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and

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Dear Colleague:

Time restraints prevented many of you from attending the 60th Annual Scientific Sessions of the American College of Cardiology (ACC) which was held during April in New Orleans, LA and the 71st Annual Scientific Sessions of the American Diabetes Association (ADA) which was held a few weeks ago in San Diego, CA. Therefore, we developed Diabetes 2011 so that important information presented at the Conferences could be shared with you on a timely basis.

Diabetes 2011, 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, Boehringer Ingelheim Pharmaceuticals, Inc., through a collaboration with Eli Lilly and Co., Merck & Co., Inc., and Novo-Nordisk Inc. This booklet contains five Diabetes 2011 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 11 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

Robert S. Sherwin, M.D.  
C.N.H. Long Professor of Medicine  
Yale University  
Director, Yale Diabetes & Endocrinology Research Center

Silvio E. Inzucchi, M.D.  
Professor of Medicine  
Yale University  
Director, Yale Diabetes Center
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 2011* 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 2011* 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™.
# Table of Contents

Editors’ Summary .................................................................................................................. 2

## 60th Annual Scientific Sessions of the American College of Cardiology

### Issue One

- Sweet-Heart ....................................................................................................................... 3
- Targeting Blood Pressure ................................................................................................... 5
- The Poor Pump .................................................................................................................. 7
- So Many Posters, So Little Time... ....................................................................................... 8

## 71st Annual Scientific Sessions of the American Diabetes Association

### Issue Two

- Neither Type 1 Nor Type 2... .............................................................................................. 11
- Feeling Low ......................................................................................................................... 13
- So Many Posters, So Little Time... ....................................................................................... 15

### Issue Three

- Metabolic Surgery: Caution & Concerns .............................................................................. 16
- Don’t Needle Me ................................................................................................................ 18
- Frontiers of Monitoring Technology .................................................................................... 21
- So Many Posters, So Little Time... ....................................................................................... 22

### Issue Four

- Diabetes in the Elderly ........................................................................................................ 23
- Controlling Glucose in the Hospital ..................................................................................... 25
- What Role for Insulin Sensitizers? ..................................................................................... 26

### Issue Five

- Cancer and Diabetes Medications: Is There a Link? ............................................................ 29
- Where Does Incretin-Based Therapy Fit In? ....................................................................... 30
- Closing the Loop ................................................................................................................ 31
- Novel Therapies .................................................................................................................. 32

- Diabetes 2011 Test .......................................................................................................... 35
- Diabetes 2011 Evaluation ................................................................................................... 36
- Diabetes 2011 Answer Form ............................................................................................. 37
In this issue of the Diabetes 2011 monograph, we summarize important new diabetes information that was presented at the 60th Scientific Sessions of the American Cardiology Association (ACC) and the 71st Annual Scientific Sessions of the American Diabetes Association (ADA).

The important link between diabetes and cardiovascular disease (CVD) was prominent among presentations made at the 60th Scientific Sessions of ACC meeting in New Orleans. Patients with diabetes are clearly at higher risk for CVD. Avoidance of cardiovascular events depends upon comprehensive management of all of the risk factors associated with diabetes, including co-existing coronary disease, dyslipidemia, and elevated blood pressure. Although HbA1c is associated with increased risk for CVD, the simple adage of “lower is better” is now in question. It is apparent that how glucose is lowered may matter and that overly aggressive attempts may be harmful rather than beneficial, at least in certain individuals. It is also becoming clear that the effect of glucose lowering on outcomes may significantly vary in different populations (with duration of diabetes, age, comorbidities such as advanced heart failure, and established diabetic complications).

At an opening day symposium of the ADA 71st Annual Scientific Sessions, investigators from around the world convened to answer the question, “Other Types of Diabetes—Have We Made Any Progress in Management?” While most patients with diabetes can be categorized as having either Type 1 or Type 2, a separate category exists, referred to as “secondary diabetes”, including a collection of conditions to which the hyperglycemia can be directly ascribed. These include other endocrinopathies (e.g., Cushing syndrome), medications (steroids), infections (mainly certain viruses), organ dysfunction (pancreatitis), and genetic abnormalities (Klinefelter syndrome). Speakers focused their comments on: 1) cystic fibrosis-related diabetes, which is becoming more frequently identified in these individuals (35% affected) as they are living longer; 2) monogenic diabetes (e.g., neonatal diabetes mellitus, maturity-onset diabetes of youth [MODY]); 3) latent autoimmune diabetes of adults (LADA), which may comprise up to 10-15% of adults diagnosed with Type 2 diabetes; and, 4) post-transplant diabetes, which occurs primarily as a consequence of immunosuppressive drugs required after transplantation.

‘Metabolic surgery’, the new term for bariatric surgery, took center stage at the ADA Scientific Sessions this year. The rapid rise in rates of obesity and its associated comorbidities have prompted a fast forward solution to a chronic medical problem. Type 2 diabetes is known to reverse in at least 2 out of 3 patients following bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB), even before significant weight loss. The responsible mechanisms are unclear, but are thought to involve alterations in gut hormones. Specifically, the dramatic increase in glucagon-like peptide-1 (GLP-1) levels (abstract 58-OR), abrupt reduction in nutrient intake, and relief of steatosis following surgery all likely play a major role. However, metabolic surgery carries a risk of both immediate surgical complications as well as late adverse outcomes, such as hypoglycemia (abstract 60-OR) and vitamin deficiencies. Additionally, we note while that weight in weight and glucose are undeniable, there is little evidence of any favorable influence of these procedures on cardiovascular outcomes – let alone mortality (Maciejewski (GLP-1) levels (abstract58-OR), abrupt reduction in nutrient intake, and relief of steatosis following surgery all likely play a major role. However, metabolic surgery carries a risk of both immediate surgical complications as well as late adverse outcomes, such as hypoglycemia (abstract 60-OR) and vitamin deficiencies. Additionally, we note while that weight in weight and glucose are undeniable, there is little evidence of any favorable influence of these procedures on cardiovascular outcomes – let alone mortality (Maciejewski et al., JAMA 2011). The long-term implications of these increasingly popular procedures need to be elucidated, particularly before they are extended, as some have proposed, to diabetic patients with lower BMIs than the currently considered threshold (>35 kg/m²).

At this year’s ADA meeting, several groups reported major progress in the development of functional ‘closed-loop’ systems (i.e., where the glucose concentration as measured by a subcutaneous sensor triggers insulin delivery by an exogenous insulin pump without additional input by the patient). Presenters included Bergental and North American co-investigators (abstract 407-P), Youssef from Oregon (abstract 149-OR), Danne from Germany (abstract 150-OR), Elleri from the UK (abstract 153-OR), Sherr from Connecticut (abstract 154-OR), and Renard and collaborators from France, Italy and the US (abstracts 151-OR & 155-OR). Each of these groups reported impressive improvements in maintaining targeted glucose control with sensor-augmented insulin pumps, as compared to traditional ‘open-loop’ systems (where the sensor output is simply interpreted by the patient user who then decides what changes should be made by the pump). Most of the studies reported were in the controlled environment of clinical research centers, however. We look forward to ongoing improvements and the creation of a fully functional and reliable artificial pancreas for our patients with Type 1 diabetes.

A central mechanism for appetite control, as suggested by the findings Lee et al. from the UK (ADA abstract 1700) and others, is an appealing target for weight reduction therapies. The investigators observed that changes in regional cerebral blood flow (rCBF) occurred in brain regions involved in appetite control, nutrient sensing, and taste following food ingestion. They found differential changes in rCBF in older vs. younger subjects and suggested that these areas were therefore not activated normally in older patients. In turn, this may contribute to weight gain and increased risk of Type 2 diabetes with advancing age. We anticipate this to be an area of ongoing future study.

Research continues to expand our understanding of currently available agents and uncover new agents of potential value in diabetes care. The role of the DPP-4 inhibitors, sitagliptin (as an add-on to suboptimal dual therapy) and linagliptin, in the management of patients with Type 2 diabetes was discussed (ADA abstracts 1120-P, 413-PP), as were the addition of the GLP-1 receptor agonist liraglutide* to continuous subcutaneous insulin infusion (CSI) in patients with Type 1 disease (ADA abstract 411-PP) and long-term results with a longer-acting once weekly formulation of another GLP-1 based therapy, exenatide* (ADA abstracts 277-OR, 969-P). The future of insulin treatment may include one or more of several agents currently in development. These include ultra-rapid formulations that mimic meal-time insulin secretion of a healthy pancreas following either subcutaneous injection (e.g., Linjeta**, recombinant human insulin combined with an EDTA-containing diluent [ADA abstracts 1024-P, 1025-P]) or an alternative route of administration (e.g., inhaled insulin [Technosphere***, ADA abstracts 917-P, 941-P]). Also under study are longer-acting insulins that may result in less glucose variability (e.g., insulin degludec* [ADA abstracts 70-OR, 74-OR, 1064-P]). Degludec is distinct from the currently available basal insulins, glargine and detemir, insofar as it may be combined in the same solution (and, accordingly, in the same injection) with rapid acting insulin analogues. Other anti-hyperglycemic medications in various stages of development include: the renal sodium-glucose co-transporter-Type 2 (SGLT-2) inhibitors (e.g., dapagliflozin*, ADA abstract 307-OR); salicylate (e.g., salsalate*, ADA abstract 50-OR); glucokinase activators (LY2599506*, ADA abstract 933-PP); and, GPR (G-protein coupled receptor) agonists (GPR40* [TAK-875, ADA abstract 414-P] and GPR119* [PSN821, ADA abstract 306-OR]). Which of these agents, if any, might eventually become commercially available to our patients remains to be seen.

Current intensive management of diabetes hinges on repeated blood glucose testing, which causes discomfort, leading to compliance issues, and is expensive. It therefore comes as no surprise that novel, less invasive monitoring methods are under intensive investigation, some presented at this year’s ADA Scientific Sessions: ocular mini insert (OMI) (Eyesense*) (abstract 237-OR), breath analysis of exhaled volatile organic compounds* (VOCs) (abstract 875-P), and transdermal glucose sensor* (abstract 899-P). Clearly, more study is needed on these and other methods of glucose testing. If newer methods show good accuracy and precision in the future, this could represent a major advance in diabetes care.

More details on these and other topics are found in this volume of Diabetes 2011.

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

Editors’ Summary
Cardiovascular disease (CVD) is the number one cause of morbidity and mortality in diabetes mellitus. Therefore, development of effective strategies to reduce its risk among patients with diabetes is of critical importance. At the American College of Cardiology (ACC) meeting in New Orleans this week, Dr. Donna Polk from Hartford discussed the important link between diabetes and CVD.

She opened her talk with a series of map graphics showing how the obesity epidemic in the US has been paralleled by a rapid increase in the prevalence of diabetes, estimated to affect 8.2% of the population in 2008. The common risk factor for both diabetes and CVD is, of course, abdominal obesity.

Diabetes has long been recognized to be a coronary artery disease (CAD) equivalent (although this has recently been disputed—see below). In an often-quoted, older study by Haasner et al. (NEJM 1998), the 7-year incidence of fatal and non-fatal myocardial infarction (MI) was similar among patients without diabetes but with prior MI (18.8%) and those with diabetes and no prior MI (20.2%). Not unexpectedly, the incidence of subsequent MI was highest in those with a history of both prior MI and diabetes (45.0%)—a group at extremely high risk for subsequent CVD events. Even though the relationship between diabetes and CVD is strong and well-recognized, individuals with diabetes are less likely to report concern about their risk for cardiovascular complications than for microvascular complications, such as limb amputations or blindness, which tend to occur comparatively much less frequently. In fact, over half of patients with diabetes do not realize that their disease is a risk factor for CAD.

There is a continuum of risk for cardiovascular events in patients with disorders of glucose metabolism. Insulin resistance, which is followed by impaired glucose tolerance, appears long before overt hyperglycemia supervenes. Coronary heart disease, CVD, and all-cause mortalities increase across the spectrum of patients, progressing from those with normal glucose metabolism, to those with metabolic syndrome, individuals with overt diabetes, patients with prior CVD, and, finally, those with both co-existing CVD and diabetes.

How do we prevent diabetes and avoid its complications? Dr. Polk reviewed the data from the Diabetes Prevention Program study in which patients with impaired glucose tolerance, and therefore at high risk for diabetes, were randomized to placebo, metformin therapy, or intensive lifestyle intervention (NEJM 2002). The trial demonstrated a 31% decrease in diabetes incidence with metformin and a 58% decrease with lifestyle intervention (which included 150 minutes/week of exercise and 7% body weight reduction), compared to the control group. This landmark trial showed that it is clearly possible to prevent diabetes in high-risk individuals. One can make extrapolations regarding downstream CVD risk, but the study was not designed to assess these—larger and longer-term trials would be needed to answer this important question.

Once diabetes ensues, the focus is on reduction of risk for subsequent complications. What is the impact of glycemic control on these outcomes? In epidemiological studies, there is a strong association between glucose measures (fasting plasma glucose, post-prandial glucose, HbA1c) with subsequent mortality and coronary heart disease risk. Data from the UKPDS trial (Lancet 1998) showed that intensive glucose lowering (HbA1c 7 vs. 7.9%) reduced microvascular events by 33% (p<0.01), MI by 16% (p=0.052), and any diabetes complications by 12% (p=0.03). Data from the small UKPDS subgroup of obese patients treated with metformin showed a significant decrease in MI and coronary death.* Long-term follow-up from the UKPDS study showed a 15% reduction in MI (now with a p-value of 0.01), suggesting that the benefits of intensive glucose lowering may not be apparent for many years.

More recent trials (ACCORD, ADVANCE, VADT), however, demonstrate that aggressive glucose lowering with HbA1c targets below 7%
are not associated with macrovascular benefits. Recent guidelines from the ACC/ADA/AHA 2009 still suggest a target HbA1c <7% in most uncomplicated patients and in those with macrovascular disease, and state that lower goals may be appropriate to reduce microvascular disease risk. However, the focus has shifted to individual goal setting, with less stringent targets in those with multiple comorbidities and advanced diabetes.

Although Haffner's study showed that diabetes (at least in the 1990s) was a CAD equivalent, this assertion has been recently questioned by several studies. With comprehensive management of diabetes in clinical trials, cardiovascular event rates have been surprisingly low—have we improved the risk profile of these patients to the extent that this older assertion no longer applies? Saely and colleagues from Liechtenstein hypothesized that diabetes may simply be a marker for subclinical coronary lesions (abstract 1006-362). They prospectively followed 750 patients who presented for evaluation of stable coronary disease (baseline age 63 years, male 68%, BMI 27.2 kg/m², Type 2 diabetes 22%, HbA1c 5.8% in those without and 7.5% in those with diabetes). All patients underwent coronary angiography and 61% were found to have significant (>50%) stenoses. As in prior studies, the presence of any coronary lesion and significant stenoses, as well as the extent of coronary disease, were increased in patients with diabetes. Over 8 years of follow-up, 257 vascular events occurred, defined as cardiovascular mortality, MI, stroke, coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), and non-cardiac revascularization. The incidence of vascular events was higher in patients with diabetes (p <0.001) and in those with significant coronary artery stenoses at baseline. Patients were then stratified into four groups based upon diabetes status and the presence of significant coronary lesions at baseline. The investigators found that the incidence of vascular events was similar in patients who had neither diabetes nor CAD at baseline and those who had diabetes but no CAD (Figure 1). In contrast, patients with coronary artery lesions but no diabetes and those with both diabetes and CAD had a significantly higher incidence of vascular events. The investigators stated that it is the baseline CAD status that determines cardiovascular risk in patients with Type 2 diabetes. Therefore, they concluded that diabetes per se can no longer be considered a coronary artery equivalent.

Patients with Type 2 diabetes may have atypical symptoms of CAD or may present with no symptoms at all. Similarly, women are known to present with acute MI more frequently having atypical symptoms. Yet, the presentation of patients with Type 2 diabetes and stable coronary disease has not been systematically studied. Using the large BARI-2D study, Krishnaswami and colleagues from San Jose and Pittsburgh analyzed symptoms in a large population of patients with diabetes (abstract 1074-361). BARI 2D randomized patients with Type 2 diabetes and stable CAD (defined as either a ≥50 percent stenosis of a major epicardial coronary artery associated with a positive stress test, or ≥70 percent stenosis and classic angina) in a factorial design to prompt revascularization vs. medical therapy, as well as to insulin sensitizing agents (metformin, rosiglitazone) vs. an insulin providing strategy (sulfonylureas, insulin). The trials' overall findings showed no differences in outcomes between the groups. Among the 2319 patients evaluated in BARI 2D, 19% had typical angina, 21% had atypical symptoms, 42% had both typical and atypical symptoms, and 18% had no angina symptoms at all. In multivariable analyses, prior PCI and beta-blocker use were both associated with typical angina symptoms whereas age >60 years, male gender, regular exercise, and thiazolidinedione (TZD) use were associated with atypical symptoms or lack of symptoms. Regardless of revascularization status, men presented without symptoms more often than women. Overall, an overwhelming majority (82%) of patients with Type 2 diabetes undergoing angiography for stable CAD presented with symptoms. More than 60% of these patients with diabetes had typical angina, either with or without other atypical symptoms. Certainly, this study was limited by the original inclusion criteria for the BARI 2D trial (one of which involved having angina!) and further investigations into the association of symptoms with eventual patient outcomes will be needed.

The association between elevated HbA1c levels and the presence of CAD in patients with diabetes has been previously reported. However, there are no data on the association between HbA1c levels and angiographic severity of CAD in non-diabetic patients. Bourji and collaborators from New York studied 100 patients undergoing elective angiography with no prior history of CAD or diabetes and HbA1c <6.5% (abstract 1006-361). Twenty-five patients had CAD on coronary angiography: 12 had single vessel and 13 multi-vessel disease. Interestingly, HbA1c level did not correlate with the presence of CAD (HbA1c 5.9% vs. 5.8% in those with and without CAD, p =0.11). Among the patients with CAD on angiography, HbA1c levels were slightly higher in those with multi-vessel disease (HbA1c 6.0%) vs. in those with single-vessel disease (HbA1c 5.8%, p =0.005). There was no correlation between HbA1c and whether or not patients underwent revascularization. In this study, there was no significant association between HbA1c levels in patients without diabetes and the presence of CAD on coronary angiography, but the study was limited by its small size. Of note, several epidemiological studies (Norfolk Study, Ann Intern Med 2004; Atherosclerosis Risk in Communities Study, NEJM 2010) have shown that the risks for CVD events and/or mortality do not reach a nadir until the HbA1c is well within the normal range (<5%).

The role of aggressive HbA1c-lowering to improve long-term outcomes of patients with diabetes has been controversial. As mentioned above, recent trials showed no benefit of intensive glucose lowering on macrovascular events. To establish the value of pre-procedural HbA1c levels for cardiovascular complications, Goo et al. from South Korea followed a large population of patients with diabetes undergoing PCI with stent placement (abstract 2515-562). Patients from a registry of the Korean Working Group on Myocardial Infarction (n=952) underwent PCI in 2008-2009 and were stratified according to pre-procedural HbA1c: <7% (n=429) and >7% (n=523). The primary outcome was major cardiovascular events at one year defined as cardiac and non-cardiac mortality, MI, and target vessel revascularization. At baseline, patients in the higher HbA1c (≥7%) group were more likely to have Type 1 diabetes (45.5% vs. 26.3%, p<0.001), larger BMI, and higher baseline blood glucose levels (201 vs. 138 mg/dl, p<0.001). There were no differences with respect to NSTEMI vs. STEMI status, treatment at discharge with anti-platelet agents, beta-blockers, angiotensin converting enzyme (ACE)-inhibitors, or statins, and no angiographic or procedural differences between the two groups. At 1-year, HbA1c was not
an independent predictor of major cardiovascular events (HR 0.85, 95% CI 0.54-1.28, p = 0.35) in multivariable analysis. In contrast, age, STEMI, cardiogenic shock, history of heart failure, and chronic kidney disease were all predictors in these analyses. When death, MI, and target vessel revascularization were analyzed separately, there was still no association between pre-procedural HbA1c and these outcomes. The investigators concluded that Hba1c does not predict cardiovascular morbidity in patients with diabetes and CAD undergoing PCI. We would point out that these were observational data and it is possible that post-procedural medical therapy may have impacted these associations. However, they provide further evidence that HbA1c levels in very advanced CAD may not have the same prognostic value as they do in those with less established disease.

Once CAD is present in patients with diabetes, management is aimed at secondary prevention. Subgroup analyses from prior trials suggest that patients with diabetes and multivessel disease have a better event-free survival after CABG compared to PCI. The original BARI trial randomized 1,829 patients with two- or three-vessel disease to CABG or PCI. Among a subgroup of patients with diabetes, CABG was associated with significantly lower mortality compared to PCI at 5.4 years (19% vs. 34%) and this benefit was seen at 7 and 10 years of follow-up. Patients with diabetes requiring insulin therapy appeared more likely to benefit from CABG. The aforementioned BARI 2D trial randomized 2,368 patients with Type 2 diabetes and stable CAD to either revascularization (CABG or PCI, based upon cardiologist's recommendations) and intensive medical therapy or to intensive medical therapy alone. After 5 years, mortality and major cardiovascular events did not differ between the two groups. However, in a subgroup analysis, patients in the CABG stratum had a lower rate of major cardiovascular events in the revascularization group (22.4%) than in the medical-therapy group (30.5%).

Therefore, our evidence base is currently confined to sub-group analyses of several randomized controlled trials that overall suggest that patients with diabetes and multi-vessel CAD have better outcomes with CABG than with PCI. Stu and Australian investigators (abstract 2512-353) compared long-term mortality using the National Death Index data in an observational study of 3,455 patients with diabetes who underwent PCI (n = 1,112) or CABG (n = 2,343) between 2004-2008. Both PCI and CABG groups had similar age, ejection fraction, and BMI. Patients undergoing CABG were more likely to be male, dyslipidemic, hypertensive, have cerebrovascular and peripheral arterial disease, prior MI, heart failure, greater need for an intra-aortic balloon pump (IABP), and multi-vessel CAD (all p < 0.0001). Over 2.2 years of follow-up, mortality was similar between the CABG and PCI cohorts (6.0% vs. 5.4%, p = 0.47). Significant predictors of mortality in multivariable analysis included age (HR 1.05 per year; 95% CI 1.03-1.06, p < 0.0001), creatinine (HR 4.3 per each unit increase in creatinine; 95% CI 2.9-6.4, p < 0.0001), IABP use (HR 3.0; 95% CI 1.7-5.3, p < 0.0001), and prior MI (HR 1.5; 95% CI 1.1-2.1, p = 0.01), but not the mode of revascularization (HR 0.99; 95% CI 0.7-1.5, p = 0.94). Based upon this registry data, it appears that physicians in Australia are selecting patients for PCI and CABG with resulting similar mortality outcomes. However, given non-randomized design, this data cannot be used as evidence for equivalent benefits of CABG and PCI in patients with diabetes.

Patients with diabetes are clearly at high risk for CVD. Effective risk reduction depends upon comprehensive management of all of the risk factors associated with diabetes, including co-existing coronary disease, dyslipidemia, and elevated blood pressure. Although HbA1c is associated with increased risk for CVD, the simple adage of “lower is better” is now in question. It is apparent that how glucose is lowered may matter and that overly aggressive attempts may be harmful rather than beneficial. It is also becoming clear that the effect of glucose lowering on outcomes may significantly vary in different populations (with duration of diabetes, age, comorbidities such as advanced heart failure, and established diabetic complications). More data are needed to guide us to effectively lower the risk of CVD in our patients with diabetes.

**Targeting Blood Pressure**

An opening-day session on hypertension management, Drs. Stanley Franklin, University of California Irvine and William Cushman, University of Tennessee College of Medicine and VA Medical Center, Memphis, discussed whether the target blood pressure in diabetes patients should be below 130/80 mmHg, or not. This is the current blood pressure goal for diabetes patients set by both the American Diabetes Association (ADA) and Joint National Committee (JNC)-7 on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Franklin began his presentation by reminding us that cardiovascular event rates and mortality are strongly and directly related to blood pressure, regardless of age, down to at least 115/80 mmHg, below which there is little evidence of additional advantage.

The results of several hypertension studies of diabetes patients were discussed. While the benefit of blood pressure reduction to <140/80 mmHg has been shown in hypertensive patients with Type 2 diabetes (Table 1), there is no conclusive evidence, based on CVD risk reduction, for lowering of systolic blood pressure to <130 mmHg. The most recently conducted studies are summarized below.

**ADVANCE**

In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, 11,140 patients with Type 2 diabetes (mean age 66 ± 6 years, diabetes duration 8 ± 6 years, 32% prior history of vascular disease, BMI 28 ± 5 kg/m²) were randomized to one of two anti-hyperglycemic treatment arms and one of two blood pressure treatment arms in a 2 × 2 factorial design (25% received more intensive blood pressure lowering only, 25% more intensive blood glucose lowering only, 25% both strategies, and 25% neither). Patients were followed for 5 years. The primary endpoint was a composite of major cardiovascular events (death from a cardiovascular cause, non-fatal MI, nonfatal stroke) and major microvascular events (new or worsening retinopathy or nephropathy); these endpoints were assessed both jointly and individually.

In the blood pressure arm of the trial, patients were randomized to the combination of the ACE inhibitor, perindopril, plus the thiazide diuretic, indapamide (Patel et al., Lancet 2007; 370:829-40). The more aggressive program resulted in statistically significant relative benefits for the majority of the primary and secondary endpoints assessed: 9% less combined major cardiovascular and microvascular events, 14% less mortality, 18% less cardiovascular death, 21% less total renal...
events, and 14% less total coronary events.* Irrespective of baseline blood pressure, all patient groups experienced benefit, even those with systolic blood pressure below 130 mmHg.

**ACCORD**

In the blood pressure arm of ACCORD (Action to Control Cardiovascular Risk in Diabetes), 4,733 Type 2 diabetes patients at high risk for CVD (baseline mean age 62 years, blood pressure 139/76 mmHg, Cr 0.9 mg/dl, HbA1c 8.3%, BMI 32 kg/m², 34% with prior CVD, diabetes duration 10 years) were randomized to receive intensive blood pressure control or standard management (Cushman et al., NEJM 2010;362:1575-85). Intensive blood pressure control targeted a systolic blood pressure (SBP) <120 mmHg and achieved a mean level of 119.3 mmHg at one year. In the standard therapy group, the target SBP was <140 mmHg and the mean level was 133.5 mmHg at one year.

Over a ~5 follow-up period, there was a small absolute difference between groups for stroke, a pre-specified secondary outcome, which occurred at an annual 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). Otherwise, however, there appeared to be no benefit from more intensive blood pressure control based on the primary outcome (i.e., nonfatal MI, nonfatal stroke, or death from cardiovascular causes) or the other secondary outcomes. Adverse events (such as hypotension) were more frequent in the intensive blood pressure group. The findings in the ACCORD trial, therefore, do not support blood pressure lowering to a target of 120/80 mmHg in patients with diabetes. Prior studies of blood pressure control in diabetic patients showed reduction in cardiovascular events with tight control, but the intensively-treated patients in these trials had much higher mean SBPs (144 mmHg) than those in ACCORD (subgroup analysis of Hypertension Optimal Treatment [HOT] trial and UKPDS). Whether or not additional lowering of blood pressure from 140/90 to the current target of 130/80 mmHg is warranted is currently not entirely clear.

It was noted that the ACCORD study was limited by possible ‘type 2’ error for cardiac events, which occurred at a lower rate than was anticipated (and upon which the study sample size and power were based). White-coat hypertension may have contributed to a healthy-cohort effect (low risk based on home measurement of blood pressure), further enhanced by high use of statins and aspirin. As a consequence, a longer evaluation period may have been required to show benefit.

**INVEST**

In a post-hoc analysis of INVEST (International VErapamil SR—Trandolapril Study), a large trial of hypertensive patients with CAD, outcomes in the diabetic cohort (n=6,400) were segmented by the degree of SBP control: tight (<130 mmHg), usual (131-139 mmHg), and uncontrolled (≥140 mmHg) (Cooper-DeHoff et al., JAMA 2010; 304:61-8). During 16,893 patient-years of follow-up, there was no difference between the tight and usual blood pressure control groups based on the primary endpoint (first occurrence of all-cause death, nonfatal MI, or nonfatal stroke), which occurred in 12.7% of patients in the tight-control group and 12.6% of patients in the usual-control group (adjusted HR, 1.11; 95% CI, 0.93-1.32; p=0.24). Of note, risk of all-cause mortality was actually increased among the patients with the lowest SBP values in the tight-control group (HR=2.18, p=0.02 for SBP <110 mmHg; HR=1.63, p=0.06 for SBP 110-115 mmHg), although there was no increased risk if the SBP was maintained at 115 mmHg or above.

**Treatment Guidance**

Lifestyle modification is the first step for blood-pressure reduction (Table 2) for diabetes patients with a blood pressure of 130-139/80-89 mmHg.

For patients who do not achieve target blood pressure after 3 months of lifestyle modification and for those with more severe hypertension (≥140/≥90 mmHg), the ADA recommends pharmacotherapy with an ACE-inhibitor or an angiotensin receptor blocker (ARB), with the addition of a diuretic if needed (Figure 2). (Of note, inhibitors of the renin-angiotensin system [RAS] have collateral favorable effects on the progression of diabetic nephropathy and albuminuria.) As

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### Table 1. Impact of Systolic Blood Pressure Reduction on CVD Risk in Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Achieved Mean Blood Pressure</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Therapy</td>
<td>Intense Therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS 36</td>
<td>154/87</td>
<td>144/82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCD</td>
<td>138/86</td>
<td>132/78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOT</td>
<td>144/85</td>
<td>140/81</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>140/73*</td>
<td>136/73*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>134/71</td>
<td>119/64</td>
</tr>
<tr>
<td>INVEST†</td>
<td>149/85</td>
<td>144/85</td>
</tr>
</tbody>
</table>

* at 60 months.
† subgroup analysis.
MACE = major adverse cardiovascular events

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### Table 2. Lifestyle Modifications for Blood Pressure Control

<table>
<thead>
<tr>
<th>Modification</th>
<th>SBP Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction among individuals who are overweight or obese (target BMI of &lt;18.5 to 24.9 kg/m²)</td>
<td>5-20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which targets diet rich in vegetables, fruit, and low-fat dairy products</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Reduce sodium intake (&lt;1500 mg per day)</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity (30 minutes aerobic exercise most days of the week)</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol consumption (1 drink/day for women and 2 drinks/day for men)</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>
Patients with diabetes are at higher risk for developing heart failure than those without diabetes. This relationship with heart failure is only partly explained by the co-occurrence of other risk factors, such as CAD and hypertension. There appears to be something else about diabetes per se that raises the risk for heart failure, and better glucose control seems to attenuate this risk. However, once heart failure develops in a diabetic patient, there is no evidence that tight glucose control will change the course of heart failure. Additionally, there are important therapeutic considerations in heart failure patients with respect to the use of glucose-lowering agents. For example, metformin has been previously contraindicated in heart failure due to the possible risk for lactic acidosis. This contraindication was lifted several years ago, but caution is obviously still required, and metformin should not be used in those with severe and progressive ventricular dysfunction or acute severe decompenstions, which can be associated with hypoxemia, hypoperfusion, and lactic acidosis. On the other hand, thiazolidinedione use has been associated with increased fluid retention and increased risk for heart failure. These agents should therefore be avoided in patients with symptomatic heart failure and physicians should consider this risk when starting a diabetic patient on these agents. Given these concerns, it is critically important to know what benefits may be derived from glucose lowering in these patients — however, these data are presently lacking.

The prognosis of heart failure in patients with co-existing diabetes appears to be worse than among patients without diabetes. However, the exact relationship between diabetes, CAD, left ventricular ejection fraction (LVEF), and outcomes is uncertain. Saely et al. from Liechtenstein examined 629 patients with invasive ventriculography to determine their LVEF (age 63 years, male 68%, Type 2 diabetes 22%), and all patients underwent coronary angiography (abstract 1006-358). Although baseline CAD on angiography was more frequent in patients with diabetes, there was no difference in LVEF between patients with and without diabetes (65% vs. 67%, p = 0.25). Patients were followed prospectively for 8 years for vascular outcomes (vascular mortality, cardiac mortality, non-fatal MI and stroke, CABB, PCI and non-cardiac revascularizations). The incidence of vascular events was, not surprisingly, higher in the diabetic group (43.8% vs. 30.1%, p = 0.003) and in those with baseline CAD by angiography (p < 0.001). Likewise, LVEF was significantly predictive of vascular events in multivariable models in the entire cohort (HR 0.79, 95% CI 0.71-0.88). However, the relationship between LVEF and vascular outcomes was significantly different based upon diabetes status (interaction p-value = 0.047). Among patients with diabetes, LVEF was not associated with vascular events (HR 1.00, p = 0.71) whereas among those without diabetes, LVEF was associated with this outcome (HR 0.72, p < 0.001). In summary, both angiographically determined baseline CAD and low baseline LVEF significantly predicted vascular events in patients.
Figure 3. Two-Year Survival by HbA1c Quartiles

Table 3. Effects of Natriuretic Peptides

So Many Posters, So Little Time....
BNP levels after adjustments for age, BMI, hypertension, smoking status, serum creatinine, and other possible confounding factors (adjusted OR=1.51 for men and 1.95 for women) (Circulation 2004). Framingham data have also demonstrated that low BNP levels are associated with insulin resistance.

Dr. Everett and Women’s Health Study co-investigators evaluated the impact of NT-proBNP levels on the risk of incident Type 2 diabetes using a case-cohort approach (n=491 cases, n=561 in the reference subcohort) (abstract 1149-298). Women with incident Type 2 diabetes were younger (median age 53.3 vs. 56.9 years, p<0.001) and had higher median BMI (29.4 vs. 25.0 kg/m², p<0.001) and HbA1c (5.3 vs. 5.0%, p<0.001) than controls. Median (IQR) baseline NT-proBNP levels among women with incident Type 2 diabetes (46.8 pg/mL [26.1, 83.2]) were significantly lower than among women in the reference group (66.7 pg/mL [39.3, 124.7]; p<0.001). High levels of NT-proBNP were associated with reduced risk of incident diabetes: in proportional hazards models adjusting for age, race, BMI, and renal function, women in the highest quartile of NT-proBNP had a 45% reduced risk of incident Type 2 diabetes (Model 3, Table 4). Further adjustments for family history of diabetes, menopausal status, physical activity, and alcohol use did not affect the association (Model 4). These prospective and highly preliminary data suggest a role for BNP in the development of Type 2 diabetes.

Screening for CAD
Tandon and the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study co-investigators conducted a post-hoc analysis to determine the influence of gender on silent myocardial ischemia (SMI) and cardiac event rate in patients with diabetes and assess whether screening affects clinical outcomes (abstract 1063-228). In the DIAD study, 1,123 asymptomatic patients with Type 2 diabetes (522 women, 601 men) were randomized to screening with a nuclear pharmacological stress test (adenosine myocardial perfusion imaging [MPI]) versus no screening (Young et al., JAMA 2009;301:1547-55). In the published findings of the core study, prevalence of SMI was lower than anticipated (22%) and the 4.8-year cardiac event rate (cardiac death and nonfatal MI) was low (2.9%) and essentially unaffected by screening. According to the post-hoc analyses, the overall prevalence of abnormal MPI findings was similar between genders (19% and 24% of female and male patients, respectively; p=0.20); there was a trend for women having less moderate/large perfusion abnormalities than men (p=0.07). The cardiac event rate over a 5-year follow-up period was significantly lower among the women than among men (1.7% vs. 3.8%, p=0.05), and, within each gender sub-group, was similar between patients randomized to screening vs. no screening. When patients were stratified by their baseline risk using the UKPDS risk engine, the 5-year cardiac event rate was higher for men compared to women at high risk, but similar between genders among those at intermediate or low risk (Table 5). Taken together, these results from DIAD suggest that routine screening of asymptomatic female diabetic patients cannot be justified even in those seemingly at the highest risk. In men in the highest risk category, event rates were substantial. Although screening might be considered in this group, DIAD was not powered to evaluate the utility of screening these individuals.

Acute Hyperglycemia in Acute MI
Nicolau and coworkers from Brazil conducted a study to determine the prognostic value of diabetes and hyperglycemia for inpatient and long-term mortality following acute MI (abstract 1073-368). A total of 1,429 acute MI patients (mean age 64.5±0.34 years, 73% men, and 30% with a history of diabetes,) who were treated at a single tertiary-care institution were followed for up to 11.7 years after discharge (abstract 1073-368). Inpatient mortality rates for diabetics and non-diabetics were 12.7% and 9.6%, respectively (p=0.08). In a multivariable model which accounted for history of diabetes, admission blood glucose level, and 13 other baseline variables, glucose (OR=1.01 per each 1 mg/dL increase,

Table 4. Risk of Incident Diabetes Among Apparently Healthy Women by Level of NT-proBNP

<table>
<thead>
<tr>
<th>Quartile of NT-proBNP</th>
<th>Quartile 1 (&lt;37.8 pg/mL)</th>
<th>Quartile 2 (37.8 to &lt;64.3 pg/mL)</th>
<th>Quartile 3 (64.3 to &lt;117.4 pg/mL)</th>
<th>Quartile 4 (≥117.4 pg/mL)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=195</td>
<td>N=117</td>
<td>N=116</td>
<td>N=63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 HR (95% CI)</td>
<td>1.0 (0.40-0.78)</td>
<td>0.61 (0.43-0.86)</td>
<td>0.40 (0.27-0.61)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Model 2 HR (95% CI)</td>
<td>1.0 (0.56-1.25)</td>
<td>0.94 (0.62-1.43)</td>
<td>0.55 (0.34-0.89)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Model 3 HR (95% CI)</td>
<td>1.0 (0.57-1.26)</td>
<td>0.95 (0.63-1.45)</td>
<td>0.55 (0.34-0.91)</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>Model 4 HR (95% CI)</td>
<td>1.0 (0.58-1.33)</td>
<td>0.97 (0.63-1.52)</td>
<td>0.51 (0.31-0.85)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

NT-proBNP=N-terminal fragment, B-type natriuretic peptide.
Model 1: adjusted for age and race.
Model 2: adjusted for age, race, BMI.
Model 3: adjusted for age, race, BMI, and estimated GFR.
Model 4: adjusted for age, race, BMI, estimated GFR, hormone use, exercise, alcohol, and family history of diabetes.

Table 5. 5-Year Coronary Event Rate by Baseline Risk (UKPDS)

<table>
<thead>
<tr>
<th>Baseline Risk (UKPDS)</th>
<th>Female Patients (n=522)</th>
<th>Male Patients (n=601)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence of Risk</td>
<td>Cardiac Events Over 5 Years n (%)</td>
</tr>
<tr>
<td>Low</td>
<td>73%</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Medium</td>
<td>24%</td>
<td>5 (4.1%)</td>
</tr>
<tr>
<td>High</td>
<td>3%</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Comparing cardiac event rate between female and male patients.
of CA C score to the prediction model significantly improved the estimation of mortality risk, regardless of diabetic status.

**HDL and CVD Risk**

High-density lipoprotein cholesterol (HDL-C) is considered critically important in the removal of cholesterol from atherosclerotic plaque for transport back to the liver (reverse cholesterol transport). It also has potent anti-oxidant effects. Clinical and epidemiologic studies have consistently shown that low levels of HDL-C are strongly associated with increased risk of CAD. Moreover, mice with genetic defects in HDL-C metabolism are markedly atherosclerotic, providing evidence for HDL as a key modulator of CVD in animal models. These observations, combined with the residual risk of statin-treated patients with coronary disease, have prompted investigations of interventions to raise HDL-C levels. These studies are of particular interest to those of us managing patients with diabetes, since the classical diabetic dyslipidemia is marked by low HDL-C concentrations.

Interested in the association between changes in HDL-C and CVD risk, Nichols and associates from Georgia and Oregon conducted an observational cohort study of 30,067 members of Kaiser Permanente (mean age 60.9 ± 12.6 years, 51% male, mean diabetes duration 5.4 ± 4.3 years) who had Type 2 diabetes and 2 HDL-cholesterol (HDL-C) measurements 6-24 months apart in 2001 to 2006 (abstract 920-7). After calculating change in HDL-C, they used the date of the second measurement as the index date and followed patients through 2009. Over a mean follow-up of 4.7 years, 3,717 (12.4%) patients had a CVD-related hospitalization. After multivariable adjustment (baseline HDL-C, demographic and clinical risk factors, comorbidities, and use of pharmacologic agents), higher baseline HDL-C was significantly associated with lower CVD risk (HR 0.93 per 5 mg/dL, 95% CI 0.92-0.95) and each 5 mg/dL increase in HDL-C was associated with a 5% reduction in CVD risk (HR 0.95, 95% CI 0.93-0.97). In categorical, adjusted analyses (relative to individuals with stable HDL-C), a 6.5 mg/dL decrease in HDL-C was associated with a 15% increase in CVD risk (HR 1.15, 95% CI 1.05-1.27), whereas a 6.5 mg/dL increase was associated with a 10% reduction in risk (HR 0.90, 95% CI 0.83-0.98). These results are consistent with the findings from multiple other clinical and epidemiologic studies in which low levels of HDL-C have been shown to be strongly associated with increased risk of CAD.

These results are limited by the observational nature of the study, but they are consistent with atheroprotective properties of HDL seen in cell culture and animal models. Benefit in primary or secondary prevention studies of HDL-C raising will be needed before pharmacotherapy targeting HDL is added to treatment guidelines for Type 2 diabetes patients.

Although there are non-pharmacologic means of increasing HDL-C (eg, weight loss, exercise, smoking cessation, modest ethanol ingestion), drug therapy may ultimately prove to be more efficient. In this regard, of currently available agents, niacin likely has the greatest impact, with an average increase in HDL-C of 2-14%, respectively. Despite these findings, primary prevention data supporting the use of HDL-C-raising therapy are lacking. For example, in FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD, fenofibrate had no overall effect on the composite primary cardiovascular outcomes. Moreover, initial studies using drugs known as cholesterol ester transfer protein (CETP)-inhibitors, which markedly raise HDL-C concentrations (>50%), were disappointing. The effect on cardiovascular outcomes of pioglitazone remains controversial and that drug activates many more pathways with possible antiatherogenic properties than solely HDL. Finally, statins likely exert their beneficial cardiovascular effects through LDL-lowering and anti-inflammatory properties. In summary, the role of HDL-C as a therapeutic target remains uncertain.

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

**Prognostic Value of CAC**

Rana and associates from California used computed tomography to measure coronary artery calcium (CAC) scores in 36,138 asymptomatic individuals (men ≥ 40 yrs, women ≥ 50; n = 2,067 with diabetes) who were referred for assessment of possible sub-clinical atherosclerosis (abstract 1170-198). Cox proportional hazards models were used to estimate 5-year risk for all-cause mortality. One model included traditional risk factors (age, sex, tobacco use, history of hypertension, high cholesterol) and a second model added CAC score to these factors.

During a median 5-year follow-up period, estimated mortality rate was significantly higher for patients with than without diabetes (6.7% vs. 2.2%; p < 0.001). Among patients with a CAC score of 0, the event rate was low, irrespective of diabetic status (Figure 4). There was no difference in event rates between the non-diabetic and diabetic cohorts when categorized into risk groups based on traditional risk factors. Addition of CAC score to the prediction model significantly improved the estimation of mortality risk, regardless of diabetic status.

**Figure 4. 5-Year All-Cause Mortality Rate by CAC Score**

![Figure 4. 5-Year All-Cause Mortality Rate by CAC Score](image-url)}
At an opening day symposium in San Diego, investigators from around the world convened to answer the question, “Other Types of Diabetes—Have We Made Any Progress in Management?” While most patients with diabetes can be categorized as having either Type 1 or Type 2, a separate category exists, referred to as “Secondary Diabetes” (Table 1). This distinction is not necessarily biologically based, but describes merely a collection of various conditions to which the hyperglycemia can be directly ascribed. These include other endocrinopathies (e.g., Cushing syndrome), medications (steroids), infections (mainly certain viruses), organ dysfunction (pancreatitis), or genetic abnormalities (Klinefelter syndrome).

Opening the session was Dr. Arlene Stecenko from Emory University, who discussed “Cystic Fibrosis-Related Diabetes (CFRD).” This is now thought to occur in 35% of patients with this genetic disorder of chloride transport that leads to severe pulmonary complications. With better antibiotic and respiratory treatments over the past two decades, patients with cystic fibrosis (CF) are living longer—often into their 40s and beyond. As such, diabetes is becoming even more frequently identified in these individuals. Moreover, the presence of CFRD is known to increase a patient’s morbidity and mortality.

The pathophysiological nature of CFRD appears to consist of a primary defect in β-cell insulin secretion. Since many CF patients develop destructive exocrine pancreatic insufficiency, it has always been assumed that concurrent islet cell injury plays a major role. Indeed, CF patients without exocrine pancreatic failure are typically protected against developing diabetes. However, the degree of pancreatic parenchymal damage does not necessarily correlate with the severity of CFRD when it is present. Accordingly, other theories concerning β-cell dysfunction in CF have emerged.

For example, pancreatic islets express the cystic fibrosis transmembrane conductance regulator (CFTR) gene, known to be mutated in CF. (The CFTR protein functions as a chloride channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes. The transport of chloride ions controls the movement of water into cells necessary for the production of thin and freely flowing secretions. A dysfunctional CFTR leads to inspissated secretions, tissue damage, inflammation, and infection—particularly in the lung.) Its role in the β cell is not at all understood, but some have proposed that CFTR may somehow influence insulin secretory capacity.

Several other potentially diabetogenic factors were discussed, including diet (CF patients are encouraged to consume at least 50% more calories than normal to maintain their body weight); the effects of inflammation on both insulin secretion and action; genetics; and the influence of oxidative stress, known to be extremely high in CF.

The peak age for the development of CFRD is 20-24 years. Patients tend to be normal to underweight. The degree of the insulin deficiency is severe—but not complete as it is in Type 1 diabetes. There is also a component of insulin resistance, but this waxes and wanes in association with activity of any underlying infection. Patients do not demonstrate circulating autoimmune markers and are not ketosis prone. Interestingly, neither micro- nor macro-vascular complications are seen in CF patients, perhaps due to their reduced life expectancy.

Regarding treatment, Dr. Stecenko underscored the importance of insulin therapy, best delivered with pre-meal rapid-acting analogues or via an insulin pump. This appears to work best, since fasting glucose is not typically as deranged as post-prandial glucose. Importantly, randomized clinical trials have demonstrated better weight gain when insulin is used, as opposed to oral secretagogues. There are few data to show any effects on longer-term clinical outcomes, although it is generally felt that the longer CF patients are able to maintain their body weight, the better they do overall. Some observational studies have suggested that better diabetic control may improve lung function.
Next, Dr. Fabrizio Barbetti from Rome, Italy discussed “Monogenic Diabetes,” restricting his comments predominately to his area of specialty, namely neonatal diabetes mellitus (NDM). This is defined as diabetes diagnosed within the first 6 months of life, and is clearly distinct from the more common Type 1 diabetes in children. NDM occurs in only 1 in 100,000 to 1 in 500,000 live births. Two specific genetic abnormalities have been defined leading to NDM, both resulting in abnormal sulfonylurea receptors (or SURs) on pancreatic β cells. This leads to dysfunction of ATP-sensitive potassium (KATP) channels and marked impairment of insulin secretion. While many of these infants continue to be treated with insulin injections, they actually usually respond nicely to sulfonylurea drugs, such as glyburide, often requiring high doses. One mutation in the KCNJ11 gene results in an abnormal SUR1 and leads to permanent diabetes. A second involving the ABCC8 gene affects the SUR2 receptor. This type may be transient, but can also recur during teenage years. SUR receptors are also expressed in a variety of other tissues, including the brain and skeletal muscle. Motor and mental dysfunctions are sometimes seen in conjunction with NDM, and, interestingly, there may be improvement with sulfonylurea treatment. Dr. Barbetti emphasized the importance of genetic testing of patients with NDM, given that documentation of this disease leads directly to different therapy, with the potential for significant cost savings over time.

Dr. Barbetti briefly reviewed other genetic syndromes associated with diabetes, including Rabson-Mendenhall syndrome and leprechaunism, both associated with an abnormal insulin receptor. The former has been successfully treated with injections of recombinant insulin-like growth factor-1* (IGF-1), which utilizes a separate cell surface receptor to stimulate glucose uptake by cells. Maturity-onset diabetes of youth (MODY) syndromes were also mentioned (Table 6)—these are another heterogeneous collection of monogenic diabetes diagnosed typically in adolescence or early adulthood. A variety of gene mutations have been associated with MODY, each of which appear to limit the ability of the β cell to produce insulin. There is typically a strong family history, often in multiple generations. MODY may account for 1-5% of all cases of diabetes in the US. Depending on the specific MODY form and its severity, hyperglycemia can usually be managed with sulfonylureas, but sometimes insulin injections are required. MODY patients can also be identified through genetic testing.

Dr. Jerry Palmer, the third speaker, addressed “Latent Autoimmune Diabetes of Adults (LADA).” Dr. Palmer took exception to the name, since it is not really latent and can sometimes occur in children. In fact, nomenclature for this condition has been historically very labile, depending on who is describing the syndrome. For example, it has been variably referred to as “Type 1.5 Diabetes,” “Antibody-Positive Type 2 Diabetes,” “Latent Type 1 Diabetes,” “Double Diabetes,” and “Youth Onset Diabetes of Maturity (YODM).” Such inconsistency has led to significant confusion in the literature.

LADA may comprise up to 10-15% of adults diagnosed with Type 2 diabetes. Initially, it presents phenotypically as Type 2, but autoimmune markers, such as anti-GAD antibodies, are present. Accordingly, many consider LADA to be a slowly progressive form of Type 1 diabetes. Early sulfonylurea failure is a universal characteristic, with an earlier need for insulin therapy than in classic Type 2. By definition, LADA patients are insulin independent for at least 6 months after diagnosis. Obesity does not protect against autoimmunity, so Dr. Palmer emphasized that there is a significant overlap in BMI s in patients with Type 2 diabetes and LADA. Statistically, however, LADA patients tend to be leaner. Dr. Palmer went on to wonder whether it is proper to consider LADA as a form of Type 1 diabetes, masquerading, at least initially, as Type 2. Instead, he proposed that an autoimmune response to the islet cell injury that already characterizes...
Type 2 diabetes may fail to be regulated in certain individuals. That is, LADA may simply be a reasonably common variant of Type 2 diabetes, in which autoimmunity is just one of many factors (Table 7) that lead to β-cell failure, albeit of a more severe degree.

In support of this theory, Dr. Palmer pointed to emerging clinical studies that have employed immunotherapy* directed at either β-lymphocytes or T-lymphocytes, which appear to improve insulin secretion in patients with ordinary Type 2 diabetes. In addition, a separate and highly preliminary body of evidence has raised the possibility that autoimmune in Type 2 diabetes may extend to the fat cell itself, since similar immunomodulatory therapy has been shown to improve the adipocyte’s pro-inflammatory milieu and whole body insulin sensitivity. As Dr. Palmer suggested, the historical distinct separation of Type 1 and Type 2 diabetes may need to be reevaluated.

The final discussant, Dr. Jennifer Larsen from the University of Nebraska, reviewed “Post-Transplant Diabetes (PTDM).” With almost 500,000 organ transplants now performed in the US annually, this is becoming a more frequently encountered syndrome. Actually, transplant patients, who are now living longer with their functioning grafts, are commonly beset by a variety of metabolic complications, mainly related to their immunosuppressive regimen, requiring the care of multiple specialists. Following renal transplantation, for example, diabetes may be present in up to 50%. A recent consensus statement from the transplant community suggested that aggressive screening for PTDM is needed, since its presence appears to have a negative impact on both graft as well as patient survival. Risk factors for PTDM are shown in the Table 8.

Table 7. Causes of β-Cell Failure in Type 2 Diabetes

- Glucotoxicity
- Lipotoxicity
- Islet Amyloid Polypeptide (IAPP)
- Inflammation
- Oxidative stress
- Endoplasmic reticulum stress
- ? Autoimmunity

Commonly used immunosuppressive drugs appear to be an important, if not the major, driver of PTDM. The effects of glucocorticoids on insulin sensitivity are well known. These drugs also impair insulin secretion. Regimens that minimize steroid exposure may therefore be advantageous. On the other hand, non-steroid immunosuppressive drugs, such as the ubiquitous calcineurin inhibitors (e.g., tacrolimus and sirolimus) also have deleterious effects on both β-cell function and insulin sensitivity. Other less commonly used medications such as mycophenolate mofetil (MMF) and azathioprine seem to have no effect on glucose metabolism. Of course, as Dr. Larsen emphasized, effective immunosuppression is the primary goal—to avoid graft rejection—and, therefore, the metabolic ‘fallout’ of this therapy must simply be dealt with as aggressively as possible.

As for treatment, many of the commonly used oral agents for diabetes are contraindicated in this sicker cohort of patients, who often have significant renal and hepatic impairment and complex medication regimens that predispose them to drug-drug interactions. Accordingly, insulin is often the safest agent to use. Transplant patients are also frequently hospitalized for episodes of rejection or infections during which time they are often treated with stress doses of steroids and may experience abrupt interruptions in calorie intake. This renders them at risk for both hyperglycemic and hypoglycemic excursions. Meticulous care is therefore necessary.

Dr. Larsen closed by encouraging more research on ways to prevent the development of PTDM. This might involve safer immunosuppressive drugs, better management of obesity, and the use of certain drugs that may improve β-cell function—such as thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Table 8. Risk Factors for Post-Transplant Diabetes

General Risk Factors
- Non-white race/ethnicity
- Age > 40 years
- Obesity, metabolic syndrome
- Polycystic Ovary Syndrome (PCOS)
- Impaired glucose tolerance (IGT)
- Family history of diabetes
- Hepatitis C, CMV infection
- Hypertensive vascular disease

Organ-Specific Risk Factors
- Kidney
  - Recipient of a deceased donor kidney
  - Vitamin D receptor polymorphisms
  - Polycystic kidney disease
- Liver
  - Steatosis in liver graft

The major limiting step in intensive insulin therapy remains hypoglycemia, classically defined as a blood glucose concentration <70 mg/dl. Although hypoglycemia is often merely an inconvenience, when severe it can lead to significant deterioration in mental status, including coma—and in certain circumstances may be life threatening. Patients with Type 1 diabetes are at greater risk for this condition than those with insulin-requiring Type 2 diabetes for several reasons. First, patients with Type 1 diabetes tend to be more intensively treated and are also usually more insulin sensitive. Perhaps more importantly, by definition, Type 1 diabetic patients produce no endogenous insulin and are therefore entirely reliant on exogenous insulin injections. In the setting of a mismatch between insulin requirements and insulin supply, significant perturbations of blood glucose concentrations occur. When supply exceeds requirements, for example, hypoglycemia results. In contrast, the Type 2 diabetic patient would still be able to auto-regulate by reducing endogenous insulin secretion.

At this week’s meeting, several presentations delved into this important issue of clinical care. Dube et al. from Canada were interested in the prevention of exercise-induced hypoglycemia in a small group of Type 1 diabetes patients on a basal-bolus insulin (glargine + glulisine) (abstract 774-P). Intermittent high-intensity exercise has been proposed as a way to minimize hypoglycemia during moderate exercise, presumably related to surges in counter-regulatory hormones. The investigators therefore studied the effects of 3 different approaches on blood glucose (BG) concentrations during exercise post-lunch. Each of 11 subjects performed 60 minutes of moderate intensity afternoon exercise on a bicycle ergometer. The patients were randomly assigned to a pre-exercise beverage containing no glucose (control), 30-g of an oral glucose drink, or intermittent bursts of high-intensity exercise. The latter consisted of 10 seconds

Feeling Low

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of maximal sprint effort every 2 minutes during the 60-minute moderate exercise session. A rescue dextrose infusion was given to any patient whose BG fell <72 mg/dl.

There was no significant difference in the pre-exercise BG (mean, 128-151 mg/dl). After the beverage, the glucose beverage group experienced a mean BG increase to 206 mg/dl and by the end of the exercise period, this had fallen to a mean of 144 mg/dl. In the other two groups, the post-exercise BG had fallen to means of 95 (control) and 112 mg/dl (high-intensity exercise) (Figure 5). Only 9% of individuals receiving the glucose drink required dextrose infusion, whereas this was necessary in 64% of those drinking the no-glucose solution and 36% of those who performed the high-intensity exercise. The results suggest that a 30-g glucose beverage prior to moderate intensity exercise may be the safest practice in patients on basal-bolus insulin therapy.

Singh et al. from Virginia studied risk factors for severe hypoglycemia in Type 1 diabetes (abstract 803-P). The investigators had previously developed the “Risk Assessment of Severe Hypoglycemia (RASH)”, a 40-item questionnaire that identifies the chance of experiencing a severe hypoglycemic event, defined as that needing assistance from another person. Using a 5-point Likert scale, RASH explores several domains, including BG management habits during exercise, the frequency of hypoglycemic episodes, resistance to addressing early signs of hypoglycemia, hypoglycemia unawareness, and involvement of others in the management of hypoglycemia. A total of 503 patients (mean age 43 years, diabetes duration 25 years, 52% women) completed the questionnaire. Subsequently, patients were contacted monthly for one year to record any episodes of severe hypoglycemia.

After weighting responses for discrimination, the investigators found that the domain concerning involvement of others in hypoglycemia management remained independently predictive for future severe hypoglycemia. Questions here included “How often did others recognize your hypoglycemia because of how you acted?”, suggesting that inability for the patient to recognize and correct hypoglycemia was the most important factor. It was suggested that inquiring about the extent to which others are involved in the management of a patient’s low BG may identify patients at risk for future severe hypoglycemia. Targeted education and interventions may therefore be considered in these individuals.

Table 9. Risk of Hypoglycemia in Type 2 Diabetes Patients Treated with Oral Anti-Hyperglycemic Agents

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-lowering therapy (each vs. diet therapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin monotherapy</td>
<td>2.28</td>
<td>2.01-2.59</td>
</tr>
<tr>
<td>Sulfonylurea monotherapy</td>
<td>1.16</td>
<td>1.06-1.26</td>
</tr>
<tr>
<td>Glitide monotherapy</td>
<td>1.40</td>
<td>1.02-1.93</td>
</tr>
<tr>
<td>Metformin monotherapy</td>
<td>0.77</td>
<td>0.72-0.83</td>
</tr>
<tr>
<td>Thiazolidinedione monotherapy</td>
<td>0.87</td>
<td>0.78-0.96</td>
</tr>
<tr>
<td>DPP-4 inhibitor monotherapy</td>
<td>0.89</td>
<td>0.68-1.18</td>
</tr>
<tr>
<td>Other medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>1.12</td>
<td>1.03-1.21</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.14</td>
<td>1.06-1.22</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.34</td>
<td>1.18-1.54</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.46</td>
<td>1.35-1.58</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>2.11</td>
<td>1.92-2.33</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>2.24</td>
<td>1.92-2.61</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent macrovascular disease</td>
<td>1.78</td>
<td>1.68-1.89</td>
</tr>
<tr>
<td>Prevalent microvascular disease</td>
<td>2.80</td>
<td>2.64-2.97</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.31</td>
<td>1.20-1.43</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.54</td>
<td>1.29-1.82</td>
</tr>
</tbody>
</table>

Although less frequent, hypoglycemia still occurs in patients with Type 2 diabetes. Simone and Quilliam of the US conducted a nested case-control analysis of a database that included adults on oral anti-hyperglycemic drugs who maintained enrollment in a health insurance plan for at least 12 months (abstract 493-P). The investigators identified 11,375 cases who had an ICD-9 code for hypoglycemia for an outpatient or emergency room visit. Using a 6:1 match, they then identified 68,247 controls without hypoglycemia. Using a logistic regression model, adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. In addition to greater use of drugs like insulin and insulin secretagogues, cases with hypoglycemia were more likely than controls to have diabetic complications and other comorbidities. They were also more likely to be treated with certain non-diabetes medications. Men were less likely to be affected (Table 9).

The investigators suggested that both diabetes and non-diabetes medications be chosen carefully for patients at risk for hypoglycemia—especially those with established diabetic complications, hypothyroidism, and liver disease. (We would add chronic kidney disease as well, even though these patients were not identified in this specific trial to be at greater risk.) These sentiments echo the findings of ACCORD, published in 2008 (see Diabetes 2008, Volume 17, page 26). In that large, randomized clinical trial examining the effects of intensive vs. conventional anti-hyperglycemic therapy in high-risk Type 2 diabetes patients, a surprising increased risk of mortality was found in those randomized to the former strategy. While this cohort did experience increased hypoglycemia rates, it remains unknown if that risk was directly linked to any adverse outcomes that influenced mortality.

Figure 5. Glycemia Over Time Following Moderate-Intensity Exercise

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>20</td>
<td>120</td>
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<td>30</td>
<td>120</td>
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<td>210</td>
<td>120</td>
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</tbody>
</table>
Diagnosing Diabetes

Scherrnthaler et al. from Austria compared diagnostic criteria for diabetes in 781 patients with morbid obesity and unknown diabetes status (abstract 61-OR). They found that fasting plasma glucose underestimates the existence of diabetes in these patients. The prevalence of ‘undiagnosed Type 2 diabetes’ was 6.9% using the latest HbA1c criterion of the American Diabetes Association (≥6.5%), 7.1% using the 2-hour criterion during an oral glucose tolerance test (OGTT; ≥200mg/dl), but only 3.6% using the fasting plasma glucose criterion (≥126mg/dl). Only 2.4% (n=19) of the patients met all 3 criteria for diabetes. Prevalence of metabolic syndrome using the ATP III criteria was similar in patients diagnosed as having diabetes by HbA1c (83%), 2-hour post-challenge glucose (87%), and fasting plasma glucose (79%). These data add to a growing body of literature indicating that the various methods to diagnose diabetes identify different patients, with few meeting all criteria. The best test to use remains controversial—there is an inherent attractiveness of the HbA1c, which requires no fasting. The OGTT is falling into even more disfavor since endorsement of the HbA1c, which in part captures post-prandial glucose.

Counting Sheep

Matsunaga and Japanese co-investigators evaluated the association between glycemic control and sleep quality in a diabetes registry that was comprised of 3,462 patients with Type 1 (n=167) or Type 2 diabetes (n=3295) (mean ±SD age =64.7±16.6 years; duration of diabetes =14.0±9.8 years) (abstract 1311-P). Insomnia was assessed by patients’ responses to a global sleep quality questionnaire (the Pittsburgh Sleep Quality Index [PSQI]; score range 0-21). The prevalence of comorbid insomnia (PSQI score >5) was 39.1% and 37.2% in patients with Type 1 and Type 2 diabetes, respectively. The investigators went on to observe a U-shaped association between glycemic control and the prevalence of insomnia, with the prevalence being lowest in patients with an HbA1c between 6.9-8.3% in both forms of diabetes, versus the other glycemic categories (Figure 6). In a multivariable-adjusted modified Poisson regression model, significant risk factors for insomnia were neurological symptoms in the lower extremities (RR 1.39, 95%CI1.27-1.51), symptomatic nocturnal hypoglycemia (RR 1.37, 1.19-1.57), the presence of anemia (RR 1.12, 1.01-1.23), female gender (RR 1.33, 1.21-1.46), and BMI (RR 1.01 per 1 kg/m², 1.00-1.02).

Prescription Drug Use in US Adults with Diabetes

Nair et al. used data from the 2005-2008 National Health and Nutrition Examination Survey (NHANES) to characterize prescription drug use among US adults with diabetes (abstract 1367-P). Information on prescriptions during the preceding month was obtained during a household interview of 1,261 adults with self-reported, diagnosed diabetes mellitus, from which the investigators estimated usage of antihyperglycemic and other classes of prescription drugs. 83% of US adults with diabetes used oral hypoglycemic agents and/or insulin. The most commonly used oral hypoglycemic agents were metformin (47%), sulfonylureas (36%), and thiazolidinediones (22%). Less than a third (29%) used insulin, 13% as their only glucose-lowering agent. Treatment of comorbidities was reflected in the frequent use of antihypertensive drugs (71%) and lipid-lowering drugs (54%). Notably, the mean number of drugs per person was 5.5; 20% used ≤2 drugs, 25% 3-4 drugs, 29% 5-7 drugs, and 26% ≥8 drugs. The distribution varied across age groups (Figure 7). Given the multiple medications diabetes patients require, clinicians treating them must be cognizant of potential drug-drug interactions and adverse effects. Efforts should be taken to minimize these when possible.

The Food-Brain Connection

Lee et al. from the UK quantified regional cerebral blood flow (rCBF), using functional magnetic resonance imaging (fMRI) with continuous arterial spin labeling (cASL), to investigate response to a 554 kcal mixed meal ingestion ('fed'), compared to 50 ml of water ('fasted'), in 2 groups of healthy volunteers, 11 young adults (19-33 years; 4 female) and 11 older adults (38-52 years; 8 female) (abstract 1700). Following food ingestion, changes in rCBF occurred in brain regions involved in appetite control, nutrient sensing, and taste. The investigators found differential changes in rCBF in older vs. younger subjects and suggested that these areas were therefore not activated normally in older patients. In turn, this may contribute to weight gain and increased risk of Type 2 diabetes with advancing age. A central mechanism for appetite control is an appealing target for weight reduction therapies, but we need to know more about the physiological implications of the changes found by this group.

Figure 6. Prevalence of Insomnia by HbA1c

Figure 7. Number of Prescription Drugs Used by Age Group

* 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
‘Metabolic surgery’ is the new term for bariatric surgery, and it took center stage at the ADA Scientific Sessions this year. The rapid rise in rates of obesity and its associated comorbidities have prompted a fast surgical solution to a chronic medical problem. Type 2 diabetes is known to reverse in at least 2 out of 3 patients following bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB), even before significant weight loss. The responsible mechanisms are unclear, but thought to involve alterations in gut hormones. Specifically, the dramatic increase in glucagon-like peptide 1 (GLP-1) levels, abrupt reduction in nutrient intake, and relief of steatosis following surgery all likely play a major role. However, all ‘quick fixes’ come at a cost, and metabolic surgery carries a risk of both immediate surgical complications as well as late adverse outcomes, such as hypoglycemia and vitamin deficiencies. These concerns and the latest research involving metabolic changes were addressed during several presentations in San Diego this week.

Sayeed Ikramuddin, MD a bariatric surgeon from the University of Michigan, reviewed indications for surgery and the types of surgery now available. According to the 1991 NIH consensus conference guidelines, eligible persons should have a BMI $\geq 40$ kg/m$^2$, or a BMI $\geq 35$ to 39.9 kg/m$^2$ in the presence of severe obesity-related comorbidities, such as Type 2 diabetes, obstructive sleep apnea, cardiomyopathy, or severe joint disease. Given the major alterations in food intake that occur following these procedures, surgery should only be considered in persons who commit to a diet and exercise regimen. In Figure 8, the various currently available bariatric procedures are shown.

The major changes in glucose metabolism post-metabolic surgery have encouraged new research into the role of the enteric hormone system on insulin sensitivity and the pathophysiology of obesity-induced diabetes. Nils Jorgensen, MD from Denmark (abstract 58-OR) measured fasting and 2-hour post-liquid meal glucose and insulin levels in 13 obese people with Type 2 diabetes (BMI $43.1\pm1.4$ kg/m$^2$; age $52\pm2$ years) and a
group of 12 matched normal glucose tolerant (NGT) subjects (age 43±4 years) 3 days before and 5 days and 3 months after RYGB. In both groups, fasting glucose and insulin levels decreased significantly (p<0.01) compared to pre-surgical levels (Table 10). Following meal ingestion, 2-hour postprandial glucose levels decreased in Type 2 diabetes patients, whereas levels were unchanged in obese NGT subjects immediately after RYGB but decreased by 3 months. C-peptide levels increased in both groups after RYGB, indicating improved insulin secretion. The most dramatic finding was that the GLP-1 integrated area-under-the-curve (iAUC) was increased by a factor of 20 to 40 in both groups, whereas glucose-dependent insulinotropic peptide (GIP) showed very little change in either group. The investigators concluded that resolution of diabetes after RYGB is explained by an early improvement in both insulin sensitivity and insulin secretion. An exaggerated GLP-1 response may explain the potentiated insulin secretion after RYGB.

Unfortunately, the potential disadvantages of hypoglycemia sometimes accompany augmented insulin secretion following RYGB. Johanna Maria Brix, MD from Vienna, Austria (abstract 60-OR) presented data on 789 patients with morbid obesity (mean BMI 43.8±9.6 kg/m^2, mean age 38±12 years, 80.7% female), of whom 219 consecutive patients were evaluated with an oral glucose tolerance test (OGTT) before and 2 years after bariatric surgery. Hypoglycemia (defined as a glucose ≤50 mg/dl) was found during the OGTT in 0.9% patients before surgery, but increased significantly after surgery to 18.7%. Additionally, there was a marked difference in prevalence of hypoglycemia for each type of surgery: 34% of patients after gastric bypass, 18% after sleeve gastrectomy, and 2% after gastric banding. Predicting factors in patients with hypoglycemia versus those without hypoglycemia were a greater change in BMI (15.0 vs. 5.7 kg/m^2, p<0.001), lower fasting levels of glucose (74±7 vs. 81±11 mg/dl, p<0.001), and insulin (7±3 vs. 11±9 µU/ml, p<0.001), but higher 1-hour post challenge insulin values (155±103 vs. 94±81 µU/ml, p<0.001). HOMA-IR, a calculated indirect measure of insulin resistance, was also significantly lower in the patients with hypoglycemia (0.2±0.3 vs. 1.2±1.7, p<0.001).

In summary, the risk for hypoglycemia was higher in patients with greater weight loss associated with lower insulin resistance but still having high postprandial insulin levels. Routinely checking an OGTT 2 years after metabolic surgery was recommended by the investigators to identify those patients at higher risk of hypoglycemia, although it was noted that the majority of patients found to have hypoglycemia on OGTT were also symptomatic after meals (statistics not available at time of presentation). While it is acknowledged that some normal individuals respond to the artificial stimulus of an OGTT with mild-moderate hypoglycemia, it was noted that the majority of patients found to have high postprandial insulin levels (155±103 vs. 94±81 µU/ml, p<0.001). HOMA-IR, a calculated indirect measure of insulin resistance, was also significantly lower in the patients with hypoglycemia (0.2±0.3 vs. 1.2±1.7, p<0.001).

Margaret Furtado, RD from Johns Hopkins Bay View Medical Center discussed the nutritional consequences of metabolic surgery. Iron is the most common deficiency, with anemia occurring in half by 20 years post-gastric bypass. Vitamin B12 is the second most common deficiency, but can be missed in up to half of cases if only a serum level is measured. She recommended checking a methylmalonic acid level, which many consider a more accurate screening method. While thiamine deficiency is less common, it has severe neurological sequelae, and should be considered in anyone who experiences frequent vomiting after bariatric procedures. Copper deficiency may also present with neurological deficits such as ataxia and peripheral neuropathy, and should not be forgotten in routine clinical evaluation. Calcium metabolism may also be altered post-procedure so calcium supplementation is recommended, and an increased risk of renal stones should be recognized. For patients with a pre-operative BMI over 50 kg/m^2, a bilipancreatic diversion with duodenal switch is sometimes considered. This involves removing 80% of the stomach and connecting the duodenum closer to the end of the intestine, resulting in significant fat malabsorption in up to 70% of patients. In this circumstance, the fat-soluble vitamins (A, D, E, and K) must be supplemented twice daily in these patients.

Finally, Jason Lebowitz and colleagues from California (abstract 249-OR) reported a cost comparison of clinical care required by patients with Type 2 diabetes before and after laparoscopic adjustable gastric banding (LAGB) and RYGB. Health care resource use was analyzed across prescription claims, physician office visits, and hospital visits. All patients experienced an increase in health care utilization from 1 year pre-procedure up to the procedure date. Both surgical procedures appeared to reduce care consumption and overall costs in the shorter term. However, interestingly, longer-term costs significantly increased in patients undergoing RYGB, whereas patients with LAGB had a reduction in cost and utilization (Table 11).
Metabolic surgery provides an opportunity for rapid correction of obesity and insulin resistance, and peri-operative morbidity and mortality have certainly improved over the last decade. However, the chronic sequelae of altering gastric anatomy and physiology remain poorly understood. This uncertainty, we feel, should restrain the current growing widespread enthusiasm for these procedures. Additionally, we note that while changes in weight and glucose are undeniable, there is little evidence of any influence of these procedures on cardiovascular outcomes, let alone mortality. Non-randomized studies from Utah (Adams et al., N Engl J Med 2007; 357:753) and Scandinavia (Sjostrom et al., N Engl J Med 2007;357:741) suggested a mortality benefit, but a more recent report, also non-randomized, from the VA system (Maciejewski et al. JAMA 2011;305:2419) suggested otherwise. In this study 850 veterans who underwent bariatric surgery had lower mortality compared to obese non-surgical controls (HR, 0.80; 95% CI, 0.63-0.99) after covariate adjustment. However, this became non-significant after propensity score matching in unadjusted and time-adjusted Cox regression (HR, 0.94; 95% CI, 0.64-1.39). (Propensity score matching is a technique used to minimize the selection bias in non-randomized analyses of interventions. Selection bias may occur because there are inherent characteristics of patients that may make them more or less likely to undergo bariatric surgery, but which may also influence the ultimate outcome. Propensity score matching has been shown to lessen this bias more than simple multivariable adjustment.) In conclusion, we need to know more about the long-term implications of these increasingly popular procedures, particularly before they are extended, as some have proposed, to diabetic patients with lower BMIs (e.g., 30-35 kg/m^2).

Optimizing the use of insulins that are currently available, and soon to be released, was the topic of the afternoon symposium entitled "Insulin Treatment—Still Room for Improvement?" This theme was complemented by many presentations throughout the 71st ADA Scientific Sessions. Dr. Matthew Riddle, Oregon, immediately answered a resounding ‘yes,’ there is still room for pharmacological improvement over insulins currently available. He gave an overview of the available basal insulins, and then discussed degludec,* an ultra-long acting basal insulin (duration of action, 48 hours) currently under investigation. Desirable characteristics of basal insulins include: (1) a long duration of action; (2) low variability providing a peakless action profile and day-to-day intra-patient and inter-patient consistency; and, (3) clinical effectiveness in terms of HbA1c and safety in terms of low rates of hypoglycemia. He then profiled detemir and glargine and how each might be rated relative to the desired traits of basal insulins (Table 12). A discussion of degludec followed, based on a review of 3 recently published studies (Birkeland KI, et al. Diabetes Care 2011; Zinman B, et al. Lancet 2011; Heise T, et al. Diabetes Care 2011) comparing degludec to insulin glargine. Overall, daily or every 3 day degludec appears to be comparable to glargine with respect to impact on fasting plasma glucose (FPG), HbA1c, and self-monitored blood glucose (SMBG) values. In addition, there is a tendency for decreased hypoglycemia. This observation was confirmed by 3 abstracts presented earlier in the day.

The first was a study in Type 1 diabetes patients conducted by Heller and European colleagues (abstract 70-OR) who evaluated 629 patients previously treated with basal bolus insulin regimens for at least one year. In a 3:1 distribution, patients were randomized to receive either degludec once-daily or glargine, in addition to mealtime aspart, with titration to a FPG <90 mg/dl. At one year, the groups were similar with respect to overall glycemic control (HbA1c decreased by 0.4% in each group), proportion of patients achieving HbA1c <7% (40% degludec, 43% glargine, p=NS), and mean reduction in FPG (-23 mg/dl degludec, -25 mg/dl glargine, p=NS). However, the degludec group demonstrated a decrease in the number of confirmed nocturnal hypoglycemia cases (FPG <56 mg/dl or ADA-defined severe episode) (Levemi r®) (Lantus™) (under investigation) (Table 12). A discussion of detemir followed, based on a review of 3 recently published studies (Birkeland KI, et al. Diabetes Care 2011; Zinman B, et al. Lancet 2011; Heise T, et al. Diabetes Care 2011) comparing detemir to insulin glargine. Overall, daily or every 3 day detemir appears to be comparable to glargine with respect to impact on fasting plasma glucose (FPG), HbA1c, and self-monitored blood glucose (SMBG) values. In addition, there is a tendency for decreased hypoglycemia. This observation was confirmed by 3 abstracts presented earlier in the day.

The second study by Garber et al. (abstract 74-OR) assessed the comparative efficacy and safety of degludec and glargine in patients with Type 2 diabetes. The treat-to-target (basal insulin self-titrated to FPG <90 mg/dl) trial was a one-year, open-label study that randomized 992 subjects, also 3:1, to degludec or glargine once-daily, each with mealtime aspart ± metformin ± pioglitazone. As with the previous study, both groups achieved similar glycemic control (HbA1c: -1.2% degludec and -1.3% glargine; percent with HbA1c <7%: 50% each group; FPG: -43 mg/dl degludec and -38 mg/dl glargine; all, p=NS). However, patients assigned to degludec experienced lower rates of both nocturnal (PG <56 mg/dl or ADA-defined severe episode) and overall hypoglycemia. Nocturnal rates for degludec and glargine were 1.4 versus 1.8 episodes per patient-year, respectively (ERR: 0.75 [95% CI: 0.58, 0.99], p=0.04). Overall rates were 11.1 (degludec) versus 13.6 (glargine) episodes per patient-year (ERR: 0.82 [95% CI 0.69, 0.99], p=0.04).

It was concluded that degludec offers comparable glycemic control relative to glargine with the advantage of a significantly lower risk of nocturnal hypoglycemia and, in the case of the Garber investigation, overall hypoglycemia as well. These findings are consistent with the published

Don’t Needle Me

<table>
<thead>
<tr>
<th>Duration of Action</th>
<th>Detemir (Levemir®)</th>
<th>Glargine (Lantus™)</th>
<th>Degludec (under investigation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>18 - 24 hours daily or BID</td>
<td>24+ hours daily</td>
<td>48+ hours daily or q 2-3 days</td>
</tr>
<tr>
<td>Low Variability</td>
<td>No</td>
<td>Nearly</td>
<td>Yes</td>
</tr>
<tr>
<td>Peakless</td>
<td>Good</td>
<td>Fair</td>
<td>?</td>
</tr>
<tr>
<td>Day-to-day variability</td>
<td>Good</td>
<td>Fair</td>
<td>?</td>
</tr>
<tr>
<td>Intercetivity</td>
<td>Fair</td>
<td>Good</td>
<td>?</td>
</tr>
<tr>
<td>Clinical Efficacy</td>
<td>HbA1c</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good</td>
<td>Better</td>
</tr>
</tbody>
</table>
data reviewed by Dr. Riddle in his presentation. An unrelated, but interesting theme during the question and answer session was the high rates of hypoglycemia in all treatment groups and the speculation that the targeted FPG of <90 mg/dL in these studies is likely too aggressive. One therefore wonders if a more acceptable, conservative insulin strategy would have resulted in the same discrepancy between the two insulin groups.

The third study was presented by Hirsch and international colleagues (abstract 1064-P) which utilized a degludec (70%)/aspart (30%) combination formulation once daily in Type 1 patients. Degludec is distinct from the currently available basal insulins, glargine and detemir, insofar as it may be combined in the same solution (and, accordingly, in the same injection) with rapid acting insulin analogues. In a 26-week, open-label trial, patients were randomized to receive the degludec combination (n=366) at any meal and aspart at remaining meals or insulin detemir (n=182) with mealtime aspart. Similar to the other studies, glycemic control (HbA1c, FPG) was improved, but not significantly greater in the degludec group. Confirmed nocturnal hypoglycemia occurred 37% less frequently in the group receiving degludec (3.7 versus 5.7 episodes per patient-year, RR 0.63 [95% CI: 0.49-0.81], p=0.003). Weight gain was, however, greater in the degludec group (by 1.04 kg [0.38; 1.69], p=0.002).

Riddle closed his portion of the symposium by identifying barriers limiting the current success of the basal insulins. One is the persistence of post-prandial hyperglycemia. He contends that despite advances in controlling FPG with basal insulin, post-prandial glucose remains suboptimal. Controlling post-prandial hyperglycemia will complement the advances seen with basal insulin therapy. Methods to do so might include: progression to basal/bolus therapy; addition of a prandial insulin single dose with the main meal; addition of pramlintide; addition of a GLP-1 agonist and/or addition of a sodium glucose co-transporter (SGLT)-2 inhibitor. A combination of approaches will likely improve overall use of insulin therapy.

The second portion of the symposium focused on the topic of “biosimilar insulins” and the implications for regulatory agencies, pharmaceutical manufacturers, and clinicians as patents on several proprietary insulin analogues (e.g., Lantus™, Humalog™, and Novolog™) are soon to expire. A biosimilar is a generic version of a prototypic biologic. Dr. Philip Home, Newcastle University, UK emphasized that although intended to be clinically identical to the reference product or prototype, given the complexity of the biologic molecules in question, one should not consider these simple generic equivalents. These are biologic hormones developed from cell cultures that produce therapeutic proteins and typically entail complex manufacturing processes involving fermentation, purification, and processing. One slight deviation from the original manufacturing technique could result in products that differ in pharmacodynamics such as receptor affinity, enhanced antigenicity, and other unforeseen sequelae. In contrast, generic drugs are small, well-defined molecules produced using standard manufacturing techniques. Thus, the simplistic generic drug approval process that requires solely the demonstration of “good manufacturing processes” along with minimal pharmacokinetic data may not be suitable for the regulatory approval process for biosimilars.

Home shared examples of recent difficulties with biosimilar approvals. Specifically, the biosimilarity of somatropin was associated with the development of antibodies in 57% of patients, which was linked to a faulty purification process during manufacturing. In Europe, an α-interferon formulation was shown to have differences in viral replication rates in comparison with the reference product. Deaths from red cell aplasia were traced to a change in manufacturing process for an erythropoietin biosimilar. Specific guidelines from the FDA for the review and approval process for biosimilars are unclear, but are expected in late 2011.

Dr. Home projected types of data that might be required for insulins, suggesting pharmacokinetics, pharmacodynamics, clinical efficacy, immunogenicity, and clinical safety data. With this in mind, approval of a biosimilar insulin analog could potentially mandate a randomized controlled trial in 800 Type 1 diabetes patients assessing HbA1c, FPG, insulin antibodies, hypoglycemia rates, and standard adverse drug event profiles. Two other issues that remain in question for the practitioner are interchangeability and traceability. Specifically, could one seamlessly change their practice to use a biosimilar without concern about any clinical impact to the patient? Also, if biosimilars are interchange or substituted, how would the side effect profiles be tracked or traced? For this reason, the British National Formulary 2009 has required the use of brand names for the prescribing of biologics and at least 15 European countries have regulations preventing pharmacists from automatic substitution of one biologic product for another (as occurs freely with generic drugs). Lastly, given the implications and complexities of the pending approval processes, it is likely that these agents will be much more costly to produce than traditional generic drug products and may not provide the significant cost savings that are anticipated. This field clearly remains open to great debate with multiple issues requiring resolution.

In the final presentation of the symposium, William Tamborlane, MD, from Yale University explored the need for faster, ultra-rapid acting insulins. He provided a pediatric perspective stating that there are specific challenges in adolescent patients with diabetes. They often require large pre-meal bolus doses of insulin to overcome peripheral insulin resistance that characterizes puberty. They are also vulnerable to post-meal hyperglycemia. Insulins with earlier peaks and shorter durations of action might therefore be beneficial in this patient population. In addition, the current rapid-acting agents are still not rapid enough for fully automated closed loop systems. Dr. Tamborlane reviewed some of the current approaches to improve the onset and bioavailability of insulin including formulations with intrinsically faster onset, warming the infusion site to enhance absorption, co-formulation with hyaluronidase which also hastens absorption, and alternative routes of administration.

A new formulation of human insulin, Linjeta™ (formerly VIAject™) uses EDTA-removal of zinc to destabilize hexamers of insulin, allowing for rapid dissociation and absorption. Initial data demonstrate a more rapid onset of action than insulin lispro. Linjeta™ is currently in clinical trials. The second approach, warming the infusion site, has been used to accelerate the rate of insulin absorption. For example, Cengiz et al. from Dr. Tamborlane’s group (abstract 916-P) examined the infusion site warming device, InsuPatch™ and its impact on the pharmacodynamics of an aspart bolus in 12 pump-treated patients undergoing euglycemic clamp studies. The maximum glucose infusion rate (GIRmax) was not impacted by the patch. However, time to achieve half maximum action and maximum insulin action were 19 minutes and 36 minutes earlier, respectively, after application of the InsuPatch™. Area under the curve (AUC) and mean GIR for the first 90 minutes were significantly greater (AUC0-90 min: p=0.004; GIR0-90 min: p=0.002) in the InsuPatch™ group. The investigators project that improved onset and peak action of the patch-enhanced insulin may be useful in reducing post-prandial glucose excursions.

The final approach is utilizing alternative routes of administration. Intradermal administration with micro needle infusion sets is under investigation and has preliminarily demonstrated to have faster onset of action than subcutaneous insulin. Inhaled* and intraperitoneal* routes of
administration are also under examination. While each of the aforementioned approaches has promise, they each raise specific concerns. None of the approaches described has resulted in enhanced clinical efficacy or has been tested in closed loop systems. It is possible that a combination of two or more methods may prove to be successful.

**We** might add that while smoother basal insulins may likely provide an important advantage, we have concerns about dosing these any less frequently than once daily given potential negative impact on compliance. Also, inadvertent overdoses may take that much longer to clear. On the rapid side of the insulin issue, our question might be whether the currently available analogues are quick enough for clinical use. That is, is a slight increase in the onset of action going to necessarily affect either glycemic, to say nothing of clinical outcomes? We’ll know soon as more studies emerge.

In addition to developing insulins with unique pharmacokinetic profiles, researchers continue to study methods to optimize currently available products. Rosenstock and US colleagues (abstract 73-OR) examined the glycemic and non-glycemic (body weight) effects of 3 insulin regimens in uncontrolled patients (mean HbA1c 9.4%) with Type 2 diabetes on oral agents. Patients were randomized to receive twice daily premixed insulin (70% aspart protamine/30% aspart), basal glargine and single-dose prandial glulisine, or basal glargine and prandial glulisine (stepwise up to 3 daily doses). Patients were titrated to a FPG <100 mg and assessed at 60 weeks. Changes in HbA1c were similar for the 3 regimens (-1.8% pre-mixed, -2.2% glargine + one prandial dose, -2.3% glargine + multiple prandial doses). FPG was higher in the pre-mixed group versus glargine, but was similar between both glargine-based regimens. Weight gain was similar in all three groups and paralleled insulin dose. Confirmed symptomatic hypoglycemia (<50 mg/dl) was significantly greater in the pre-mixed insulin group with a rate ratio of 0.43 (p<0.001) versus glargine/single prandial dose of 0.46 (p<0.001) versus glargine/multiple dose prandial. The investigators suggested, that when comparing pre-mixed insulin to basal-bolus with glargine and 1-3 doses of prandial glulisine, hypoglycemia occurs less frequently and FPG is significantly (p<0.001) lower with the glargine regimens. Increase in body weight occurs, however, regardless of regimen and is proportional to overall insulin dose. We note that covering simply the largest meal of the day with a rapid analogue is a technique that makes some sense, particularly in patients unwilling to undertake a more classical (and complicated!) QID basal-bolus regimen. Given the findings of Hirsch et al., using a premixed digludec-glulisine combination, one could conceivably provide reasonable insulin coverage—a step beyond basal alone—but still with one injection per day.

**Zisman** and colleagues from the US addressed the issue of when prandial insulin should be added in patients managed on basal insulin therapy. They hypothesized that basal insulin therapy should parallel hepatic glucose production, which would in turn maintain a narrow blood glucose range, specifically at night. Once the difference in bedtime and morning values increases, this suggests maximum titration of basal insulin has been reached and prandial doses may be needed to further improve glycemic control. He termed this the BeAM (difference between Bedtime and AM glucose) factor. (For example, a patient awakens with a blood glucose [BG] of 133 mg/dl. By the time he retires that evening, his BG has climbed to 203 mg/dl. His BeAM is the difference or 70.) Utilizing pooled data from 6 randomized trials (n=1,666) involving glargine and prandial insulins in patients titrated to FPG <100 mg/dl, data from insulin initiation to week 24 were analyzed. The relationship between a potential BeAM factor and HbA1c was examined using Pearson’s correlation coefficient and ANCOVA. This was repeated for FPG (Table 13). A BeAM factor of 55 mg/dl or greater was established as the point at which patients may benefit from the addition of prandial insulin to the regimen. Of course, the presenter recognized that prospective trials are needed to validate this method. Despite considerable gains in fine-tuning insulin regimens, adherence to therapy remains a consistent problem for patients and clinicians. The GAP (Global Attitudes of Patients and Physicians

### Table 14. Factors Associated with Adherence to Insulin Therapy

<table>
<thead>
<tr>
<th>Psychosocial Factors</th>
<th>Regression Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction with insulin therapy</td>
<td>-0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Barriers to insulin adherence</td>
<td>0.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adherence perceived as important</td>
<td>-0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Injections perceived to affect lifestyle</td>
<td>0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Success of non medication regimen adherence</td>
<td>-0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Injections perceived as painful</td>
<td>0.03</td>
<td>ns</td>
</tr>
<tr>
<td>Injections perceived as easy</td>
<td>0.01</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Patient Reported Factors** (in those who report ≥1 monthly omission/non-adherence, n=530)

- Too busy: 19.1%
- Traveling: 17.0%
- Skipped meal: 15.8%
- Stress or emotional problems: 11.5%
- Embarrassing to inject in public: 10.6%
- Challenging to take at same time every day: 10.6%
- Forgot, too many injections, avoid weight gain, regimen too complicated, painful, asleep, hypoglycemia: <10%

### Table 13. Relationship Between HbA1c and BeAM* Factor at Week 24

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>BeAM Factor, mg/dl, LS Mean (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7%</td>
<td>38.4 (1.9)</td>
<td>n/a</td>
</tr>
<tr>
<td>7 &lt; HbA1c ≤7.5%</td>
<td>46.3 (3.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>7.5 ≤ HbA1c ≤8.0%</td>
<td>51.3 (3.5)</td>
<td>0.0007</td>
</tr>
<tr>
<td>HbA1c ≥8.0%</td>
<td>58.8 (3.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*BeAM = Blood glucose difference between Bedtime and AM measures that indicates need to begin prandial insulin therapy in patients maintained on basal insulin; FPG=fasting plasma glucose.
in Insulin Therapy) investigators, Peyrot and international colleagues reported on factors associated with insulin regimen adherence (abstract 830-P). Adult patients (n=1,530) with Type 1 (12%) and Type 2 (88%) diabetes from 9 countries (US, Europe, and Asia) were queried via telephone interviews about insulin adherence and omission of injections. Over one-third of patients reported non-adherence (omission of insulin injection ≥ 1 day) during the previous month. Factors associated with lack of adherence were identified via multiple regression analysis and ANCOVA. Older age (p=0.001) and Middle Eastern origin (p<0.001) were associated with less adherence, as was frequent hypoglycemia (p=0.004). Multiple psychosocial factors were examined as well (Table 14). These data suggest that flexibility of an insulin regimen may be preferential when managing patients. Also, patient education, as with all medications and health conditions, is likely to be very important in this regard.

Optimizing use of insulin therapy continues to be a major research focus at international diabetes meetings. This encompasses multiple factors—ranging from the development of agents with more desirable time action profiles, to assessing patient factors that influence outcomes, to clinical tools that enable the practitioner to enhance the safety and efficacy of this important therapy.

Frontiers of Monitoring Technology

Current intensive management of diabetes hinges on repeated blood glucose testing, which causes discomfort, leading to compliance issues, and is expensive (refer to “SMBG is Costly Component of Treatment Costs for Insulin-Treated Diabetes Patients”, page 22). It therefore comes as no surprise that novel, less invasive monitoring methods are under intensive investigation, some presented at this week’s ADA Scientific Sessions.

I Only Have Eyes For You

Hasslacher and German coworkers performed a 9-month study of an ocular mini insert (OMI) (Eyesense),* which was subconjunctivally implanted under local anesthesia in 28 insulin-dependent diabetes patients (20 Type 1; 8 Type 2) (abstract 237-OR). The OMI contains a glucose-binding lectin dispersed throughout a hydrogel as well as competitive-binding fluorophore; glucose-dependent fluorescence is measured by a small hand-held fluorophotometer. Six patients spontaneously lost the OMI without any local complications. The prevalence of working OMI s 1, 3, 6, and 9 months after implantation was 100%, 88%, 74%, and 50%. Corresponding mean average relative error (MARE) was 18%, 27%, 28%, and 28% at these time points. At the end of the observation period, 40% of the working OMI s had high accuracy (MARE <20%) and 70% had fair accuracy (MARE <30%). The reason for the time-dependent decreased function of the OMI s was a thin encapsulation of the implant as detected by ophthalmological examination and confirmed by histological examination. With regard to tolerance, most patients developed a small subconjunctival hemorrhage and minor foreign body sensation immediately after implantation, which disappeared within a few days. Eight patients developed mild conjunctivitis, and 1 patient had prolonged wound healing that was successfully treated with local agents. Taken together, the study showed the ocular implant to be reasonably well tolerated. However, more than 20% of the OMI s did not stay in place over the study, and the majority of the working OMI s only had fair accuracy 9 months after implantation. The investigators suggested that encapsulation of the OMI may be prevented by special coatings in the future. Clearly, considerable technical issues need to be worked out with this device.

You Take My Breath Away

Minh et al. from California studied breath analysis of exhaled volatile organic compounds* (VOCs) as an alternative, non-invasive technique for glycemic testing (abstract 875-P). Eight Type 1 diabetes patients (5 female, mean age 25.8±1.7 years) and 17 healthy subjects (9 female, mean age 28.0±1.0 years) underwent 30 4-hour studies in which IV dextrose/insulin infusion was used to induce glycemic fluctuations (1 hour baseline, 2 hour hyperglycemia-hyperinsulinemia, 1 hour euglycemia-hyperinsulinemia). Breath, room air, and blood samples were simultaneously collected at 12 time points. Concentrations of VOCs were determined by gas chromatography and matched with direct plasma glucose measurements. Multi-linear models were developed to reconstruct plasma glucose concentrations for each subject; 2 groups of 4 gases (Cluster A: acetone, methyl nitrate, ethanol, ethyl benzene; Cluster B: 2-pentyl nitrate, propane, methanol, acetone) were used as covariates for the models, each resulting in strong correlation with direct measurements (0.883 and 0.869, respectively) across 300 samples. Using Parkes’ Consensus Error Grids, 286/290 and 293/295 predictions fell into Zone A or B using Clusters A and B, respectively (Figure 9).

Figure 9. Parkes Consensus Error Plot Grid of Predicted (from VOC in Breath) vs. Measured Blood Glucose

Plasma glucose predicted from Clusters A and B are plotted against direct measurements for 30 visits (Type 1 and healthy subjects) on Clarke Error Grids.
The grid is a scatterplot modeled after the original Clarke Error Grids, which were developed in the 1980s to correlate one form of glucose monitoring results with another (i.e., a standard), often used in the analysis of continuous glucose sensors. In the updated version, the grid is divided into zones signifying the degree of risk posed by the degree of correlation between the two methods. Zone A represents good correlation—which would have no effect on clinical action. Zone B values would result in altered clinical action, but with little or no effect on clinical outcome. Zone C represents altered clinical action, which is likely to affect clinical outcome. Zone D consists of values leading to altered clinical action, which could have significant medical risk. Finally, Zone E represents altered clinical action, which could actually have dangerous consequences. Accordingly, more readings in Zones A and B, as in the Clarke Error Grids, indicate a better system, as compared to the standard measurement of blood glucose. The results of Minh et al. therefore show that a non-invasive breath-based methodology can predict plasma glucose over a broad range of clinically relevant experimental conditions fairly accurately in both healthy subjects and Type 1 patients. If this methodology can be developed into portable, affordable, and clinically applicable devices, it might greatly facilitate diabetes screening and daily monitoring.

Transdermal Glucose Sensor

Caduff et al. from Switzerland conducted a study of a prototype, non-invasive glucose multisensor* (with fully integrated sensors and battery) that is topically applied (abstract 899-P).

Twenty Type 1 diabetes patients (mean age 38±13 years, BMI 24.1±3.0 kg/m², duration of diabetes 17±13 years, HbA1c 7.5±0.9%) performed 1 in-clinic training day of sensor use (A), followed by 10 days of home-use (B), another 3 days in-clinic (C), then nearly unrestricted use in daily life conditions (D), performing a total of 753 home-use days. Data from periods A, B and C were used to generate a global model, which was prospectively applied to data from period D for external validation using a single blood glucose value for calibration (baseline adjustment) at the beginning of the study day. The model yielded a mean absolute relative difference (MARD) of 35.4%. Clarke Error Grid analyses showed 86.6% in regions A+B, 0.6% in C, 12.1% in D, and 0.4% in E. Some patients experienced skin sensitization, particularly in the beginning of home-use, which the investigators suggested could be reduced or eliminated with retraining and fine-tuning of multisensor attachment. As a prototype, the system may be worth pursuing, but there are obvious concerns here about accuracy. Clearly, more study is needed on this and other transdermal glucose sensors. If they are found to be more accurate and reliable in the future, this could represent a major advance in diabetes care.

1,5 Anhydroglucitol Testing in Type 1 Diabetes?

Glycomark® is an approved test for the measurement of 1,5 anhydroglucitol (AG) concentration in plasma, which is decreased in diabetic patients compared to healthy volunteers (Akanuma et al., Diabetes 1981). Lower values correlate with worse post-prandial glucose control, and the test is gaining in popularity for the assessment of how to best target therapy. 1,5-AG is widely found in all foods and is normally ingested in the diet. 1,5-AG is not metabolized and maintains a relatively constant concentration in the blood. It is filtered by the kidney and reabsorbed back into the bloodstream in the proximal tubule of the nephron. In diabetes, when BG exceeds 180 mg/dl the reclamation capacity of the kidney for glucose is exceeded and glucosuria occurs. Simultaneously, 1,5-AG reabsorption is blocked and more of it enters the urine, quickly dropping the blood concentration. Duran-Valdez et al. from New Mexico compared 1,5-AG to other glucose indices in Type 1 diabetes patients (abstract 903-P). One hundred and five studies were performed. A fasting blood sample was drawn for both HbA1C and 1,5-AG, then patients underwent 5 days of blinded Continuous Glucose Monitoring (CGM) with simultaneous capillary blood glucose measurements. There was no statistically significant correlation between 1,5-AG level and HbA1C ($r^2=0.007$), blood glucose ($r^2=0.03$), postprandial glucose AUC ($r^2=0.027$), or % time spent above 180 mg/dl ($r^2=0.008$). These findings call into question the value of this test in this population of patients.

Clearly, there is a lot of interest in newer methods for monitoring blood glucose in our patients with diabetes, both acutely and chronically. Currently available methods include SMBG, laboratory plasma glucose, HbA1c, other glycated proteins such as glycated albumin, fructosamine, 1,5-AG, and continuous interstitial glucose monitoring (CGM). Newer methods must show good accuracy and precision before they are likely to become commercially available.

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

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**SMBG is Costly Component of Treatment Costs for Insulin-Treated Diabetes Patients**

Self-Measured Blood Glucose (SMBG) is an essential part of treating and monitoring an insulin-based treatment regimen. Yeaw et al. from the US and Denmark used the IMS LifeLink Health Plan Claims Database (medical and pharmacy claims for >71 million patients from 102 health plans) to determine the real-life frequency and costs associated with SMBG in the US (abstract 1183-P). Patients included in the analysis had ≥2 prescriptions for insulin (from January 1, 2007 through June 30, 2009), had ≥18 months of complete data (6 months for baseline + 12 months for outcomes), had a diagnosis of Type 1 or Type 2 diabetes, were ≥4 years old, and used insulin continuously throughout the 12-month follow-up period. 74,936 patients met the selection criteria. The analysis demonstrated that SMBG (strips, lancets, etc.) constitutes 20% ($602 of $2,975) of the total annual diabetes-related pharmacy costs (strips, insulin, needles, oral anti-hyperglycemic agents, etc.). Relative cost of SMBG was 15% ($399 of $2,607) for patients using basal insulin only, compared with 22% for those requiring basal/bolus ($812 of $3,666), and 15% for those using pre-mixed insulin ($395 of $2,617). In conclusion, this study shows that the cost of SMBG is substantial relative to treatment costs for insulin users. Where possible, oral agent strategies and, conceivably, newer insulins with less frequent dosing considerations may result in cost savings related to less intensive glucose monitoring.

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Silvio E. Inzucchi, MD
Robert S. Sherwin, MD
Editors, Yale University,
New Haven, Connecticut
Prevalence of diabetes among older adults is rising rapidly. Currently, 1 in 5 adults over age 50 are diagnosed with diabetes, and this number is projected to increase to 1 in 3 by year 2050. Diabetes in the elderly poses serious financial burdens for individuals, for the healthcare system as a whole, and for the Medicare program in particular. Delivering effective, efficient, and affordable diabetes care for older adults is therefore of paramount importance. Yet, evidence is lacking with respect to best strategies and targets of care. A symposium on the burgeoning prevalence of diabetes in the elderly tackled these difficult issues.

Dr. Phillip Levin from Maryland described the many challenges physicians face making treatment decisions in older patients. The recent trials of intensive glucose control (ACCORD, ADVANCE, and VADT), which included many older individuals (mean age 60s), demonstrated that aggressive strategies to lower HbA1c do not improve cardiovascular and all cause-mortality—and may even worsen survival as shown in ACCORD. Therefore, the choice of a glycemic target must be individualized, taking into account the risks and benefits of additional glucose lowering patient by patient. Intensive glucose control has been associated with increased rates of hypoglycemia, which can lead to falls, fractures, possibly cardiac arrhythmias, and cognitive decline. On the other hand, less strict glucose control may lead to peripheral neuropathy and falls, increased susceptibility to infections, and cognitive aberrations due to uncontrolled hyperglycemia. Evidence is lacking as to the exact glycemic “sweet spot” that optimizes the benefits and minimizes the risks—and clinicians lack the evidence to guide them in counseling their patients.

Reflecting this uncertainty, professional societies differ in their recommendations for glycemic targets in older patients. The Veterans Administration/Department of Defense recommend HbA1c between 7% to 9%, depending on individual conditions, the American Geriatrics Society endorses a goal HbA1c <8%, and the American Diabetes Association suggests <7% for most adults, with less strict control in those with comorbidities and frequent hypoglycemia, and emphasizes individual target setting.

A recent retrospective cohort analysis of observational data performed by Elbert Huang (who chaired the session at the ADA) and coworkers (Huang et al., Diabetes Care June 2011) investigated the range of glycemic levels associated with the lowest rates of complications and mortality among older diabetic adults. The analysis involved 71,092 patients with Type 2 diabetes, aged ≥60 years, who were enrolled in Kaiser Permanente Northern California (2004-2008). The cohort (aged 71.0±7.4 years) had an HbA1c of 7.0±1.2%. The mortality curve had a U-shaped relationship with HbA1c; compared with HbA1c < 6.0%, mortality risk was lower for HbA1c levels between 6.0 and 9.0% and higher for HbA1c ≥11.0%. Risk of any endpoint (complication or death) became significantly higher at HbA1c ≥8.0%. These observational relationships between HbA1c and combined endpoints appear to support the American Geriatrics Society target HbA1c <8.0%, and suggest that HbA1c <6.0% may be associated with increased mortality risk. However, the analysis is based on observational data that do not take into account individual decisions made with respect to glycemic targets and the types of strategies used to achieve these targets.

Glucosuria has long been recognized as a consequence of hyperglycemia and is thought to occur at an estimated blood sugar threshold of 180 mg/dl, corresponding to HbA1c of 8% or greater. Dr. Lee from San Francisco and colleagues examined the relationship between glycemia and urinary incontinence in a large diverse cohort of older women with diabetes enrolled in the Northern California Kaiser Permanente (abstract 256-OR). The cohort included 6,026 women who responded to a survey question on urinary incontinence (response rate of 62%). Mean HbA1c preceding the survey was assessed as a predictor of urinary incontinence after adjusting
for age, race, education, income, BMI, parity, treatment for diabetes, duration of diabetes, and comorbidities. The characteristics of the women with \( (n=3,916) \) and without \( (n=2,110) \) urinary incontinence were similar with respect to age (mean, 59 years), HbA1c (7.5%), proportion treated with insulin (24%), proportion treated with oral anti-diabetes agents (77%), and proportion with parity \( \geq 3 \) (50%). Interestingly, there was no association between HbA1c level and the presence of urinary incontinence—in 67% of women with HbA1c <6% reported incontinence compared to 69% of those with HbA1c 6-7%, 71% of those with HbA1c 7-8%, 69% of those with HbA1c 8-9%, and 70% of those with HbA1c \( \geq 9 \). For individuals with incontinence, HbA1c above 9% was associated with more severe limitations, however. The investigators concluded that the presence of urinary incontinence was not associated with HbA1c levels in this observational study. Although glucosuria may be more common as a result of severe hyperglycemia and may lead to urinary frequency, the causal relationship between hyperglycemia and incontinence appears tenuous.

Since glycemic targets are not very well defined for older adults and polypharmacy poses serious risks, one might hypothesize that uncontrolled diabetes is rampant in the elderly. On the other hand, the use of HbA1c as a quality measure in clinical practice could potentially result in unnecessary or even harmful over-treatment in this group. To answer the question of what actually happens in clinical practice, Dr. Yeh from Johns Hopkins and colleagues analyzed cross-sectional data from the nationally representative NHANES study (2003-2008) of 876 adults age \( \geq 65 \) years who self-reported diagnosed diabetes (abstract 255-OR). After excluding individuals with missing HbA1c or creatinine levels, the final sample included 756 individuals with a mean age of 73, HbA1c 6.8%, 46% were men, 12% African American, and 5% Mexican American, and 66% had diabetes for over 10 years. Among these older diabetic patients, 63% had an HbA1c \( <7 \), 24% between 7-7.9%, and 13% \( \geq 8 \)—actually representing impressive glycemic control. Over 80% of these diabetic elders were treated with medications (39% sulfonylureas, 37% metformin, 19% thiazolidinediones [TZDs], and 17% insulin). One in 5 patients with an HbA1c \( <7 \) was taking multiple medications for diabetes—arguably, a practice that could result in more harm than good. If the glycemic target were raised from an HbA1c of 7% to 8%, the analysis predicted that about 50% (corresponding to 3.1 million) of older adults may be able to discontinue or simplify their diabetic regimen. Clearly, it is not possible to say, based on this data, whether such a change would actually result in better outcomes, but it provides provocative food for thought.

Caroline Blaum from the University of Michigan shared a geriatrician’s view of diabetes in the elderly to explore the next frontiers of diabetes care in this population. The presence of diabetes in older individuals is associated with multiple comorbidities, which add to the complexity of management. The nationally representative Health Retirement Study (HRS) study of adults over age 50 showed that diabetes is strongly associated with both prevalent and incident geriatric conditions. Cognitive impairment, falls, urinary incontinence, dizziness, and visual impairment are all more common in those with diabetes. Interestingly, as age increases, the strength of the association of diabetes with new geriatric conditions decreased. For example, for adults age 51-60 years with diabetes, the odds of developing new geriatric conditions is 1.96 times as large as the odds for those without diabetes developing new conditions. In contrast, for adults age 71-80 years with diabetes, the odds of developing new conditions is only 1.25 times greater.

By the time people with and without diabetes reach 80, the overall effects of aging and impact of other diseases reduce the differences between the two groups. Although the mechanisms underlying the development of geriatric conditions in adults with diabetes is not fully understood, it is clear that they contribute substantially to morbidity and functional impairment. These findings suggest that adults with diabetes should be monitored for development of geriatric morbidities at a younger age. If these conditions are recognized and appropriately managed, there could be improvement in symptoms but decreases in disability.

**But does diabetes management prevent geriatric conditions and disability (Figure 10)?** The direct answer to this question is not known, but observational data provide potential clues. Compared to 1996, older adults with diabetes (70+ years) in 2006 have more comorbid conditions. They also receive a greater number of preventative services—so it is quite likely that the increase in comorbidities results from greater recognition of diagnosis during more frequent contact with providers. However, older adults (ages 71-80) with diabetes have experienced no change in disability rates (defined based on the number of activity of daily living [ADL] dependencies) between 1995 and 2006. In contrast, disability rates among older adults without diabetes are thought to be decreasing overall. The lack of improvement in older diabetic patients suggests that improved glucose management is not necessarily having a beneficial impact on disability rates. Certainly, development and delivery of strategies that improve the quality of life, as well as survival, among older patients with diabetes are needed.

**The goals of diabetes care are to prevent complications.** This is the rationale for intensive and comprehensive management of the risk factors for these sequelae, such as high glucose levels, lipids, and blood pressure. However, the risk of diabetic complications has to be weighed against the risk of the therapies themselves. Another analysis based on the Kaiser Permanente data found that diabetic syndromes and hypoglycemia affect health-related quality of life as much as, or more so, than diabetes complications in older diabetic patients (Laiteerapong N et al., *Diabetes Care* 2011). This suggests that the current goals of diabetes care, particularly in older adults, need to carefully balance the risks and benefits of therapy to arrive at outcomes that are most important to individual patients.
There continues to be a lot of interest in optimal management strategies for hyperglycemia in the hospital, as exemplified by the dozens of abstracts at this year’s ADA Scientific Sessions discussing inpatient glucose control.

Shetty and colleagues reported on the updated insulin infusion protocol (IIP) at Yale-New Haven Hospital in Connecticut (abstract 156-OR). Their IIP has been in use since 2003, following the van den Berghe studies, initially targeting a blood glucose (BG) of 100-140 mg/dl, lowered to 90-120 mg/dl in 2005. It has been adopted by many hospitals around the country, because of its validated efficacy and safety with low hypoglycemia rates. However, because of the findings of the multicenter NICE SUGAR study in 2009—which raised the possibility of increased mortality if BG is lowered too aggressively (in contrast to the earlier single-site studies)—the protocol was adjusted to comply with new national guidelines. In response to a changing evidence base, the ADA along with the American Association of Clinical Endocrinologists (AACE) now recommend that glycemia be maintained between 140-180 mg/dl in the critical care unit, whereas previous recommendations suggested absolute euglycemia. The updated Yale IIP targets 120-160 mg/dl, with the intention to keep patients closer to the lower end of the ADA/AACE target range, as suggested in their 2009 consensus statement. Based on their prior experience, Shetty et al. had noted that patients’ BGs tended to cluster in the upper end of the specified range with Yale IIPs. In this study, 115 infusions were tracked. The mean age of the patients was 62±14 years, and 51% were male. The mean BMI was 31.8±9.3 kg/m². Almost two-thirds had preexisting diabetes. Their APACHE II score was very high at 24.4±7.5, which correlates to a mortality risk of at least 30-35%. The most common admission diagnoses were acute respiratory failure, sepsis, pneumonia, and ARDS; 80% required intubation. The patients’ severity of illness was underscored by their mean length of ICU stay of 19.5±24.8 days. The mean ±SD baseline BG was 306±90 mg/dl. Time to target BG was 8.3±5.7 hours; time on infusion was 95±104 hours. Once target BG was achieved, the mean BG was 156±23 mg/dl and the median BG was 150 mg/dl (IQR 127-180) (Figure 11). Hypoglycemia rates were low. Just 0.3% of BGs fell to <70 mg/dl and only 0.02% (1 per 5000) were <40 mg/dl. Dr. Shetty remarked that the ‘per patient’ severe hypoglycemia rate of 1.7% compares favorably to an average of 2.1% in standard treatment groups from published, large intensive insulin therapy trials in the ICU.

Marso and Missouri colleagues presented interesting data from a prospective, open-label, non-randomized study, using IV exenatide; a GLP-1 receptor agonist, in hyperglycemic (BG 140-400 mg/dl) patients admitted to their hospital with a primary cardiac diagnosis (abstract 275-OR). BGs were compared to benchmark data at their institution using two insulin infusion protocols, one targeting 100-140 mg/dl and a second more intensive one, targeting 90-120 mg/dl. Exenatide was administered by infusion to 40 patients (mean age 65 years, 83% male, 63% with acute coronary syndrome, and 75% with Type 2 diabetes). The admission BG was 199±53 mg/dl, as compared to 240±44 mg/dl in the more conservative insulin infusion group (p=0.02). Time to target (<140 mg/dl) was shorter with exenatide (4 vs. 9 hours, p<0.001). Moreover, exenatide patients were maintained more frequently within the target range than with insulin infusion, although this appeared to be predominately driven by the quicker time to target (Figure 12). Hypoglycemia rates were low in both groups and not statistically different. Drug-induced nausea, however, occurred in 20% of patients and 13% needed to discontinue the medication early. BG control was tighter with the more intensive insulin infusion protocol.

The notion of controlling glucose during acute coronary syndrome (ACS) dates back several decades. Although there are many biological theories as to why hyperglycemia should be avoided during acute cardiovascular events, the data in support of tight glycemic control in the CCU is limited. Daoud and Texas colleagues conducted a retrospective study of 1504 consecutively admitted patients undergoing CABG surgery between 2007-2009 (abstract 548-P). Post-operative BG was tracked for 48 hours and patients were divided into quartiles (Q) based on their overall glycemia (means, Q1-Q4: 132, 147, 163, and 199 mg/dl). Glucose levels correlated positively with hours in the ICU, length of total hospital and post-op ventilation time, and overall...
complication rates. Of course, observational data such as these could be biased by the underlying condition or characteristics of patients, which may be driving the hyperglycemia. Therefore, the conclusions of these investigators, that early hyperglycemia after CABG adversely affects multiple post-operative outcomes, is supported but not proven by their data.

A more mechanistic study was performed by Abdelmoneim et al. from Minnesota (abstract 380-PP) who examined coronary artery flow with contrast echocardiography in 15 healthy individuals (12 female, mean age 46±5 years, BMI 25.2±4.4 kg/m²; fasting BG 99±6 mg/dl, HbA1c 5.3±0.3%). The subjects underwent a 2-step pancreatic clamp with somatostatin, glucagon, and growth hormone infusions. Insulin was then infused to mimic postprandial levels, and IV dextrose was administered to maintain euglycemia for 4 hours, followed by a period of hyperglycemia (~230 mg/dl). Myocardial contrast echocardiography was used to assess coronary flow reserve (CFR) during the final 30 minutes of each glucose step. The data are shown in Table 15, which dichotomizes patients based on how much glucose infusion they required to maintain euglycemia (GIR or glucose infusion rate)—i.e., how insulin sensitive vs. resistant they were. CFR was shown to diminish significantly in the setting of hyperglycemia as well as in those with underlying insulin resistance.

The avoidance of hypoglycemia in the hospital is important. Galati and US colleagues theorized that trends in BG monitoring could predict severe hyperglycemia in inpatients. In the AACE/ADA inpatient hyperglycemia consensus statement, reassessment of glucose-lowering therapy once the BG falls <100 mg/dl was advised. So, these investigators decided to examine BG levels in diabetic patients hospitalized on general medical/surgical wards at their hospital over a period of 1 year (abstract 887-P). During this time, 480 patients experienced at least one BG <50 mg/dl (defined as ‘severe hypoglycemia’). Of these, 365 were on insulin injections or a sulfonylurea drug with their event occurring at least 2 days after admission. All BG readings (mean, 8.2) during the antecedent 48 hours were then categorized into 5 ranges: <60, 60-69, 70-79, 80-89, and 90-99 mg/dl. For a control group, Galati chose randomly selected diabetic patients (n=2,387) without severe hypoglycemia (mean BG number, 6.5) and who were contemporaneously hospitalized. By chi-square analysis, the frequency of antecedent mild hypoglycemia was nearly 2-fold higher in those individuals who later experienced a severe episode (21.7% vs. 11.3% of BGs, p<0.0001), with the differences between the patient cohorts widening below the 90 mg/dl mark (Table 16). In addition, a greater proportion of patients with severe hypoglycemia (61.1%) had BG <100 mg/dl in the 48-hours preceding their hypoglycemia event compared to those without (37.6%; p<0.0001). While further analysis is required on this preliminary data set, the investigators concluded that hospitalized patients who experience severe hypoglycemia frequently have low-normal to mildly hypoglycemic BG readings in the 48 hours preceding the event. Accordingly, having a BG value <100 mg/dl may serve as an important trigger to consider adjustment of the glucose lowering regimen, as recommended by AACE and ADA.

As inpatient diabetes specialists further refine their approaches to the management of hyperglycemia in the hospital, we look forward to the development of safer and more effective strategies.

Several approaches to reducing hyperglycemia in patients with Type 2 diabetes exist. A common one is to improve insulin resistance, a fundamental component of the pathogenesis of this disease. Advantages of using insulin sensitizers (as opposed to drugs that increase insulin supply) include the avoidance of hypoglycemia and the potential for greater durability of effectiveness, as insulin demands from the pancreatic ß-cell are reduced. The 2 major sensitizer classes available are the biguanides, which primarily improve insulin response in the liver, and the thiazolidinediones (TZDs), which exert their predominant effects in skeletal muscle and adipocytes. Cardiovascular benefits have been proposed with both of these classes since both modestly improve lipid profiles, hyperinsulinemia, and inflammatory markers; TZDs also reduce blood pressure to some degree.

Table 16. Incidence of Hypoglycemia by Category of Blood Glucose

<table>
<thead>
<tr>
<th>BG Ranges* (mg/dl)</th>
<th>Severe hypoglycemia (2,970 BGs)</th>
<th>No severe hypoglycemia (15,576 BGs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-90</td>
<td>78.3%</td>
<td>88.7%</td>
</tr>
<tr>
<td>90-89</td>
<td>5.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>80-79</td>
<td>5.0%</td>
<td>2.8%</td>
</tr>
<tr>
<td>70-79</td>
<td>4.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>60-69</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>&lt;60</td>
<td>3.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

*Antecedent in patients with severe hypoglycemia; random in patients with no severe hypoglycemia.

<table>
<thead>
<tr>
<th>GIR (&lt;5mg/kg/min) (n=8)</th>
<th>GIR (≥5 mg/kg/min) (n=7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5±4.7</td>
<td>23.7±4.0</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>0.94±0.15</td>
<td>0.90±0.11</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>139.1±12.9</td>
<td>91.6±13.8</td>
</tr>
<tr>
<td>Triglyceride/HDL ratio</td>
<td>2.41±0.25</td>
<td>1.47±0.73</td>
</tr>
<tr>
<td>CFR at euglycemia</td>
<td>2.77±1.1</td>
<td>3.85±1.69</td>
</tr>
<tr>
<td>CFR at hyperglycemia</td>
<td>1.80±0.91</td>
<td>2.41±1.55</td>
</tr>
</tbody>
</table>

CFR=coronary flow reserve, GIR=glucose infusion rate.
metformin monotherapy versus diet alone. Epidemiological studies have also demonstrated fewer cardiovascular complications with metformin than in patients using sulfonylurea drugs. The TZD story is more complex, with direct vascular effects, which include the suppression of atherosclerosis, proposed from activation of the nuclear transcription factor, PPAR-γ. However, rosiglitazone was removed from the European market last year and is prescribed in the US with great restriction because it has been implicated in increasing myocardial ischemic events. The other TZD, pioglitazone, is either neutral or has a modest benefit on cardiovascular complications, but, as with rosiglitazone, increases the risk of heart failure from increased renal sodium retention.

The only trial that has adequately compared the two major glucose-lowering approaches in high-risk patients was BARI-2D. This found no overall cardiovascular benefit in stable coronary artery disease patients randomly assigned to either an insulin sensitizer regimen, involving metformin and, if needed, rosiglitazone, versus an insulin provision regimen, focused on sulfonylureas plus, if needed, insulin (see Diabetes 2009, volume 19, page 29). However, in a prespecified subgroup analysis, those patients who were additionally randomized to urgent revascularization and who underwent coronary artery bypass surgery had a strong trend toward less major adverse cardiovascular events if assigned to insulin sensitizer therapy (18.7% vs. 26.0% with insulin provision therapy, p = 0.066). In sum, the cardiovascular implications of insulin sensitizing drugs remains incompletely understood.

These two drug classes were the focus of many presentations at this week’s Scientific Sessions. Several prior trials have demonstrated a benefit on the objective measurement of carotid and coronary atherosclerosis from pioglitazone in patients with Type 2 diabetes and impaired glucose tolerance. Saremi and US colleagues had previously shown in the diabetes prevention trial, ACT-NOW, that patients with impaired glucose tolerance randomized to pioglitazone not only experienced a marked reduction in the development of diabetes compared to placebo (-72%) but also less progression of carotid atherosclerosis as measured by ultrasound (carotid intima-media thickness, CIMT). In the current analysis, the investigators sought to determine whether this effect could be explained by the TZD’s effects on conventional cardiovascular risk factors or measures of insulin sensitivity (abstract 36-OR). Of the original 602 study participants, 393 had 2 to 3 serial CIMT scans (pioglitazone, 194; placebo 199; mean age 53 years; BMI 33.2 kg/m²; HbA1c 5.4%; 54% female; 55% non-Hispanic white). Baseline cardiovascular risk factors were equivalent between the two treatment groups. During follow-up, however, patients assigned to pioglitazone experienced improved HDL-cholesterol levels, fasting and 2-hour plasma glucose (during an OGTT), and the calculated insulin sensitivity index of Matsuda (ISI), but with increases in BMI. After adjustment for age, gender, ethnicity, and study site, pioglitazone therapy was associated with a 36% reduction in CIMT progression. With further adjustment for cardiovascular risk factors (smoking, BMI, blood pressure, HDL-C, ISI, use of statins and anti-hypertensive drugs), the difference was essentially the same at -35% (mean CIMT 0.0054±0.0012 vs. 0.0089±0.0011 mm/year). The investigators concluded that any beneficial effect of pioglitazone on carotid atherosclerosis could not necessarily be explained by improvements in metabolic risk factors, suggesting potential direct vascular effects.

Table 17. Meta-Analysis of Mortality in Patients with Type 2 Diabetes and Heart Failure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Metformin Events</th>
<th>Metformin Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inzucchi 2005</td>
<td>93</td>
<td>406</td>
<td>768</td>
<td>2,184</td>
<td>0.92 (0.71, 1.19)</td>
<td>12.7%</td>
</tr>
<tr>
<td>Masoudi 2005</td>
<td>460</td>
<td>1861</td>
<td>4,345</td>
<td>12,069</td>
<td>0.87 (0.77, 0.98)</td>
<td>34.0%</td>
</tr>
<tr>
<td>Eurich 2005</td>
<td>29</td>
<td>208</td>
<td>200</td>
<td>773</td>
<td>0.66 (0.45, 0.98)</td>
<td>6.1%</td>
</tr>
<tr>
<td>Shah 2010</td>
<td>22</td>
<td>99</td>
<td>112</td>
<td>302</td>
<td>0.79 (0.36, 1.73)</td>
<td>1.6%</td>
</tr>
<tr>
<td>MacDonald 2010</td>
<td>155</td>
<td>376</td>
<td>733</td>
<td>1,306</td>
<td>0.65 (0.48, 0.87)</td>
<td>10.0%</td>
</tr>
<tr>
<td>Evans 2010</td>
<td>137</td>
<td>205</td>
<td>183</td>
<td>217</td>
<td>0.60 (0.37, 0.98)</td>
<td>4.0%</td>
</tr>
<tr>
<td>Aguilar 2010</td>
<td>232</td>
<td>1,437</td>
<td>285</td>
<td>1,437</td>
<td>0.76 (0.62, 0.92)</td>
<td>18.8%</td>
</tr>
<tr>
<td>Roussel 2010</td>
<td>116</td>
<td>1,220</td>
<td>419</td>
<td>2,790</td>
<td>0.69 (0.53, 0.89)</td>
<td>12.7%</td>
</tr>
<tr>
<td>(Total 95%-CI)</td>
<td>5,812</td>
<td>2,1078</td>
<td>2,1078</td>
<td>2,1078</td>
<td>0.78 (0.70, 0.86)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 8.83, df=7 (p = 0.26); r² = 21%
Test for overall effect: Z=4.81 (p < 0.0001)

*Study risk ratios represent published multivariate adjusted risk estimates. The pooled estimate reflects the overall risk estimate of metformin compared to controls after multivariate adjustment for age, sex, comorbidities, drug therapies, ± clinical data as reported in original publications.

*Eurich and Canadian collaborators conducted a systematic review and meta-analysis of the safety and effectiveness of metformin in Type 2 diabetes patients with heart failure (abstract 953-P). They searched for controlled studies of metformin that evaluated mortality and hospitalizations. Adjusted risk estimates were abstracted and pooled using random effects generic inverse variance weighting. From over 12,000 initial citations, only 8 cohort studies met their inclusion criteria and were deemed to be of sufficient quality. Metformin (Table 17) was associated with reduced mortality compared to control agents (mostly sulfonylureas) (pooled risk estimate 0.78, 95% CI 0.70-0.86; p < 0.001). Metformin was also associated with a modest reduction in all-cause hospitalization.
(0.92, 95% CI 0.87-0.98; p = 0.01). Metformin therefore appeared to be safer and more effective than other agents in diabetic heart failure patients. The investigators suggested that it might actually be the drug of choice in this population. Of note, in 2007, the US FDA changed the prescribing guidelines for metformin, such that the drug is no longer contraindicated in those with stable heart failure. Of course, if heart failure is unstable or progressive, or if associated with significant renal insufficiency, metformin should not be used, given the risk of lactic acidosis.

Metformin is not only the most commonly prescribed anti-hyperglycemic agent for Type 2 diabetes in the US, but it is also gaining in popularity as a drug for diabetes prevention. Its safety and efficacy were confirmed in the Diabetes Prevention Program (DPP). This trial demonstrated a 31% reduction in the incidence of diabetes in a large group of high-risk patients with impaired glucose tolerance assigned to metformin treatment (although such an effect was only half of what occurred in the group randomized to aggressive lifestyle intervention). DPP investigators led by Edelstein this week reported on long-term tolerability and safety of metformin in this trial and its follow-up observational study, DPPOS (abstract 254-OR). The double-blind portion of the DPP lasted on average 3.2 years, with DPPOS adding an additional 6 years in an open-label design. In the DPP, gastrointestinal side effects were nearly 10-fold as common in those participants given metformin (9.5% vs. 1.1%, p < 0.001). Such symptoms decreased over time, however, and in DPPOS, GI complaints were similar between groups. No hypoglycemia or lactic acidosis was reported in either. A slight reduction in hemoglobin/ hematocrit was observed in metformin patients, of uncertain significance. The investigators concluded that metformin is an extremely safe intervention in pre-diabetic patients to prevent the further deterioration of hyperglycemia.

Metformin–associated lactic acidosis was a topic of study for Frid et al. from Sweden (abstract 364-OR). They studied 5,408 patients in Malmö, Sweden who had three prescription fills for metformin during both 2008 and 2009, assessing their estimated glomerular filtration rate (GFR) by laboratory testing obtained, and their frequency of hospitalization for lactic acidosis. Individuals were stratified into various age groups (<60, 60-69, 70-79, and 80-89 years). The average eGFR in the three oldest groups were 87, 76, and 66 ml/min/1.73 m² for metformin-treated vs. 77, 66, and 56 ml/min/1.73 m² in controls, respectively (p < 0.001 for all comparisons). (Metformin-treated patients tend to have a higher eGFR than control, non-diabetic patients, likely due to selection bias.) In the oldest group, 38% had a highest eGFR <60 and 66% had the lowest eGFR of <60. Three cases of lactic acidosis were identified in patients on metformin, with respective eGFRs of 41, 790, and one unknown. None of these individuals was older than 79 years.

The investigators concluded that metformin associated lactic acidosis is rare, despite many patients with reduced renal function using this agent. Recently, metformin’s relatively strict renal contraindications in the US have been called into question since they may unnecessarily exclude a large number of older individuals from benefiting from this otherwise safe and effective medicine (Lipska et al., Diabetes Care 2011;34:1431). Smiley et al. from Atlanta were interested in the effect of pioglitazone in young, African American patients with hyperglycemic crisis (abstract 369-OR). Of 90 patients recruited, 35 had DKA (22 men, 13 women, mean age 43 ± 11 years, BMI 40 ± 12 kg/m², admission blood glucose 639 ± 259 mg/dl) and 55 had severe hyperglycemia (31 men, 24 women, age 44 ± 10 years, BMI 38 ± 9 kg/m², BG 645 ± 238 mg/dl). 73% of those with DKA and 59% of those with severe hyperglycemia were able to discontinue insulin within 12 weeks of presentation. 20 of the DKA patients and 24 of those with severe hyperglycemia who had stopped insulin were subsequently randomized to 30 mg/day of pioglitazone vs. placebo and followed for 36 months after their ‘remission’. β-cell function and insulin sensitivity were measured at baseline and within 1 week of stopping insulin, and OGTTs were performed upon the discontinuation of insulin and again at 3 and 6 months during the remission phase. ‘Relapse’ was defined as fasting blood glucose >130 mg/dl or a random blood glucose >180 mg/dl x 2 and a HbA1c >7.0%.

At baseline, the two groups were similar for age, gender, BMI, HbA1c, duration of insulin therapy, and GAD antibody status. Pioglitazone significantly reduced the number of patients with hyperglycemia relapse (32% vs. 68%, p = 0.03). In addition, remission proved to be longer in the pioglitazone group (809 vs. 162 days, p = 0.01). This was associated with better β-cell function and improved insulin sensitivity by OGTT. So, pioglitazone in this small, single-center study appeared to have a significant effect on preventing recurrence of hyperglycemia and in inducing a prolonged, insulin–free interval in overweight African American patients with recent hyperglycemic crisis. These data underscore the importance of insulin resistance in this cohort of patients whose initial severe hyperglycemia belies their actual residual insulin secretory capacity.

Hainefeld and German colleagues tested the combination of both insulin sensitizers, metformin plus pioglitazone, in 121 patients with Type 2 diabetes already taking insulin, with baseline HbA1c 6.5-8.5% (abstract 1156-P). The mean age was 63 ± 7.5 years, BMI 32 ± 5.3 kg/m², and HbA1c 7.3 ± 0.5%, and insulin glargine dose 36 ± 21 units. After a run-in phase of glargine monotherapy, patients were randomized to metformin 850 mg BID, pioglitazone 15 mg BID, or 30 mg of pioglitazone and 1.7 g of metformin. A variety of novel cardiovascular risk markers were measured. Hypoglycemia rates were similar, but the pioglitazone patients had more weight gain and edema. Pioglitazone reduced MMP-9 and CRP levels and increased insulin sensitivity and adiponectin levels, independent of glycemic control. However, the triple combination had no further benefit on CVD risk markers.

Several side effects of TZD medications are well known, including weight gain, edema, and in predisposed individuals, heart failure, as well as bone fractures in women. One potential adverse event associated with this drug class is macular edema—today, an association based mainly on case reports. Idris et al. from the UK assessed 103,368 Type 2 diabetes patients without macular edema at baseline, dividing them into those treated versus not treated with a TZD (abstract 135-OR). At one year the incidence of macular edema was 1.3% among TZD users and 0.2% among non-users (OR 5.78, 95% CI 4.1-7.9%). In Cox models, controlling for potential confounders (HbA1c, age, gender, blood pressure, lipids, and other medications), the OR fell to 3.3, but remained significant (95% CI, 2.2-4.9). The investigators advised avoiding this drug class in those at high risk of sight-threatening macular edema.

Looking toward the future, the insulin sensitizer category of anti-hyperglycemic drugs may also include dual and pan-PPAR agonists,* 11-β-hydroxysteroid dehydrogenase (HSD) inhibitors,* and the protein tyrosine phosphatase (PTB) 1B inhibitors.* The efficacy and side effect profiles of these agents remain to be determined. Very clearly, careful safety assessments will be crucial throughout the developmental stages of these compounds.

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

**Editors, Yale University, New Haven, Connecticut**
The association between diabetes and insulin is complex. Patients with diabetes are at increased risk for several malignancies, including cancers of the uterus, breast, pancreas, bladder, and colon. There are several biologically plausible mechanisms that link these conditions, including shared risk factors (e.g., obesity), hyperglycemia, the insulin/IGF-axis, and chronic inflammation. More recently, several anti-hyperglycemic medications have been linked to cancer risk as well. The growing use of pharmacoepidemiology plays a role in drug regulation policy, and it is critical for physicians to understand some nuances in interpreting these studies.

In September 2009, a collection of observational studies published in Diabetologia raised the concern that insulin glargine may contribute to the incidence of cancer in people with diabetes. One of these studies also indicated that metformin may be associated with a decrease in cancer rates. While these studies have been critiqued for the inherent weaknesses of retrospective analysis and mining large databases for findings, they did initiate a flurry of inquiry into the potential link between diabetes, its therapies, and cancer. Over the last three years, investigators have examined large clinical databases, such as national healthcare registries, or existing data from prior clinical studies involving diabetes medications. This task is challenging because the clinical studies were not designed to examine cancer outcomes and have a relatively short duration of follow up. The healthcare registries contain information marred by the complexities of daily clinical care, in the absence of a controlled setting. However, the utility of observational studies is immediate hypothesis generation. Until more definitive studies such as randomized control trials (RCT) are complete, we are reliant on such data and meta-analyses to serve as an initial screen for associations between medical therapies and cancer outcomes.

In a Symposium entitled “The Pharmacoepidemiology of Diabetes—Defining Unexpected Risks and Benefits,” Samy Suissa, PhD an epidemiologist from McGill University, critiqued many of the recent studies. The majority of observational studies actually have significant methodological concerns. One problem is “immortal time bias” when, for instance, “ever users” of metformin are statistically ranked equal to long-term users of metformin. In this way, metformin is given an advantage in demonstrating a protective effect from cancer incidence. Since the outcome conclusions are dependent on the way data are analyzed, he asserts that “immortal time bias” likely accounts for much of the positive effect seen in the observational analyses involving metformin. When time-dependent bias is corrected for, metformin no longer demonstrates any protective effect.

In a related poster presentation, the Metformin Trialists’ Collaboration (abstract 950-P) assessed 2,140 studies to identify 12 RCT’s of metformin versus active glucose-lowering therapy or placebo/usual care that contained data on cancer incidence. Each study was also required to have ≥500 patients and a follow-up period of at least one year. Nine RCT’s had relative risk (RR) data for a total of 407 cancers diagnosed during 50,055 person-years of follow-up. The summary RR for incident cancer in patients randomized to metformin versus any comparator was 1.07 (95% CI 0.86-1.32; I²=29%). There was no statistical difference (p=0.21) between RR’s in a subgroup analysis of metformin versus either placebo-controlled or active comparator trials. The investigators concluded that their data do not support the hypothesis that metformin lowers cancer risk.

With regard to insulin glargine, Dr. Suissa conducted a study of the United Kingdom General Practice Research Database (GPRD) involving 15,227 women over 40 years old with Type 2 diabetes on insulin therapy. 4,579 women received glargine, while 10,648 were on other insulins. 246 cancers of the breast were diagnosed during the 8 years of follow-up. He differentiated between ever users versus prevalent users of glargine, and also adjusted for duration of insulin use and duration of diabetes. For breast cancer risk, he found that all users of glargine had a RR
of 1.0 (95% CI 0.7-1.4) versus other insulins, indicating no difference. However, in women using glargine for more than 5 years, the breast cancer RR was more concerning at 1.8 (95% CI 0.8-4.0), although still not statistically significant. In prevalent users of glargine for more than 5 years, the RR increased to 2.7 (95% CI 1.1-6.5), which was significant and sufficiently powerful to require further study. Just last week, another headline made its way to this discussion. It was reported by Lewis and colleagues in Diabetes Care (2011; 34: 916-22) that the incidence of bladder cancer may be higher in users of pioglitazone for more than 2 years. The investigators employed a database from Kaiser Permanente. Overall, there appeared to be no significant relationship, with the hazard ratio (HR) for bladder cancer in pioglitazone users at 1.2 (95% CI 0.9-1.5)). However, in those having had >24 months of therapy, there was an increased risk (1.4 [1.03-2.0]).

Similarly, a recent epidemiological study by France’s health insurance agency reported 2 weeks ago concerned 1.3 million patients taking antidiabetic medications between 2006 and 2009. Of these, 155,000 persons took pioglitazone. The study found an adjusted HR of 1.22 (95% CI 1.05-1.43) for bladder cancer among those on the TZD. This report actually led to a suspension of pioglitazone sales in France, and the Germans quickly followed suit. The issue is currently under review by the European Medicines Agency (EMA), which serves as a sort of FDA in the EU. We would point out, however, that while further study is certainly needed, the ability for any drug to cause cancer within a time frame of 2 years would be unusual. Indeed, most true carcinogens exert their effects over a period of 15-20+ years. The drug that is known to be most carcinogenic in bladder, namely cyclophosphamide, has a latency period of at least 8 years. So, the findings of Lewis and the French group may reflect unmeasured confounders. For example, since diabetes itself is associated with bladder cancer, and since pioglitazone tends to be used later on in the disease course than other medications, the investigators could be uncovering a selection bias.

Pharmacoepidemiology has an important role in initiating investigation of links between diabetes, its therapies, and cancer. However, results from observational studies must be interpreted with caution due to the inherent weaknesses of the data sources and the potential biases of the methods used to analyze them. More research with higher levels of evidence remains to be done to dissect out the complexities of the relationship between diabetes and cancer.
from 39.6±10% to 22.6±7% (p<0.05). Patients who continued on liraglutide for 24 weeks maintained similar glycemic control (mean HbA1c decreased from 6.5±0.5% to 6.1±0.4%, p<0.05) to those treated for 1 week, but had further reductions in insulin doses and significant weight loss (68.0±5 to 63.5±4 kg). The withdrawal of liraglutide resulted in rapid reversal of these effects and greater glycemic oscillations.

**Figure 14. Adjusted HbA1c Changes After 12 Weeks (Full Analysis Set*)**

<table>
<thead>
<tr>
<th>Baseline HbA1c (%)</th>
<th>Linagliptin 5 mg qd</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>All Patients</td>
<td>Patients with Baseline HbA1c ≥9.0%</td>
</tr>
<tr>
<td></td>
<td>8.2</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>-0.6†</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td>-1.5‡</td>
<td></td>
</tr>
</tbody>
</table>

Analysis of covariance (last observation carried forward), adjusted for continuous HbA1c, creatinine clearance, and background antidiabetic agents at baseline.

*Patients with at least one baseline and one on treatment HbA1c value.

†p=0.0001 vs. placebo; ‡p=0.0021 vs. placebo.

These results are comparable to what is observed with sitagliptin monotherapy or as an add-on to a single other agent.

**Linagliptin**

Sloan et al. from the US and Europe added a newer DPP-4 inhibitor, linagliptin 5 mg daily (n=68) or placebo (n=65) for 12 weeks to the background, stable antihyperglycemic therapy of patients with Type 2 diabetes and severe renal impairment (glomerular filtration rate [GFR] <30 mL/min/1.73 m²) (abstract 413-PP). Mean (±SD) baseline age, HbA1c, and GFR were 64.4±10.3 years, 8.2±1.0%, and 23.5±6.7 mL/min/1.73 m², respectively. Diabetes duration was >5 years in 96% of patients. A treatment benefit based on decrease in HbA1c was observed in the full analysis set as well as among the subgroup of patients more poorly controlled (baseline HbA1c ≥9.0%) (Figure 14). Renal function remained stable throughout the study in both treatment groups. Linagliptin is unique among the DPP-4 inhibitors for undergoing no renal excision.

As we await long-term cardiovascular safety data on these agents, it is clear that the incretin-based therapies provide several unique advantages to our ever-expanding ‘tool box’ to treat our patients with Type 2 diabetes.

**Closing the Loop**

Continuous glucose monitoring (CGM) technology continues to improve and now plays an important role in the management of diabetic patients on intensive insulin regimens, particularly those using insulin pumps. CGM measures interstitial fluid glucose through a subcutaneously inserted sensor that reads glucose every 5 minutes or less. Results are reported to a pocket-sized display device or may instead be directly communicated to a pump—the latter has opened the door to a fully-automated ‘artificial pancreas’ glucose control system.
sensor; (2) a control algorithm; and (3) an insulin pump. A fully ‘closed loop’ system is one where the glucose concentration triggers insulin release and no additional insulin is administered by the patient. A ‘semi-closed loop’ system allows for the patient to administer a standard bolus which is shared with the control algorithm. Semi-closed systems often provide better postprandial glucose control. Dr. Hovorka shared that overall, these systems decrease glucose variability, increase time in target range (70-145 mg/dl), decrease risk of hypoglycemia, and generally have similar insulin requirements as continuous subcutaneous insulin infusions (CSI).

Zisser, et al. (California) presented an initial evaluation of a fully automated artificial pancreas (or closed loop system) (abstract 152-OR). The investigators developed the Artificial Pancreas System (APS)* using it to evaluate a control strategy to manage glucose, including unannounced meals. APS* uses multi-parametric model predictive control (mpMPC) and an “insulin-on-board” (IOB) safety constraint. The initial step is to use 3 days of ambulatory data from CGM, CSII, and meal information to develop a personalized model and control algorithm. This is followed by an APS* evaluation during a clinical day that includes an unannounced meal. Five such sessions have been completed to date. Post-meal challenge, all subjects returned to euglycemic range with the average time spent there being 77%. There was one episode of mild hypoglycemia that was traced to an elevated sensor signal due to sensor drift. All results were in the favorable A+B zones of the Clarke Error Grid, which quantifies the accuracy of values obtained via CGM versus blood (refer to Issue No. 3 for description of Clarke Error Grid).

Also presenting at the symposium was Edward Damiano, PhD, from Boston University, who shared experience from 1-day and 2-day inpatient feasibility studies using a ‘bi-hormonal’ closed loop artificial pancreas.* This system delivers insulin and glucagon to more finely regulate glycemia. A laptop computer served as the controller algorithm. The mean blood glucose after 51 hours in test subjects (n=6) who each returned and repeated two experiments was 141 mg/dl. The controller algorithm appears to respond well to events that cause a precipitous fall in blood glucose (i.e., exercise) with appropriate doses of glucagon. This study also permits head-to-head comparison of the various glucose sensors. Damiano’s group is now preparing for a 5-day inpatient feasibility study that will run a portable mobile device (i.e., iPod Touch). This study is anticipated to begin in late 2011/early 2012.

The final presentation was delivered by Boris Kovatchev, PhD who shared that several new glucose sensors are in development, utilizing varying technologies to improve overall accuracy and as well as the ability to detect hypoglycemia. Additionally, controller algorithms are getting “smarter.” The immediate future is likely to include dual sensors to be used for real-time detection of glucose levels should one sensor fail. Also, the portability controller algorithms will be drastically improved (i.e., portability, size).

Although much of this symposium might appear futuristic, several abstracts evaluated the here and now. Bergenstal and North American co-investigators presented data from the 6-month continuation phase of the STAR-3 Study (abstract 407-P). The initial trial randomized patients with Type 1 diabetes to receive insulin via a sensor-augmented pump (SAP) or by multiple daily injection (MDI) therapy for 12 months. The continuation phase crossed over the MDI group to SAP. The original SAP group demonstrated a sustained HbA1c response and the crossover patients demonstrated a relatively rapid and safe (hypoglycemia, 2.0 events per 100 patient-years) transition, achieving a significant decrease in HbA1c (Figure 15).

At this year’s meeting, we heard major progress in the development of functional closed-loop systems* by several other groups, including Youssif from Oregon (abstract 149-OR), Danne from Germany (abstract 150-OR), Eleri from the UK (abstract 153-OR), Sherr from Connecticut (abstract 154-OR), and Renard and collaborators from France, Italy, and the US (abstracts 151-OR & 155-OR). Each of these groups reported impressive improvements in maintaining targeted glucose control with sensor-augmented insulin pumps, as compared to traditional ‘open-loop’ systems. Most of the studies reported were in the controlled environment of clinical research centers, however. We look forward to ongoing improvements and the creation of a fully functional and reliable artificial pancreas for our patients with Type 1 diabetes.

**Novel Therapies**

There are over 100 new targets or mechanisms of action for potential drugs to manage diabetes and seemingly a nearly equal number of pharmaceutical companies in pursuit of exploring such compounds. A symposium, “Novel Therapies for Type 2 Diabetes—Today and Tomorrow;” explored agents that are in clinical trials and/or are considered to be the most promising for future clinical investigation.

Ernest Wright, PhD, UCLA began with a discussion of inhibitors of sodium glucose co-transporters 1 (SGLT1)* and 2 (SGLT2).* SGLT1 is expressed predominantly in the intestine and inhibits glucose transport in the gut. SGLT2, expressed in the kidney, is responsible for glucose reabsorption in the proximal tubule. Compounds that inhibit SGLT2 promote urinary glucose excretion, ultimately lowering plasma glucose. Although there is a SGLT1 inhibitor in Phase 1 trials (DSP-32325*), the majority of drug investigation has focused on selective SGLT2 inhibition. There are currently 3 agents in Phase 3 clinical trials: canagliflozin,* dapagliflozin,* and BI-10773.* To date, these products appear to produce favorable effects on glycemic control, as assessed by HbA1c. Also, due to their mechanism of action, which involves daily excretion of approximately 50-70 g of glucose (and therefore some 200-280 kcal), they lead to modest weight loss.

Dapagliflozin was compared to metformin (titrated to 2000 mg), each as monotherapy and in combination, in 2 randomized controlled trials in treatment-naïve patients with Type 2 diabetes.
Henry and international colleagues studied 5 mg dapagliflozin in one study and 10 mg doses in the second (abstract 307-OR). Change in HbA1c from baseline to 24 weeks was the primary endpoint for the combined analysis and secondary measures included FPG and body weight. The combination of the two modalities was more effective than monotherapy with either agent with respect to HbA1c and FPG (Table 19). However, the higher dose (10 mg) of dapagliflozin produced a significant decrease in weight when compared to metformin. Patients in the dapagliflozin arms had a higher numerical incidence of events suggestive of genital and urinary tract infections. However, statistical significance was not reported.

One concern with these products is the long-term effects of blocking this naturally occurring cotransporter in humans. That is, is a normally functioning SGLT2 needed for health? Dr. Wright opined that this fear has been tempered based on the experiences from a rare autosomal recessive disorder, Familial Renal Glucosuria. Patients with this disorder have a mutation in SGLT2, rendering it dysfunctional. Other than glucosuria, this patient population has no evidence of other renal function abnormalities and the condition is considered benign. Indeed, affected patients appear to be resistant to developing diabetes. Accordingly, other than the issue of urinary and genital infections directly related to glucosuria, this class of drugs is not expected to have additional side effects. Of course, long-term trials will be needed to confirm this.

Bile acid sequestrants (BAS) were the subject of the next presentation delivered by David Mangelsdorf, PhD, University of Texas Southwestern Medical Center, Dallas. These agents (e.g., cholestyramine and colesvelam) are well known for their impact on cholesterol synthesis. A serendipitous finding over a decade ago was that in addition to lowering cholesterol, patients with Type 2 diabetes receiving these agents had improved glucose homeostasis (Garg A, et al. Ann Int Med. 1994). Subsequent studies confirmed this unexpected finding. Dr. Mangelsdorf proceeded to describe the multiple animal studies that ensued to identify the specific mechanism of action responsible for glycemic control with BAS. The likely mechanism is one that is independent of lipid-lowering effects. BAS activate a protein receptor, TGR5, in the colon. This activation signals the release of intestinal gluconic-like peptide 1 (GLP-1). Elucidation of this pathway has opened the door for even further research relative to molecules that impact TGR5.*

Jorge Plutzky, MD, from Harvard, was the next presenter who discussed selective peroxisome proliferator-activated receptor (PPAR) agonists. The current PPAR-γ agonists, the TZDs, have an adverse event profile that is less than desirable (e.g., cardiovascular risk with rosiglitazone; increase in body weight, fluid retention, and bone fractures with rosiglitazone and pioglitazone). Plutzky introduced the concept of PPAR “modulation” versus absolute agonist activity. Modulators have partial or selective agonist activity at various PPAR receptors (alpha, delta, and gamma) and are not linked to a specific dose-response. The goal is to develop the ideal balance of selective or partial activity at various receptors to retain the desirable effects on glycemic control, but eliminate toxicities. This class of PPARs is termed SPPARMs for “Selective PPAR Modulators.” SPPARMs would each have a distinctive transcriptional response, different clinical effects, and unique side effect profiles. Even the well known PPAR agonists, pioglitazone, rosiglitazone, and troglitazone, have transcriptional profiles that are not identical (but do overlap)—which would explain their distinct effects.

Finally, Dr. Charles Burant, University of Michigan provided an overview of what he described as next-generation compounds. One group is the fatty acid elongases. These are enzymes present in liver microsomes that carry out progressive elongation of saturated and monounsaturated fatty acids. Elongase-6 inhibitors alter fatty acid composition, resulting in an increase in insulin sensitivity. Data are limited to animal models at this point, but have been promising.

The second target is the enzyme 11 beta hydroxysteroid dehydrogenase (HSD)-1. This is an NADPH-dependent enzyme highly expressed in liver, fat, and the central nervous system. It is responsible for the conversion of inactive cortisol to active cortisol in adipocytes and liver, producing metabolic changes consistent with metabolic syndrome. Inhibition of this enzyme has been demonstrated to improve insulin sensitivity and is particularly efficacious in patients with increased BMI and visceral fat. Potential side effects include increased ACTH secretion with downstream hyperandrogenism.

Another new drug class is the G-protein coupled receptors (GPRs). There are approximately 850 such proteins with a wide variety of ligands and diverse effects. GPR40 is highly expressed in β cells and enteroeendocrine cells and mediates free fatty acid-induced insulin secretion. TAK-875 is a GPR40 agonist evaluated in a Phase 1, double-blind, placebo-controlled trial by Leifke et al. of the US (abstract 414-P). In this dose-ranging study, 59 patients with Type 2 diabetes received TAK-875 or placebo for 2 weeks while pharmacokinetic and pharmacodynamic responses were tracked. TAK-875 resulted in reduced FPG and postprandial glucose versus baseline following an OGTT. There was no change in fasting insulin or C-peptide levels. It was well tolerated, with no dose-related adverse effects, including symptomatic hypoglycemia. From this preliminary investigation, the researchers suggest that TAK-875 acts as a glucose-dependent insulinotropic agent.

GPR119 is also highly expressed in the pancreatic β cells and enteroeendocrine cells. Preliminary studies have suggested an effect on both insulin as well as GLP-1 secretion. The GPR119 agonist, PSN821, was evaluated in Type 2 diabetes patients by Goodman and colleagues from the UK and the Netherlands (abstract 306-OR). Varying doses were administered, either as monotherapy or added to metformin and compared to placebo for 14 days. FPG was decreased in all treatment groups. There was also a reduction in glucose exposure following meal challenge. Active treatment groups experienced weight loss. PSN821 was well tolerated with no discontinuations due to adverse events. GPR agonists appear to be

### Table 19. Dapagliflozin versus Metformin* versus Dapagliflozin + Metformin

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted mean change from baseline</th>
<th>Metformin</th>
<th>Dapagliflozin</th>
<th>Dapagliflozin + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>HbA1c (%)</td>
<td>-1.35</td>
<td>-1.19</td>
<td>-2.05*</td>
</tr>
<tr>
<td></td>
<td>FPG (mg/dl)</td>
<td>-33.6</td>
<td>-42.0</td>
<td>-61.0†</td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>-1.29</td>
<td>-2.61</td>
<td>-2.66</td>
</tr>
</tbody>
</table>

*titrated to 2 gm.
†p<0.0001 vs. monotherapy.
‡p<0.002 vs. metformin.
promising as novel glucose-dependent insulin secretagogues for Type 2 diabetes.

Burtan concluded that alternative treatments should never exclude the standard therapy of weight loss, diet, and exercise. Also, although there are a plethora of targets for novel agents to manage diabetes, there is no perfect drug and it is unlikely we will see one in the near future.

In addition to the compounds highlighted at the symposium, several others were showcased in the oral and poster presentations. Glucokinase activators lower the plasma glucose threshold for insulin release and may also directly reduce hepatic glucose production. LY2599506, an oral glucokinase activator, was evaluated by Bue-Valleskey and co-investigators from the US and Germany (abstract 993-P) in both healthy volunteers and patients with Type 2 diabetes. The drug lowered blood glucose and postprandial glucose. While further investigation is needed, the oral GKA appeared to be well tolerated.

It is now known that diabetes is linked to chronic inflammation. Accordingly, drugs that target inflammation are being closely examined. Salicylates, through inhibition of NF-kB mediated inflammation, have been reported to improve glycemia in patients with Type 2 diabetes. Salsalate, a pro-drug that releases two molecules of salicylic acid following oral administration, was investigated for its glycemic impact in patients with pre-diabetes. Goldfine and American colleagues assessed the impact of salsalate 4 gm/day versus placebo in 70 males with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) (abstract 50-OR). Fasting glucose, HbA1c, OGTT glucose area under the curve (AUC), and C-peptide were measured at baseline and at 12 weeks. Fasting glucose was significantly deceased in the salsalate group in conjunction with a 20% fall in C-peptide (Figure 16). Total OGTT glucose AUC was also reduced by salsalate, despite a lack of impact on AUC insulin and AUC C-peptide. Interestingly, there was a strong, inverse correlation between fasting glucose and average serum salicylate levels (r = -0.64, p = 0.004).

“Enough Already?”

Obviously, drug classes and targets for drug therapy used to manage diabetes continue to proliferate. The question at this point might be, “Do we have enough already?” This was the topic of a debate on the penultimate day of the Scientific Sessions, with Dr. David Nathan from Harvard and Dr. Richard Bergenstal from the International Diabetes Center in Minnesota tackling this important question. Only 15 years ago, the diabetes armamentarium included solely sulfonylureas and insulin. Now, physicians and patients have access to 11 different classes of agents with varied mechanisms of action. Do we really need any more?

Dr. Nathan began by addressing this question in the context of diabetes prevention. He reviewed data from the Diabetes Prevention Program and its Outcomes Study and argued that we have both an effective lifestyle intervention strategy and a safe medication (metformin) for diabetes prevention. Implementation of these effective measures could substantially reduce the incidence of diabetes, particularly if applied to those individuals at highest risk. Yet, funding for implementation and delivery of these programs has been modest, while new classes of drugs flood the market.

In terms of management of patients who do go on to develop diabetes, Dr. Nathan reviewed data from the classic trials that show reduction in microvascular complications with control of glycemia and argued that a goal of HbA1c < 7% is justifiable for most individuals in order to reduce these microvascular events. How do we achieve this goal? The ADA/EASD antihyperglycemic therapy consensus document was next reviewed, which provides recommendations with respect to choice of therapy. For most patients, the recommended backbone of diabetes therapy is metformin. Addition of a second agent is primarily guided by considerations of safety, tolerability, side effect profile, effectiveness on glucose lowering, and cost. Recommended ‘first tier’ therapies include sulfonylureas and insulin, while less evidence-based regimens (‘second tier’) include addition of pioglitazone or a GLP-1 agonist. In terms of the newer agents on the market, Dr. Nathan argued that they are not as potent in achieving HbA1c reduction and considerably more expensive. We might add that long-term safety data, which is not available for newer agents, is also an important issue to consider.

The ADA/EASD consensus algorithm has never been directly tested, and Dr. Nathan argued for more comparative effectiveness research on glucose-lowering agents that are already available. Such research will eventually provide guidance to physicians and patients in making decisions about how best to individualize therapy.

Dr. Bergenstal took the opposite view on the issue of new drug development in diabetes. He argued that novel drugs can help fill the quality gap, i.e. improve glycemic control in the ~50% of patients in the US who are currently not meeting the established goal of HbA1c < 7%. He provocatively asked, “Where is the patient in these diabetes performance measures?” He argued that diabetic patients care about the effectiveness of therapy but are also concerned about tolerability, hypoglycemia risk, and quality of life. And in this respect, he argued, we need more drugs—those that are well-tolerated and to which patients are most apt to adhere.

Bergenstal argued that there has been substantial progress in drug development for diabetes, with agents that reduce HbA1c (albeit modestly), do not cause hypoglycemia or weight gain, and have minimal side effects (such as DPP-4 inhibitors). There are also other agents (such as GLP-1 receptor agonists) that result in HbA1c lowering and substantial and sustainable weight loss. Most of all, he supported an individualized approach to diabetes therapy—choosing from all the available therapeutic options—to improve glycemic control and, at the same time, address specific concerns of individual patients.

The two speakers agreed on the need to individualize therapy. But questions from the audience arose on how this individualization should be achieved. Moreover, current performance measures in diabetes care are based upon strict glycemic, blood pressure, and lipid targets. Individualization of therapy will require a decisive shift in how diabetes care is delivered and, in turn, evaluated.
1. Which of the following statements is incorrect about diabetes and heart failure?
   a. Diabetes worsens prognosis in heart failure patients.
   b. Heart failure in diabetic patients stems from underlying coronary disease, hypertension, and potential direct effects of diabetes on the myocardium.
   c. Thiazolidinediones increase the risk of heart failure.
   d. Metformin is contraindicated in all patients with heart failure.

2. Which of the following blood pressure targets is endorsed by the ADA for patients with diabetes?
   a. <120/<80 mm Hg
   b. <130/<80 mm Hg
   c. <130/<90 mm Hg
   d. <140/<90 mm Hg

3. “Lower is not necessarily better” for blood pressure control, since increased coronary events have been observed at diastolic blood pressure below 70-80 mmHg in epidemiological studies.
   a. true
   b. false

4. For diabetes patients who do not achieve target blood pressure after 3 months of lifestyle modification, the ADA recommends pharmacotherapy with which of the following agents as first-line therapy.
   a. angiotensin converting enzyme (ACE)-inhibitor
   b. calcium-channel blocker
   c. beta-blocker
   d. thiazide diuretic

5. Select the false statement from the following about HDL-cholesterol and CVD in patients with diabetes.
   a. There is an inverse relationship between HDL-cholesterol level and CVD risk.
   b. Several non-pharmacologic interventions increase HDL-cholesterol (e.g., weight loss, exercise, smoking cessation, modest ethanol ingestion).
   c. Pioglitazone increases HDL-cholesterol to a greater degree than do fenofibrates.
   d. Pharmacotherapy with slow-release niacin, which increases HDL-cholesterol by 20-25%, has recently been shown to decrease the risk of CV events.

6. Select the false statement from among the following about secondary diabetes.
   a. Cystic fibrosis-related diabetes results from a primary defect in β-cell insulin secretion.
   b. Latent Autoimmune Diabetes of Adults (LADA) is distinguished from ordinary Type 2 diabetes by a higher BMI.
   c. A number of drugs have been associated with secondary diabetes, including glucocorticoids, nicotinic acid, and thiazide diuretics.
   d. A variety of gene mutations result in maturity-onset diabetes of youth (MODY), most limiting the ability of the β-cell to produce insulin.

7. Data from the NHANES (National Health and Nutrition Examination Survey) 2005-2008 database showed that which percentage (from below) of Type 2 diabetes patients take 5 or more prescription drugs.
   a. >90%
   b. 75%
   c. 55%
   d. 10%

8. _____ Ultra short-acting insulin under investigation.
9. _____ Insulin sensitizers under investigation.
10. _____ Activate a protein receptor, TGR5, in the colon, signaling the release of intestinal GLP-1.
11. _____ After fatty acid composition, thereby increasing insulin sensitivity.
12. _____ Increase urinary excretion of glucose.
13. _____ Ultra long-acting basal insulin under investigation.

14. In a meta-analysis of cohort studies, metformin was associated with reduced mortality compared to control agents in Type 2 diabetes patients with heart failure.
   a. true
   b. false

15. Which of the following medications or strategies does not reduce postprandial hyperglycemia when used in conjunction with basal insulin?
   a. Addition of pramlintide
   b. Addition of GLP-1 agonist
   c. Addition of prandial insulin single dose with main meal
   d. Increase basal insulin dose

16. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, the main analysis demonstrated that cardiac event rates were similar between patients who were screened for coronary artery disease with nuclear stress testing and those who were not. However, a post-hoc analysis showed that in those patients at the highest cardiac risk, screening was extremely valuable.
   a. true
   b. false

17. Hospitalized patients who experience severe hypoglycemia (blood glucose <50 mg/dl) frequently have low-normal to mildly hypoglycemic glucose readings in the 48 hours preceding the event.
   a. true
   b. false

18. Select the false statement from the following about the sequelae of metabolic (bariatric) surgery in obese patients with diabetes.
   a. Fasting glucose and insulin resistance decrease significantly.
   b. The risk of hypoglycemia is significantly increased.
   c. GLP-1 response is significantly reduced.
   d. Iron, B12, and less often thiamine and copper deficiency occur.

19. Each of the following represent proposed links between Type 2 diabetes and cancer except _____.
   a. obesity
   b. hyperlipidemia
   c. inflammation
   d. hyperinsulinemia

20. What is the prevalence of diabetes in U.S. adults over age 50 years?
   a. 10%
   b. 20%
   c. 30%
   d. 40%
Please mark your answers on the Evaluation Questionnaire Form on page thirty-seven.

1. How would you rate Diabetes 2011 for content?
   a. very relevant to my practice
   b. interesting but not relevant
   c. uninteresting

2. How would you rate Diabetes 2011 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 2011 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: ________________________________________________________________
   __________________________________________________________________________________

8. Additional comments: __________________________________________________________________
   __________________________________________________________________________________

Thank you for your participation.
**Diabetes 2011 Answer Form**  
**Volume 23**

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 2011 to December 31, 2011.

**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.**

**Diabetes 2011 Test - Volume 23**

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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 2011 Evaluation - Volume 23**

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- If you currently receive the Diabetes 2011 newsletters by fax and would like to receive them by e-mail instead, please mark this box with an “X.”

Mail to: Yale Continuing Medical Education  
333 Cedar Street  
PO Box 208052  
New Haven, CT 06520-8052

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