 20g of long-chain soluble fiber (fructo-oligosaccharide) diet supplementation. Added fiber clearly improved the reactive glucose pattern of a 4-hour OGTT. Fasting plasma glucose and total cholesterol levels were also significantly reduced.

Chromium Ineffective

Chromium is widely marketed to the public with diverse health claims pertaining to muscle mass, weight control, glucose metabolism, insulin action, and diabetes prevention. Ali et al. from Connecticut conducted a double-blind, modified cross-over study in which they randomized 59 subjects with impaired fasting glucose, impaired glucose tolerance, or metabolic syndrome to 6-month sequences of supplemental chromium picolinate or placebo at one of two dose levels (500 or 1000 mcg daily), then vice versa, followed by a six-month post-intervention assessment (abstract 1763-P). No changes were seen in serum insulin levels, HOMA-IR, 2-hour postprandial glucose, or fasting plasma glucose after six months of chromium, at either dose level, compared to placebo. Chromium supplementation had absolutely no effect on insulin resistance or impaired glucose metabolism parameters, and thus is unlikely to attenuate diabetes risk.

* The product is not labeled for the use under discussion or the product is still investigational.

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New Haven, Connecticut
1. Which of the following results were not observed in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial?
   a. Intensive glycemic control in Type 2 diabetes patients with either cardiovascular disease (CVD) or cardiovascular (CV) risk factors had no impact on CV events and increased all-cause mortality.
   b. The addition of fenofibrate to simvastatin, targeting diabetic dyslipidemia, reduced the annual rate of CV events beyond that observed with statin alone.
   c. The rate of overall CV events with intensive blood pressure control (target systolic blood pressure <120 mm Hg) was similar to that with standard blood pressure management (target systolic blood pressure <140 mm Hg).
   d. Intensive blood pressure control had a beneficial effect in decreasing the annual rate of stroke, as compared to standard blood pressure management.

2. Select the false statement from the following about glucose management in the inpatient setting.
   a. Based on recent national guidelines, blood glucose levels should be maintained in the 140 to 180 mg/dl range for patients in an intensive care unit (ICU), and <140 mg/dl pre-meal for non-ICU patients.
   b. Risk for inpatient morbidity and mortality in acute MI/acute coronary syndrome patients is directly related to glycaemia, irrespective of known diabetes status.
   c. Hyperglycemia before and after contrast studies is strongly associated with reduced risk of acute kidney injury in diabetes patients.
   d. In one study, hypoglycemia (≤80 mg/dl) was associated with increased incidence of peri-procedural MI among non-diabetic patients undergoing coronary stenting, suggesting the need for caution when implementing aggressive glucose control measures in acute coronary syndrome patients.

3. In contrast to favorable findings with drugs that target insulin resistance, results of the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes research) trial suggest that targeting insulin secretion as a method to prevent diabetes is not an effective strategy.
   a. true
   b. false

4. Which of the following HbA1c cutpoints is now endorsed by the ADA for the diagnosis of diabetes?
   a. ≥6.0%
   b. ≥6.5%
   c. ≥7.0%
   d. ≥7.5%

5. Select the false statement from the following about diabetes and its CV/renal complications.
   a. Restenosis rates following percutaneous coronary intervention with a drug-eluting stent remain as high as 20-25% in patients with diabetes.
   b. Diabetic patients—either diagnosed or undiagnosed—constitute up to half of all patients undergoing revascularization procedures.
   c. Notwithstanding the ADA target for HbA1c, an individualized approach to setting glycemic targets has been suggested, with higher HbA1c targets for older diabetes patients with known CVD.
   d. CVD is the leading cause of death in patients with diabetes, but not in those with concurrent chronic kidney disease.

6. The DIAD (The Detection of Ischemia in Asymptomatic Diabetics) trial results, comparing the outcomes of screened vs. unscreened individuals, suggest that asymptomatic diabetes patients over age 50 years should be routinely screened with nuclear stress imaging to identify coronary artery disease in its early stages.
   a. true
   b. false

7. Select the false statement from among the following as it relates to diabetes, its treatment, and associated risk of cancer.
   a. The risk for endometrial and liver cancers are increased by more than 2-fold in patients with Type 2 diabetes vs. non-diabetic individuals.
   b. The mortality rate from breast cancer is lower among diabetic vs. non-diabetic women.
   c. Insulin may conceivably stimulate growth in cells that have already undergone neoplastic transformation, but experts believe it does not cause de novo cancers.
   d. The risk of certain cancers appears to be decreased in patients taking metformin.

8. Select the false statement from among the following about bariatric surgery for diabetes patients.
   a. The mortality rate following bariatric surgery is low and similar to that following hip replacement or laparoscopic cholecystectomy.
   b. Roux-en-Y gastric bypass surgery has been associated with a syndrome characterized by postprandial hypoglycemia and hyperinsulinemia.
   c. Studies have demonstrated that diabetes patients who have undergone gastric bypass surgery experience reduction in insulin resistance and normalization of glycemia only after significant weight loss has occurred.
   d. According to the ADA, bariatric surgery may be considered in patients with diabetes who have a BMI ≥35 kg/m².

9. Ultra-fast acting insulins under investigation may control postprandial glucose better than currently available mealtime insulins.
   a. true
   b. false

10. Lowering lipids and blood pressure reduces CV events to a greater extent than does glycemic control in patients with Type 2 diabetes, underscoring the need for a multi-interventional treatment approach.
    a. true
    b. false

   Early combination therapy for Type 2 diabetes should be based on agents with complementary mechanisms of action. Match the antihyperglycemic agent with its action.
   a. Sulfonylureas
   b. α-Glucosidase inhibitors (acarbose, miglitol)
   c. Biguanides (metformin)
   d. Dopamine 2 agonists (bromocriptine)
   e. GLP-1 agonists (exenatide, liraglutide)

11. Decrease hepatic glucose production.
15. Increase pancreatic insulin secretion.

16. The PIPOD and Act Now trials demonstrated that pioglitazone decreases new-onset diabetes among individuals at high risk. This drug exerts its antihyperglycemic effect through which mechanism?
    a. insulin sensitization
    b. augmentation of insulin secretion
    c. delay in gastric emptying
    d. suppression of glucagon secretion

17. Exposure to severe hypoglycemia before the age of 10 in people with Type 1 diabetes was shown to be associated with reduced cognitive function (e.g., problem solving, verbal function) in adulthood.
    a. true
    b. false

18. There is a bi-directional association between diabetes and depression that, based on preliminary evidence, may be related to inflammatory factors (IL-6, CRP).
    a. true
    b. false

19. Results of the DURATION and LEAD trials confirm evidence from animal studies showing that GLP-1 agonists may have deleterious effects on the CV system.
    a. true
    b. false

20. After controlling for baseline risk factors, one group of investigators found no increased risk of acute pancreatitis in diabetes patients receiving GLP-1 agonists or DPP-4 inhibitors. However, the FDA recommends that the threshold of suspicion remain low and rechallenge be avoided in incretin mimetic-treated patients in whom acute pancreatitis is confirmed.
    a. true
    b. false
1. **How would you rate Diabetes 2010 for content?**
   a. very relevant to my practice
   b. interesting but not relevant
   c. uninteresting

2. **How would you rate Diabetes 2010 for coverage?**
   a. broad coverage of the most important diabetes-related topics
   b. too focused on “headlines”
   c. too much scientific data

3. **What percentage of the material is new to you?**
   a. 90%
   b. 70%
   c. 50%
   d. 30%
   e. 10%

4. **How would you rate Diabetes 2010 in meeting the educational objectives of the CME program?**
   a. the objectives of CME program were met
   b. some of the program objectives were met
   c. the program content did not satisfy the objectives

5. **Please indicate if specific educational objectives were met (yes/no):**
   a. Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
   b. Describe the evolving cellular mechanisms associated with β-cell failure, the progression of diabetes, and its complications.
   c. Implement strategies for the early diagnosis and treatment of diabetes.
   d. Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
   e. Recognize the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
   f. Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
   g. Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
   h. Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
   i. Identify unique management issues among special sub-populations of patients with diabetes.
   j. Discuss the impact of diabetes on the healthcare system.

6. **Will you make changes that will benefit patient care as a result of information received?**
   If yes, please describe: ____________________________________________________________
                                                                                       ____________________________________________________________

7. **Do you anticipate any barriers to making these changes?**
   If yes, please describe: ____________________________________________________________
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8. **Additional comments:** ____________________________________________________________
                                                                                       ____________________________________________________________

*Thank you for your participation.*
**Diabetes 2010 Answer Form**

**Volume 21**

To receive 5.5 AMA PRA Category 1 Credits™, you must successfully complete the test and evaluation answer form. Please print clearly, and mail this form to the address below. Term of approval: July 2010 to December 31, 2010.

Name ________________________________________________________ Degree ____________________________________
Address ___________________________________________________________________________________________
City __________________________ State ______________________ Zip Code ________________________________
Telephone Number ______________________________ E-mail address _____________________________________

*This post-test can also be taken on-line at www.cme.yale.edu*

All answers should be recorded on the answer form below. For each question, decide which choice is the best answer, and place an X in pencil or ink through the letter representing your choice. If you change an answer, be sure to erase it completely. 80% constitutes a passing grade.

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Please indicate the number of hours actually spent in this educational activity, up to a maximum of 5.5 hours: ___________

### Diabetes 2010 Evaluation - Volume 21

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6. Will you make changes that will benefit patient care as a result of information received? If yes, please describe: ______________

7. Do you anticipate any barriers to making these changes? If yes, please describe: ________________________________________________

8. Additional comments: ________________________________________________________________________________________________

- If you currently receive the *Diabetes 2010* newsletters by fax and would like to receive them by e-mail instead, please mark this box with an “X”.

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