Volume 22

Highlights from the
46th Annual Meeting of
the European Association
for the Study of Diabetes

September 20-24, 2010
Stockholm, Sweden

and

2010 Scientific Sessions of
the American Heart Association

November 13-17, 2010
Chicago, IL

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December 2010

Dear Colleague:

Time restraints prevented many of you from attending the 46th Annual Meeting of the European Association for the Study of Diabetes (EASD) which was held during September in Stockholm, Sweden and the 2010 Scientific Sessions of the American Heart Association (AHA) which was held a few weeks ago in Chicago, Illinois. Therefore, we developed Diabetes 2010 so that important information presented at the Conferences could be shared with you on a timely basis.

Diabetes 2010, a newsletter CME program, is being offered to you by Yale School of Medicine with the support of educational grants from Takeda Pharmaceuticals North America, Inc., Amylin Pharmaceuticals, Inc. and Lilly USA, LLC, Bayer HealthCare Diabetes Care, Boehringer Ingelheim Pharmaceuticals, Inc., Medtronic MiniMed, Inc. d/b/a Medtronic Diabetes, Merck & Co., Inc., and Novo-Nordisk Inc. This booklet contains four Diabetes 2010 newsletters and a post-test. After successfully completing the test you will qualify for a maximum of 5.5 AMA PRA Category 1 Credits™ to be issued by Yale 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 ß-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

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

Sincerely,

Robert S. Sherwin, M.D.
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**Educational Needs**

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

**Learning Objectives**

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

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Describe the evolving cellular mechanisms associated with β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

**Target Audience**

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

**Educational Methods**

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

**Evaluation**

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

**Accreditation**

This program has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Yale School of Medicine. Yale 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**

The Yale School of Medicine designates this continuing enduring material for a maximum of 11 *AMA PRA Category 1 Credits™* (5.5 credit hours per test). Physicians should claim only the 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 Credits™*. 
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In this issue of the *Diabetes 2010* monograph, we summarize important new diabetes information that was presented at the 46th Annual Meeting of the European Association for the Study of Diabetes (EASD) and the 2010 Scientific Sessions of the American Heart Association (AHA).

During an opening-day session of the EASD Annual Meeting, new criteria for the diagnosis of gestational diabetes mellitus (GDM), as proposed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG), were presented and discussed. According to current American Diabetes Association (ADA) guidelines, the diagnosis of GDM is based on a 2-step process, consisting of a 1-hour 50-g glucose challenge test at 24-28 weeks, with those women whose plasma glucose exceed 140 mg/dl proceeding to a 3-hour 100-g OGTT; the diagnosis of GDM is made if 2 or more of specific glycemic thresholds are reached, either fasting or at hours 1, 2, or 3. (The term “overt diabetes” is additionally applied to women meeting traditional criteria for diabetes.) The proposed IADPSG criteria require just one abnormal glucose level during a 2-hr 75-g OGTT, as well as lowering the thresholds slightly for fasting glucose from 95 to 92 mg/dl and the 2-hour glucose from 155 to 153 mg/dl, as compared to current guidelines. In studies using the proposed vs. current ADA guidelines, the prevalence of GDM increased by an absolute minimum of 3%, and in some countries doubling the risk to ~15%. Studies also showed that including women with milder glucose intolerance identified pregnancies at greater risk for adverse outcomes, and treating them mainly through lifestyle changes conferred modest benefit on various gestational and fetal parameters. Whether the IADPSG recommendations are ultimately endorsed by international groups who set clinical policies, such as the ADA, the World Health Organization (WHO), and the American College of Obstetrics and Gynecology (ACOG), remains to be seen.

Interest in the optimal test(s) for diagnosing (non-gestational) diabetes was the subject of several presentations made at the EASD meeting. In the summer of 2009, the International Expert Committee recommended that HbA1c become the preferred test for the diagnosis of diabetes. Then earlier this year, the ADA added HbA1c (≥6.5% for diabetes, 5.7-6.4% for pre-diabetes) to then existing criteria for diabetes diagnosis (i.e., fasting plasma glucose [FPG] ≥126 mg/dl, 2-hour plasma glucose during an oral glucose tolerance test [OGTT] ≥200 mg/dl), but did not stipulate that one test be used in preference to another. Study after study have documented substantial discordance between HbA1c and glucose-based test results, although each parameter correlates well with microvascular complications of diabetes as well as with the risk of developing diabetes among patients in the so-called high-risk categories (i.e., ‘pre-diabetes’). The optimal method for diagnosis remains hotly debated, and each test has its advantages and disadvantages.

Bariatric surgery to address both obesity and diabetes remains a controversial, yet increasingly utilized intervention. Presenting their results of a systematic meta-analysis of 8 published clinical trials (44,022 participants) at the EASD Annual Meeting, Morabito and Pontiroli discovered that bariatric surgery (gastric banding and Roux-en-Y gastric banding [RYGB]) was associated with a reduced risk (odds ratio) of cardiovascular (CV) mortality (0.43) and all-cause mortality (0.60), as compared to controls who did not undergo any bariatric procedure (EASD abstract 85). Others discussed the benefits of bariatric surgery on glucose metabolism and Type 2 diabetes. Jorgensen and Danish colleagues studied the mechanistic effects behind diabetes remission, which is observed in approximately 75% of patients within days following the surgery (EASD abstract 668). The investigators observed major improvements (near doubling) in measures of both insulin sensitivity and beta-cell function following RYGB, predating any significant weight loss. Beta-cell function changes are likely the result of marked (> 5-fold) increases in secretion of glucagon-like peptide-1 (GLP-1), a known insulin secretagogue. Others proposed that improvements in glucose metabolism following RYGB result primarily from increased insulin sensitivity (EASD abstract 775). Clearly, more work is necessary before we fully understand the fine physiological details underpinning the post-surgical effects of bariatric surgery. Likewise, prospective, randomized clinical trials, including a lifestyle intervention control group, with long-term follow-up are needed before we can know, with certainty, whether or not bariatric surgery reduces CV events and/or mortality.

Our appreciation for the impact of sleep apnea on glycemia was furthered by the results of two studies, one showing that the majority (73%) of obese Type 2 diabetes patients meet the criteria for sleep disordered breathing based on overnight polysomnography (EASD abstract 622), and the other showing a higher prevalence of diabetic neuropathy in patients with sleep apnea than in those without (EASD abstract 28). Taken together, these studies point to the need to consider sleep apnea in all obese patients with Type 2 diabetes, who may need more aggressive treatment for both their sleep disturbance and any associated risk factors for micro- or macrovascular complications of their diabetes.

Ongoing research continues to expand our understanding of currently available agents and uncover new agents of potential value in diabetes care. The role of liraglutide and sitagliptin in the management of patients with Type 1 diabetes* was discussed (EASD abstracts 77 and 853), as were ways to administer exenatide less frequently (i.e., with a longer-acting once weekly formulation* [EASD abstract 843] or combined with ITCA 650*, a continuous subcutaneous delivery device [abstract 78]). 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., lisper co-injected with recombinant human hyaluronidase* [EASD abstract 2]; VIAject**, recombinant human insulin combined with an EDTA-containing diluent [EASD abstract 6]) or an alternative route of administration (e.g., inhaled insulin [Technosphere**, EASD abstract 5]). Also under study are longer-acting insulins that result in less glucose variability (e.g., insulin degludec* [EASD abstract 4]). Other anti-hyperglycemic medications in various stages of development include: the renal sodium-glucose co-transporter-Type 2 (SGLT-2) inhibitors (e.g., canagliflozin*, dapagliflozin*, and BI 10773*, EASD abstracts 869, 874, and 877); glinides (e.g., lixisenatide*, EASD abstract 884); dual PPARα/PPARγ agonists* (EASD abstract 880); glucokinase activators* (EASD abstract 242); and, GPR (G-protein coupled receptor) agonists (GPR40* [EASD abstract 882] and GPR119* [EASD abstract 878]). Exploring an unconventional approach to weight loss, Adrian et al. found that colon administration of taurocholic acid* (bile salt) stimulated intestinal L-cell secretion, leading to increased release of neuropoendocrine satiety hormones, with consequent decreased food intake (EASD abstract 89). While this approach has obvious practical limitations, the line of research is interesting in an area where effective therapies are essentially non-existent. Which of these agents, if any, might eventually become commercially available to our patients remains to be seen.

More details on these and other topics are found in this volume of *Diabetes 2010*. 
Bariatric surgery to address both obesity and diabetes remains a controversial topic. Three types of bariatric surgery—gastric banding, Roux-en-Y gastric bypass (RYGB), and sleeve gastrectomy (Figure 1)—are currently being performed, with gastric banding the most popular followed by RYGB. With an increasing number of these procedures in the US each year, studies are now emerging, attesting to its overall safety and effectiveness in inducing substantive weight loss as well as remission of diabetes. Its proponents argue that bariatric surgery may be the best solution for the obesity epidemic throughout the world, whereas its critics emphasize the procedure’s costs and both the short-term and long-term risks, while underscoring the need for additional societal efforts at promoting healthy lifestyles. Several presentations this week explored these and related issues.

Morabito and Pontiroli from Italy performed a systematic meta-analysis of published clinical trials of gastric banding and RYGB, focusing on relationships with all-cause and cardiovascular mortality (abstract 85). Pooled-random effects of estimates of the mortality risks in patients undergoing a bariatric procedure versus controls were calculated using the DerSimonian-Laird model. In all, data from 44,022 participants in 8 clinical trials were included. After adjustments, compared to controls, bariatric surgery was associated with a reduced risk of all-cause mortality (odds ratio [OR] 0.60, 95% CI 0.37-0.97) and cardiovascular mortality (OR 0.43 [0.24-0.77]). In meta-regression analysis, mortality reduction was significantly associated with increasing body mass index (BMI; p=0.036). The effect of gastric banding (n=3,797) and gastric bypass (n=10,255) was not significantly different for either outcome. The investigators concluded that bariatric surgery reduces mortality, and specifically cardiovascular mortality, with an effect more apparent at higher BMIs and with no differences in the apparent benefits between the 2 types of procedures.
Of course, such conclusions may be premature. It is not possible to assess the effects of these or any procedure on any clinical endpoint without an adequate control group. Importantly, this would consist of patients who are willing to be randomly assigned to lifestyle interventions instead. Obviously, such studies are extremely challenging to conduct, especially in the long-term. Nonetheless, the benefits of bariatric surgery on body weight and (at least temporary) resolution of Type 2 diabetes are irrefutable. Whether these interventions actually reduce cardiovascular events and/or mortality remains, in our minds, uncertain.

Jorgensen and Danish colleagues were more focused on the mechanistic effects of bariatric procedures on glucose metabolism, specifically the physiological explanation for Type 2 diabetes remission. This is reported in approximately 75% of patients and, interestingly, often occurs within days of surgery—before any significant weight loss (abstract 658). The group studied 12 patients with Type 2 diabetes before and after RYGB for morbid obesity. Each had a fasting plasma glucose >126 mg/dl prior to surgery, on oral agents or diet. Mean age was 52±3 years, BMI 45±1.8 kg/m², and HbA1c 7.0±0.3%. A mixed meal tolerance test (200 ml liquid meal consisting of 300 kcal, 15% protein, 50% carbohydrates, and 35% fat) was conducted before and then again 4-6 days after surgery. Plasma glucose, insulin, and C-peptide were measured during the test. Based on these data, several standard measures of insulin sensitivity (HOMA-IR and the Matsuda index) and beta-cell function ('disposition index' [DI] and 'insulinogenic index' [IGI]) were then calculated.

The main measured results are seen in Table 1. In terms of HOMA-IR, Matsuda index, DI, and IGI, all increased by a factor of almost 2-fold. So, within 1 week after RYGB, before any major changes in weight could occur (-2.2%), there was a near doubling of insulin sensitivity and beta-cell function, resulting in marked reductions in both plasma glucose in the fasting and post-prandial settings. The investigators went on to measure peak glucagon-like peptide-1 (GLP-1) levels during the mixed meal test—remarkably, these increased more than 5-fold, from 17±1.2 to 95±14 pmol/l, with total area-under-the-curve (AUC) GLP-1 increasing by 16-fold. The investigators concluded that there are major improvements in measures of both insulin sensitivity and beta-cell function following RYGB before any significant weight loss occurs. Beta-cell function changes are likely the result of marked increases in secretion of GLP-1, a known insulin secretagogue. The measures of insulin sensitivity are more difficult to explain, but could result from rapid depletion of hepatic fat and glycogen stores due to marked decrease in calorie intake in the post-op period.

As previously reported in this newsletter (Diabetes 2009, Issue 1), other investigators have also detected major changes in incretin physiology to explain the improvements in glucose metabolism following RYGB—but others have found little change. We would point out that the Jorgensen study cohort had relatively early and mild diabetes. Accordingly, these data may not apply to the more typical diabetic patients undergoing bariatric surgery, who likely have had many more years of poorly controlled diabetes. What might beta-cell recovery look like in those individuals? Clearly, further study is needed.

Underscoring the controversy in this field, contrasting findings were reported by Austrian collaborators, led by Schultes, who also explored the physiological nature of diabetes remission after gastric bypass (abstract 775). In this preliminary study, the investigators reported on beta-cell function and insulin sensitivity in 6 patients undergoing RYGB. Their method involved an oral glucose tolerance test (OGTT), an IV glucose tolerance test (to better assess early phase insulin secretion), as well as a hyperinsulinemic, euglycemic clamp (to more precisely calculate insulin sensitivity). These were conducted before and 8-21 days after surgery. Mean duration of diabetes in this small group was 8.2 years (range 1-14). From the pre-operative baseline to when the glucose testing was performed, mean body weight had decreased from 121.4±9.2 to 113.7±8.4 kg and mean BMI from 43.3±1.5 to 40.7±1.6 kg/m² (both p<0.005). Medical treatment was also reduced, with all oral agents being eliminated and the 4 insulin-treated patients experiencing marked reductions in dose. HbA1c, fasting plasma glucose, and 2-hour plasma glucose during the OGTT were each significantly reduced after surgery (all p<0.05), and insulin sensitivity trended up (e.g., M-value 1.65 ± 0.59 vs. 3.67 ± 0.52; p=0.07). However, in contrast to the Danish study, none of the calculated indices of insulin secretion (e.g., acute insulin response [AIR] to glucose) were appreciably altered.

Table 1. Glucose, Insulin, and C-Peptide Levels Before and After RYGB in Patients with Type 2 Diabetes

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<th>Before</th>
<th>After</th>
<th>p-value</th>
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<td>Fasting plasma glucose (mg/dl)</td>
<td>158 ± 13</td>
<td>126 ± 5.4</td>
<td>&lt;0.005</td>
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<tr>
<td>2-hour plasma glucose (mg/dl)</td>
<td>205 ± 14</td>
<td>148 ± 13</td>
<td>&lt;0.001</td>
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<tr>
<td>Fasting insulin (pmol/l)</td>
<td>132 ± 22</td>
<td>73 ± 9</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Fasting C-peptide (pmol/l)</td>
<td>1542 ± 151</td>
<td>1175 ± 172</td>
<td>&lt;0.001</td>
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</table>

These investigators proposed that the marked improvement in glucose metabolism post RYGB is primarily the result of improvement in insulin sensitivity. As noted above, we wonder if the Austrian patients may have had more advanced diabetes and whether this difference in baseline characteristics may explain the conflicting findings. Of course, both studies were reasonably small, so it is difficult to make any firm conclusions. Nonetheless, these fine physiological details are actually of significant importance as professional societies and governmental organizations struggle with the optimal indications for these increasingly popular anti-obesity interventions.

In a related abstract, Adrian et al. from the US and the United Arab Emirates took an unusual approach to weight loss, focusing on the enteroendocrine system. The investigators noted that intestinal L-cells produce glucagon gene products, including GLP-1 and oxyntomodulin. Both serve as satiety factors, with the former, an incretin hormone, additionally functioning as an insulin secretagogue. L-cells also secrete peptide YY (PYY), another satiety hormone. Finally, it is recognized that L-cells increase in number distally through the gut, with the highest concentrations actually in the rectum. This group previously reported that bile salts infused intracolonically in humans stimulate the secretion of neuroendocrine cells, apparently by triggering the TGR5 membrane receptors.

The study presented this week investigated the effects of taurocholic acid* (TA) on circulating concentration of these neuroendocrine satiety factors and their clinical impact, following colonic administration in 10 obese Type 2 diabetic patients (abstract 89). Each subject was studied on 5 separate occasions following overnight fasting. 100 mg of sitagliptin, a DPP-4 inhibitor, was administered 10 hours before the study (to enhance the levels of GLP-1). In a randomized, blinded fashion, the investigators proceeded to infuse intracolically 1 of 4 amounts of TA (0.66, 2, 6.66, or 20 mmoles) or placebo. Infusions were administered over 1 minute, and plasma hormonal and glucose measurements were conducted over the following hour. Post-infusion, the patients
were presented with an unlimited amount of a previously selected favorite meal and were allowed to eat until satisfied. There were dose-dependent increases in GLP-1, PYY, and insulin following the TA infusions, with peak concentrations (7-fold, 4-fold, and 3-fold increased, respectively, all p<0.0001) achieved with the highest dose but no effect from placebo. Correspondingly, glucose levels fell, with a reduction of 50 mg/dl at the highest TA dose (p<0.0001). As a biomarker of satiety, calorie consumption subsequently decreased progressively when patients received TA, with the maximal inhibition of 45±6 % occurring with the highest dose.

The investigators concluded that intrarectal bile salts stimulate L-cell secretion, leading to an increase in the release of neuroendocrine satiety hormones, with consequent decreased food intake. They conjectured that their findings might explain the modest glucose-lowering effects of oral bile acid sequestrants (BAS), which were recently approved for use in patients with Type 2 diabetes.

We feel that the two issues may not be related given the upper gastrointestinal tract effect of BAS. While the Adrian et al. data are provocative, it remains unclear how such a system can be applied practically. However, it may certainly give new meaning to the age-old toast, “Bottoms up!”

Continuous glucose monitoring (CGM) is becoming well established as an integral aspect of diabetes care in patients with Type 1 diabetes under intensive management programs, such as insulin pump therapy. The broader role of these ‘sensors’ in patients under less aggressive regimens, such as those with Type 2 diabetes and in different care settings (e.g., hospital) is not yet known but under active investigation. Setting aside cost issues, there continue to be concerns about accuracy and relative ‘value added’ of these devices. Dozens of presentations at this week’s meeting reflected the great interest in this technology to improve the care of patients with diabetes.

In a prospective trial, Gottlieb and American investigators explored the effects of CGM over 6 months in 60 adult Type 1 diabetes patients on insulin pumps (CSII) or multiple daily insulin injections (MDI) (abstract 44). Thirty patients on insulin pumps and 30 on MDI were placed on CGM (DexCom SEVEN® PLUS device), blinded to sensor output for the first 2 weeks and then unblinded for the remaining 20 weeks (i.e., ‘live-read’ CGM output made available to the patients).

Of note, in this pre-specified analysis, only those patients who used CGM for at least 6 days per week were included, based on the realization from published studies that the benefits of CGM are greatest in those patients who maximize its use.

Mean (±SD) age in the pump and MDI groups was 36±11 and 39±8 years and duration of diabetes was 22±11 and 23±10 years, respectively. The corresponding baseline HbA1c levels were 7.6±0.8% and 7.6±0.7%. Only 17 patients (57%) in each group actually used the sensor for at least 6 days, and these individuals ultimately constituted the studied cohort. In both subgroups, HbA1c and time spent in the glycemic target range (Figure 2) modestly improved and both simultaneously reduced the time spent in the hypoglycemic range (<80 mg/dl) (by 1 hour in pump patients and 2 hours in MDI patients). The investigators concluded that improved glucose control can be achieved through the use of CGM in Type 1 diabetes patients being treated with either insulin pumps or MDI.

Tamborlane and US colleagues reported results from a one-year multicenter trial that compared so-called sensor-augmented pump (SAP) therapy to MDI in 156 youth with Type 1 diabetes and suboptimal diabetes control (abstract 1004). Patients previously on MDI were randomly assigned to an experimental group consisting of an insulin pump integrated with a CGM device (Guardian® REAL-Time CGMS) or a control group, which continued MDI alone. The primary endpoint was change in HbA1c from baseline at 12 months. Results were then stratified by age (children vs. teens) and then by the amount of time the sensors were actually worn in the SAP group.

Baseline HbA1c was similar between groups (~8.3%); its change from baseline in the SAP group was -0.39±0.93% versus +0.16±0.95% in MDI patients, for a between-groups difference of -0.49% (95% CI, -0.75 to -0.18; p=0.002). The proportion of patients reaching an HbA1c of <7.5% was almost 3-fold higher in the SAP vs. MDI groups (29.5% vs. 10.3%, p=0.007.) The change in HbA1c at 12 months was numerically greater in teens (ages 13-18; -0.62% [95% CI, -1.09 to -0.15, p=0.01 vs. MDI]) than in children (ages 7-12; -0.44% [95% CI, -0.80 to -0.07; p=0.02 vs. MDI] (Figure 3). In the entire SAP cohort, greater lowering of HbA1c was associated with increasing sensor use time. Of note, rates of severe hypoglycemia (<10 events/100 patient-years) and diabetic ketoacidosis were both low, with no differences between the two treatment arms.

The investigators concluded that SAP therapy is effective in improving metabolic control and achieving glycemic targets in younger individuals with Type 1 diabetes as compared to continuing MDI. Not surprisingly, success was in part predicated on the amount of time the sensor was used. We note that this study is somewhat difficult to interpret given the combined approach (i.e., pump + sensor) used in the experimental group, rendering it impossible to determine the individual effects of each component on the primary outcome.

One of the challenges of CGM remains its accuracy, particularly in the hypoglycemic range.
Heckerman and German collaborators tested the performance of the Guardian® Real-Time CGMS device in 17 Type 1 diabetes patients on MDI (abstract 48). Each patient was admitted to a research unit for 7 days and provided standardized meals. They were connected to the sensor and reference blood glucose measurements for calibration purposes were obtained on a laboratory glucose analyzer at least every 4 hours. Throughout the study, a total of 2,328 paired (CGM-blood glucose) readings were obtained.

The mean age of the patients was 43 (range 26-61) years, with HbA1c of 8.3% (7.6-8.9%). The mean absolute difference between sensor and blood glucose was 24.5±24.0 mg/dl, with a mean absolute deviation of 18.3±18.7%. Frequent calibration did not appear to improve CGM accuracy, with no changes in relative absolute deviations for those CGM values obtained within 1 hour post calibration (18.8±18.6%). Clarke Error Grid analysis (Figure 4) is a standardized method to evaluate the accuracy of CGM. On the grid, zone A indicates those values that are concordant between CGM and the standard method (in this study, analyzer blood glucose). Zone B identifies those values that are discordant between the methods, but not to a degree or direction that would result in a different therapeutic decision. Zones C and D represent discordant regions of the grid that might result in treatment errors. In the Heckerman study, 93% of paired values were located in zones A (67.4%) and B (25.6%). However, 6.4% were found in zone D. There were 145 episodes of hypoglycemia (<70 mg/dl) but only 43 of these were detected by CGM. Conversely, 60 additional CGM readings (2.6%) were in the hypoglycemia range, but not confirmed by the analyzer — i.e., the reference measurement was >90 mg/dl. Accordingly, although CGM demonstrated a high specificity (97%) and good negative predictive value (95%) for hypoglycemia, its positive predictive value (42%) and sensitivity (30%) were deemed to be poor. The investigators felt that further improvements in CGM accuracy are necessary, particularly in the detection of hypoglycemia.

CGM presents a new and potentially exciting method by which our patients on intensive management programs can monitor their progress. Further research and refinements in the technology will be necessary to optimize its benefits for improving diabetes control.

Newer Insulins: Is Quicker Better? (and Other Questions...)

The initial sessions of the 46th Annual Meeting of the EASD included several oral presentations of studies investigating new formulations and/or enhanced delivery of insulin. Hompesch and US colleagues utilized hyaluronidase* (an enzyme that increases tissue permeability, accelerating insulin absorption) in combination with the rapid-acting insulin analogue, lispro, to determine if postprandial glycemic variability can be improved in both Type 1 (n=22) and Type 2 (n=23) diabetic patients (abstract 2). Two hours prior to administration of a standardized liquid meal, patients were titrated to a target glucose of 110 ± 20 mg/dl with intravenous glucose and/or insulin. Immediately pre-meal, lispro was injected with or without hyaluronidase; plasma insulin and glucose concentrations were then measured for 8 hours. Co-injection with hyaluronidase reduced hyperglycemic excursions in both populations with equal (Type 1) or less (Type 2) risk of hypoglycemia. This resulted in a greater percentage of patients in the Type 1 group meeting the American Diabetes Association (ADA) postprandial glucose goal of <180 mg/dl (91% with hyaluronidase/lispro vs. 55% lispro monotherapy). Peak post-prandial glucose was significantly reduced in this group (Figure 5). Similarly, 71% of patients on combination therapy compared with 48% receiving lispro alone met the ADA postprandial goal in patients with Type 2 diabetes. Based on this investigation, the investigators concluded that the combination of hyaluronidase with lispro leads to improved mealtime glucose control in both Type 1 and Type 2 diabetes.

An ultra rapid acting inhaled insulin formulation, Technosphere insulin (TI)*, was studied in patients with Type 2 diabetes. Boss and US investigators compared TI (n=656) when incorporated into baseline antihyperglycemic regimens, which could include insulin, oral agents, and/or diet and exercise, vs. usual care (n=678) over 2 years (abstract 5). Baseline characteristics were similar between groups. Overall reductions in mean HbA1c (Figure 6, p=0.30) and changes in weight (p=0.67) were both similar between the treatment groups. Rates of hypoglycemia were greater in the usual care group receiving insulin versus TI: 0.24 vs. 0.15 total events per patient-month.
respectively ($p=0.03$); 0.24 vs. 0.15 mild to moderate events per patient-month, respectively ($p=0.04$); and, 1.17 vs. 0.53 severe hypoglycemia events per 100 patient-months, respectively ($p=0.08$). From these data, the researchers suggested that TI, when incorporated into standard treatment regimens, results in comparable HbA1c reductions while reducing the likelihood of hypoglycemic events.

The pharmacokinetics and pharmacodynamics of 2 concentrations of VIAject™, an ultra rapidly absorbed form of regular human insulin, and insulin lispro were compared by Nosek and co-investigators from Germany and the US (abstract 6). VIAject 25 units/ml, pH 4 (VJ25), VIAject 100 units/ml, pH 7 (VJ7), or lispro were administered to 43 patients with Type 1 diabetes. All patients received 12 units of one of the three insulin formulations in 1 unit increments. Insulin-naïve patients with Type 2 diabetes received one of four dosage regimens in combination with metformin: 1) 4 times weekly degludec (n=62); 2) once daily degludec (n=60); 3) three times weekly degludec (n=62); 4) once daily insulin glargine (n=62); or 5) an alternative degludec formulation, development discontinued, with data not included in the abstract (n=62).

On the other end of the spectrum, degludec,* an ultra long-acting insulin formulation, allowing for administration once daily to even 3 times weekly, was studied in a phase 2 trial by Mathieu and multinational co-investigators (abstract 4). Upon injection subcutaneously, degludec forms soluble multi-hexameric structures, resulting in a protracted pharmacological profile. Insulin-naïve patients with Type 2 diabetes received one of four dosage regimens in combination with metformin in a 16-week, open-label, randomized, treat-to-target trial: (1) once daily degludec (n=60); (2) three times weekly degludec (n=62); (3) once daily insulin glargine (n=62); or (4) an alternative degludec formulation, development discontinued, with data not included in the abstract (n=62).

Outcomes were comparable in the three groups reported, including mean change in HbA1c from baseline, final mean HbA1c, mean change in FPG from baseline, final mean FPG, as well as final mean weekly insulin dose. Only one case of severe hypoglycemia (defined conventionally as needing the assistance of another; actual plasma glucose = 55.8 mg/dl) was reported in the three times weekly degludec group. Overall, hypoglycemia rates were similar between the three cohorts. Adverse events were mild to moderate and incidence was comparably low. Based on these initial findings, degludec once daily or three times weekly appeared to result in glycemic control similar to daily dosed glargine.

In stepping back for a moment to review these and other similar presentations, several questions come to mind. While the pharmacokinetic properties of one or another insulin formulation may appear more ‘physiological’ than current basal or bolus products on the market (Table 2), is our current therapeutic armamentarium ‘good enough’? That is, will these newer products, should they succeed through the regulatory process, provide our patients with any definitive clinical advantage, either in terms of degree of glycemic control or in quality of life? One might propose that inhaled insulins are truly different, offering insulin therapy perhaps to patients who would not previously agree to injections. TI’s data on hypoglycemia are also potentially interesting. However, safety concerns have been raised with similar products (e.g., Exubera®) in the past. And what about the ultra-rapid or ultralow injectable insulins—will investigators and industry be able to demonstrate clear clinical advantages or simply subtle pharmacokinetic differences? The answers to these questions are not yet known but worth pondering in an era of tight resource allocation.

### Table 2. Pharmacokinetics of Currently Available Rapid-Acting and Long-Acting Insulins

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>10-15 min</td>
<td>1-2 hr</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>Aspart</td>
<td>10-15 min</td>
<td>1-2 hr</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>Glulisine</td>
<td>10-15 min</td>
<td>1-2 hr</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>Long-Acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>2-3 hr</td>
<td>No peak</td>
<td>24+ hr</td>
</tr>
<tr>
<td>Detemir</td>
<td>1 hr</td>
<td>No peak</td>
<td>Up to 24 hr</td>
</tr>
</tbody>
</table>

**Striking a Nerve**

Diabetic peripheral neuropathy is a common complication of long-standing diabetes (Table 3). Although its pathogenesis is incompletely understood, current evidence suggests that metabolic and ischemic factors result in oxidative stress, which in turn is thought to play a central role in nerve damage. Tahran and colleagues from the United Kingdom examined the relationship between obstructive sleep apnea (OSA) and...
diabetic peripheral neuropathy (abstract 28). They hypothesized that because OSA results in increased oxidative stress, it may be an important risk factor for peripheral neuropathy. To date, they have examined 190 diabetic patients (45% Caucasian/55% South Asian, 58% men, mean age 57±12 years, mean BMI 33.5 kg/m², mean HbA1c 8.2%/±1.6) who were recruited from outpatient clinics of a single tertiary-care center. Those with known respiratory problems, including known OSA, were excluded. 54% of subjects were diagnosed with OSA based upon an apnea-hypopnea index (AHI) ≥5 events/hour using a home-based respiratory monitoring system. 44% had peripheral neuropathy by the Michigan Neuropathy Screening Instrument, a standard measure of the severity of this complication.

The prevalence of diabetic neuropathy was significantly higher in those with OSA (58.3%) than in those without (29.9%). OSA remained a significant predictor of diabetic neuropathy after adjustment for blood pressure, HbA1c, cholesterol, triglycerides, duration of diabetes, smoking, alcohol, gender, renal function, BMI, age, and use of antihypertensive, antiplatelet, and lipid-lowering agents (OR 2.3, 95% CI 1.14-4.6; p=0.02). Moreover, the AHI significantly correlated with the neuropathy score. This is the first time that OSA has been linked to diabetic neuropathy; the investigators are planning further studies to confirm this association and evaluate it with relation to other microvascular complications.

Chronic hyperglycemia increases oxidative stress through multiple mechanisms and is a strong and consistent risk factor for diabetic neuropathy. The Diabetes Control and Complications Trial (DCCT) showed that glycemic control reduces, but does not completely prevent, the risk of peripheral neuropathy. Ziegler and Roden from Germany hypothesized that early glycemic control in Type 1 diabetes may prevent the development of diabetic neuropathy (abstract 25). In an observational study, the investigators examined 32 patients with newly-diagnosed Type 1 diabetes (treated with insulin for 1-10 weeks prior to study entry) and followed them biennially for an impressive 24-year period: 7.0%/n=11, mean 6.5%/±0.1) and ≥7.0%/n=21, mean 8.3%/±0.2). In the first 4 years, patients in the higher HbA1c group had reduced sensory nerve conduction velocity and reduced cardiac autonomic function compared to those in the lower HbA1c group. After 24 years, those in the more poorly controlled group had reduced motor nerve conduction velocity (in the median, ulnar, and peroneal nerves) and reduced sensory nerve conduction velocity (in the median, ulnar, and sural nerves), compared to those with lower HbA1c’s. In addition, impairments in vibration perception threshold, thermal detection threshold, and the coefficient of R-R interval variation (a marker of cardiac autonomic dysfunction) at rest developed faster in the higher HbA1c group. Twelve (57%) of these patients and none in the lower HbA1c group developed clinical polyneuropathy, confirmed by nerve conduction studies, after 24 years of follow-up. Although the investigators concluded that near-normoglycemia prevents the development of polyneuropathy, the lack of a randomized design makes interpretation less definitive. Treatment for painful diabetic neuropathy remains a challenge for many clinicians. Currently, only duloxetine and pregabalin are formally approved by the US Food and Drug Administration (and the European Medicines Agency) for treatment of this condition. Many other agents are also used in clinical practice, such as tricyclic antidepressants,* gabapentin,* etc., but few trials have compared the efficacy of various medications. Gribble and colleagues from the United Kingdom studied 83 patients with neuropathic pain (based upon Leeds Assessment of Neuropathic Symptoms and Signs score >12) and diabetes for at least one year, who were recruited from 2 hospital diabetes clinics (abstract 26). The patients were treated with placebo on days 1-8 of the 36-day study and then randomized to either amitryptiline* (50 mg followed by 75 mg/day), pregabalin (300 mg followed by 600 mg/day), or duloxetine (60 mg followed by 120 mg/day). Pain was assessed by daily diaries for pain (Brief Pain Inventory and the short-form McGill visual analogue scale). In all 3 groups, there was a significant decrease in pain severity over time but there were no differences among the 3 treatments. Additionally, duloxetine improved pain interference and mood over time. The researchers concluded that the optimal medication for treatment of painful diabetic neuropathy remains unclear, and larger longitudinal studies are needed to further validate these study data.

### Table 3: The Prokene Manifestations of Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Type of Neuropathy</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal somatosensory polyneuropathy</td>
<td>Pain or loss of sensation in toes, feet, hands, and arms (“stocking-glove” sensory loss)</td>
</tr>
<tr>
<td>Acute mononeuropathies</td>
<td>Cranial: most commonly affecting III, IV, and VI (diabetic ophthalmoplegia), or facial nerve (Bell’s palsy)</td>
</tr>
<tr>
<td></td>
<td>Lumbar polyradiculopathy (most commonly affects L2-L4 roots): pain in the thighs, hips, or buttocks, weakness in the legs</td>
</tr>
<tr>
<td></td>
<td>Thoracic polyradiculopathy (less common, affects T4-T12 roots): severe abdominal pain, often with band-like pattern</td>
</tr>
<tr>
<td></td>
<td>Peripheral: most commonly affecting the median or peroneal nerves</td>
</tr>
<tr>
<td></td>
<td>Mononeuropathy multiplex: multiple mononeuropathies in the same patient</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>CV: postural hypotension, postprandial hypotension, fixed tachycardia, silent MI, sudden cardiac death</td>
</tr>
<tr>
<td></td>
<td>GI: esophageal motility disorders, gastroparesis, constipation, diarrhea, incontinence</td>
</tr>
<tr>
<td></td>
<td>GU: bladder dysfunction, incontinence, sexual dysfunction</td>
</tr>
<tr>
<td></td>
<td>Distal anhidrosis, gustatory sweating</td>
</tr>
<tr>
<td></td>
<td>Abnormal pupillary responses</td>
</tr>
</tbody>
</table>
Statins Underutilized in Type 2 Diabetes

Using a large electronic medical records database, Radican et al. from the US assessed the need for and prescription of statin medications in a large population (n=113,906; 48% male, 63±13 years) of adults with Type 2 diabetes (abstract 1302). Eligible patients had received an antihyperglycemic agent (oral or insulin) prescription between July 2006 and June 2008 (study period), a time during which the LDL-cholesterol (C) treatment guidelines according to the ADA were to achieve a target of <100 mg/dl. The index date was determined by the first prescription for an antihyperglycemic agent during the study period. Patient eligibility for statin therapy was assessed 1 year prior to (baseline) and 1 year after (follow-up) this date. At baseline, LDL-C was ≥100 mg/dl in 49% of the patients who were not being treated and in 34% of the patients who were taking a lipid-lowering agent. The majority (98%) of study patients met ADA eligibility standards for statin therapy, however only 64% of patients received a statin during the follow-up period. In adjusted logistic regression analyses, older age, male, smoking, baseline anti-hypertensive therapy, and baseline anticoagulant usage were significantly associated with increased likelihood of statin use (all p<0.001). A more integrated approach has been suggested to increase the use of atorvastatin, thereby reducing cardiovascular risk in patients with Type 2 diabetes.

OSA Associated with Severe Metabolic Derangements

In a study by Wangnoo et al. from India, 22 of 30 (73%) consecutive obese patients with Type 2 diabetes were determined to have OSA based on an AHImeasured ≥10/hour observed during polysomnography (abstract 622). Patients with OSA had higher HbA1c levels (9.7% vs. 8.9% for controls; p=0.03), BMI (33.8 vs. 29.4 kg/m², respectively; p=NS), triglycerides, insulin resistance scores, C-reactive protein, and lower HDL-C, as compared to controls. Of these variables, HbA1c seemed to correlate best with AHImeasured (r=0.29, p=0.001). Although not evaluated in this study, these data raise the concern that OSA and diabetes may have additive, or perhaps even synergistic, effects on risk of cardiovascular events.

The study's results point to the need to consider OSA in all obese patients with Type 2 diabetes, especially those with poor control, with the understanding that they may need more aggressive therapy for both their sleep disturbance and any associated metabolic or cardiovascular risk factors.

Donor Steatosis & Post-transplant Diabetes

Many risk factors for post-liver transplant diabetes mellitus have been identified, including hepatitis C infection, immunosuppressant use (including steroid and calcineurin inhibitors), age >45 years, family history of diabetes, obesity, impaired glucose tolerance, CMV infection, acute rejection, and cirrhosis. Yu et al. from China retrospectively analyzed 438 patients who underwent orthotopic liver transplantation, excluding those with a history of steroid use or those who died within the first 3 months following surgery. The investigators' purpose was to determine the relationship between steatosis in the donor's liver and post-transplant diabetes mellitus (PTDM) in the recipient (abstract 361). Nearly one-third of patients (140 [32%]) developed PTDM, and 298 in 103 (34.6%) patients who did not develop PTDM. In univariate analyses, liver function (according to the Child-Pugh grade system) and fasting plasma glucose prior to transplantation, the use of interleukin 2 receptor antagonists (IL-2RA) and calcineurin inhibitors, and steatosis of the donor's liver were significantly related with PTDM (p≤0.05). In multivariate regression analyses, baseline (presurgical) FPG (OR 1.9, p<0.01) and steatosis of the donor's liver (OR 1.8, p<0.05) increased the risk of PTDM, whereas the use of IL-2RAs actually appeared to reduce the risk (OR=0.427, p<0.01). These surprising findings address the important role of the liver in gluco regulation.

HbA1c after Erythropoietin Therapy

Ng et al. from the United Kingdom conducted a prospective study of 15 patients with Type 2 diabetes and chronic kidney disease (CKD) stage 3 or 4 (11 males, median age, 70 years) who were selected for treatment with erythropoietin stimulating agents (ESA) during January to December, 2009 (abstract 1202). They asked all patients to perform 7-point glucose monitoring 3-times weekly for the month before and during ESA treatment. Interstitial glucose levels were additionally determined via CGM. Over a mean follow-up period of 17.3 ±3.3 weeks, hemoglobin and hematocrit levels increased significantly (Table 4), while estimated GFR remained stable. Notably, HbA1c levels decreased (from 7.3 to 6.6%, p=0.001) without a discernible change in glucemic control (Table 4, mean blood glucose based on averaging daily capillary glucose readings on days with ≥3 readings as well as results of CGM). It appears that HbA1c decreases, independently of glucemic status, as a result of ESA treatment in patients with diabetes and CKD—likely the result of increased red cell turnover. These data suggest that alternative markers of glycemia may be needed to accurately assess glucose control in this population. Fructosamine and glycated albumin come to mind, but there are few data correlating these to the risk of diabetes complications.

Table 4. Impact of Erythropoietin Therapy in Patients with Type 2 Diabetes and CKD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before ESA</th>
<th>After ESA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.31 (6.42, 8.54)</td>
<td>6.63 (6.03, 7.36)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.5 (9.2, 9.9)</td>
<td>11.5 (11.2, 11.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32.4 (29.6, 35.0)</td>
<td>37.8 (34.1, 39.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean blood glucose (mg/dl)</td>
<td>157 (132, 182)</td>
<td>158 (134,180)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

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

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD
Editors, Yale University,
New Haven, Connecticut
The diagnosis of gestational diabetes mellitus (GDM) has evolved steadily since 1964 when Dr. John O’Sullivan and Claire Mahan published the first diagnostic criteria based on a statistical assessment of glycemic normality in pregnancy (O’Sullivan, Diabetes). Drs. Carpenter and Coustan later modified the criteria in 1982 based on accumulating data on neonatal and maternal outcomes in association with maternal hyperglycemia (Table 1). Over the last 3 decades, these standards have taken various forms from different professional organizations because there was no unifying data to inform a single criteria set. To say the least, it was confusing to have different cut-offs for ‘abnormal’ glycemia, determined from a single or combination of a 50, 75, or 100 grams of oral glucose over 2 or 3 hours.

While there remain dissenters regarding the clinical importance of identifying hyperglycemia in pregnancy, women with GDM are clearly at risk for many complications, including pre-term delivery, pre-eclampsia, and higher C-section rates. Also, their babies tend to be larger, with hyperinsulinemia and greater adiposity, leaving them at increased risk for shoulder dystocia and neonatal hypoglycemia. Recent investigations have also raised the possibility that these offspring are at greater risk for childhood obesity and Type 2 diabetes. This increased risk may result from a metabolically abnormal intrauterine environment and/or epigenetic phenomena, as well as post-natal environmental factors.

The standard therapeutic approach in women with GDM is to normalize blood glucose concentrations, focusing especially on postprandial readings, first with lifestyle change. Insulin is used if dietary interventions are not successful. In some centers, oral agents, such as glyburide and even metformin, have been incorporated into treatment regimens. Modest decreases in pregnancy and fetal/neonatal complications have generally been demonstrated in clinical trials. Thankfully, most women with GDM will experience a reprieve post-partum, when their severe insulin resistance, which was heightened by circulating placental factors, abates. They do, however, remain at considerable risk of future GDM and even frank Type 2 diabetes.

The landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study has shifted the paradigm over the past 2 years. HAPO further distinguished GDM from ordinary Type 2 diabetes by confirming a linear relationship between maternal blood glucose levels and the risk for neonatal and maternal complications (HAPO Study Cooperative Research Group, NEJM, 2008; Figure 1). This important observation has led to a challenging reconsideration of diagnostic cut-points for GDM.

Six months ago the International Association of Diabetes in Pregnancy Study Groups (IADPSG) published recommendations for the diagnosis of GDM, based directly on the HAPO data (Table 2). The proposed criteria require just one abnormal glucose level during a 75-g OGTT as well as lowering the threshold for fasting glucose from 95 to 92 mg/dl and the 2-hour glucose from 155 to 153 mg/dl, as compared to current American Diabetes Association (ADA) guidelines (Table 1). The latter were based on the criteria of 1997 4th International Workshop Conference of GDM, which endorsed a 2-step process and the Carpenter-Coustan thresholds (see above). This consists of a 1-hour 50-g glucose challenge test (GCT) at 24-28 weeks.
with those women whose plasma glucose exceed 140 mg/dl proceeding to a 3-hour 100-g OGTT; the diagnosis of GDM is made if 2 or more of the glycemic thresholds are reached, either fasting or at hours 1, 2, or 3. The term “ovoid diabetes” is additionally applied to women meeting traditional criteria for diabetes, and is meant to describe likely pre-gestational diabetes and a higher risk profile for both adverse neonatal and maternal outcomes.

The implications of these more stringent—and quite controversial—criteria were presented during an opening-day symposium, and may provide evidence in support of the IADPSG criteria. We note that the recommendations are currently being considered, but have not yet been endorsed, by international groups who set clinical policies, such as the ADA, the World Health Organization (WHO), and the American College of Obstetrics and Gynecology (ACOG).

David Hadden, MD from Ireland, the first speaker, reported the frequency of GDM within the HAPO study using the new IADPSG criteria. The overall frequency of GDM was 17.8%, including 1.7% overt diabetes, but the frequency varied substantially among sites, ranging from 8.7% in Israel to 23.7% in Cleveland, Ohio. Of note, all the U.S. sites were among the highest for GDM. This variation between sites persisted even when body mass index (BMI) was taken into account as a potential confounder. Dr. Hadden concluded that the variation was most likely a result of ethnic differences, and more detailed analyses are currently in progress.

Dr. Annunziata Lapolla also applied the new IADPSG criteria to a retrospective analysis of 26,549 pregnancies in Italy, finding that the more stringent criteria incorporated 112 (2.8%) more women into the GDM group, previously classified as having normal glucose tolerance (NGT). Interestingly, 85% of these women met the new criteria because of elevated fasting glucose levels. The newly GDM/NGT (GDM-NGT) women were younger (32.4 ± 4.5 vs. 33.4 ± 4.4 years, p=0.0039) and had a lower pre-pregnancy BMI (23.7 ± 4.3 vs. 24.7 ± 5.1 kg/m², p=0.005) than their traditional GDM counterparts. In comparison to women who remained NGT with the new criteria, GDM-NGT women had more C-sections (43.6% vs. 31.1%, p=0.008). However, there were no differences in gestational age at delivery or birthweight between the groups. Dr. Lapolla concluded that the women newly included into the GDM category showed similar metabolic characteristics and certain adverse pregnancy outcomes to those women currently being identified as GDM.

In a similar study re-analysis, Dr. Alexander Kautzky-Willer from Austria presented their longitudinal data of 1,466 pregnant women, comparing the impact of using the IADPSG versus older criteria on neonatal complications and maternal postpartum glucose tolerance. Invoking the new cutpoints increased the prevalence of GDM by 3%; women newly identified were older and had higher parity and higher blood pressures than women previously defined. IADPSG-diagnosed women proved to have 6.1% more large-for-gestational-age (LGA) neonates (p=0.0047), with 4.5% more babies > 4,000 gram birth weight (p=0.0047), and 3.3% more C-sections (p=0.0001) than if the current criteria were used. However, no difference in impaired postpartum glucose tolerance was detected between the two groups. Based on these findings, the speaker also supported the use of the IADPSG definition of GDM, and reported that Austria has actually been using it over the past year.

The new IADPSG criteria, if adopted, will obviously create an immediate increase by at least 3% in the overall prevalence of GDM, in some societies perhaps doubling the risk to the 15-16% range. In addition, an increase in GDM is anticipated as obesity rates continue to increase in women of reproductive age. What are the societal implications of doing so? Will resources be made available to address this new large group of patients? Yet, the studies from Italy and Austria, as well as from other centers, indicate that the inclusion of women with milder glucose intolerance does identify pregnancies at greater risk for adverse outcomes. Moreover, two studies suggest some benefit by treating these more mildly hyperglycemic mothers through lifestyle changes. Also, given concerns for epigenetic influences on future obesity and diabetes risk in offspring, the hope is that identification and treatment of GDM may play a downstream role in obesity and diabetes prevention.

Additional data will, of course, be required to understand how more aggressive glycemic control in pregnancy will affect long-term outcomes, especially weighed against the cost of resources required to supply the necessary medical care. Unfortunately, there is no randomized clinical trial that has yet been designed to specifically test diagnosis and treatment approaches based on the IADPSG criteria. Whether professional societies will eventually adopt the proposed criteria is unknown but scenarios should be made within the next year. All of these important issues will

### Table 2. IADPSG Criteria for Gestational Diabetes Based on 75-g OGTT

<table>
<thead>
<tr>
<th>Glucose Measure</th>
<th>Glucose Threshold (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>92</td>
</tr>
<tr>
<td>75-g OGTT</td>
<td>180</td>
</tr>
<tr>
<td>1-hour plasma glucose</td>
<td>153</td>
</tr>
</tbody>
</table>

Source: *Diabetes Care* 2010;33:676-682.
obviously need close consideration.

Sven Carlsen of Norway, the last speaker of the GDM symposium, addressed a related concern—the prevention of GDM with pharmacological therapy in a high-risk group. In the first trimester of pregnancy, 273 women with PCOS by the Rotterdam criteria (2 of 3: polycystic ovaries on ultrasonography, amenorrhea, or hyperandrogenism/hyperandrogenemia) were treated with diet and lifestyle intervention, and randomized to either metformin 1000 mg bid or placebo. A 75-g OGTT was performed before 13 weeks, then at weeks 19 and 32, with GDM defined as a fasting glucose ≥126 mg/dl or 2-hour glucose ≥140 mg/dl. 

The frequency of GDM was similar in the metformin and placebo groups (17.6% vs. 16.9%, p=0.87), although insulin was required in 4 patients in the placebo group and none in the metformin patients. It must be noted that the majority of patients in this study were Caucasian, young, and lean, with only 2 out of 3 meeting the NIH criteria for PCOS. This suggests that they represent a milder metabolic phenotype of PCOS, at likely lower risk for GDM. Also, 41 of 43 women were classified as having GDM by their 2-hour glucose value, which was set at a lower threshold than the IADPSG criteria.

In conclusion, it is unclear whether metformin may improve glucose tolerance in higher-risk pregnant women with PCOS. However, this study demonstrates that diet and exercise are effective in preventing glucose intolerance, and should remain the focus of prevention interventions.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with diabetes. How to detect it early and its connection to glucose control was the subject of multiple presentations this week.

Bouchi and colleagues from Japan examined the effect of HbA1c fluctuations on incident CVD in 689 Japanese Type 2 diabetes patients (abstract 79). Patients were included if they had at least 3 HbA1c measures per year and at least 12 months of follow-up. Fluctuations were defined as the intra-individual standard deviation (SD) of serially measured HbA1c values during follow-up. Patients had an average of 26 ± 14 HbA1c values during a mean follow-up period of 3.3 years. 61 patients met the primary endpoint, which included all incident CVD events (i.e., stroke, myocardial infarction, or angina requiring revascularization). Patients in higher quartiles of SD had a higher incidence of CVD (5-year cumulative incidence was 4.9, 8.7, 17.1, and 26.2% in the first to fourth SD quartiles, respectively; p<0.001).

As expected, cumulative incidence of events was also higher in patients with higher mean HbA1c; indeed, the HbA1c SD and the mean HbA1c were significantly correlated (r=0.54, p<0.001). In multivariate Cox analysis (adjusting for traditional CVD risk factors, including mean HbA1c and the number of HbA1c measures), the fourth (i.e., highest) quartile of SD HbA1c was associated with significantly higher incidence of CVD (HR 3.6, 95% CI 1.1-10.6) compared to the first quartile.

Patients undergoing coronary angiography for CAD (abstract 84) based upon the results of patients undergoing coronary angiography for established or suspected coronary artery disease (CAD) (abstract 84). Based upon the results of angiography, presence of significant CAD was defined as coronary stenoses ≥50%. Patients were prospectively followed for 8 years and vascular events (vascular mortality, cardiac death, non-fatal myocardial infarction or stroke, CABG, percutaneous coronary intervention, or non-coronary revascularization) were recorded. Event rate in those with neither Type 2 diabetes nor CAD was similar to that among patients with Type 2 diabetes and no CAD, higher in those without Type 2 diabetes but with CAD, and highest among those with both conditions (Figure 3). Although Type 2 diabetes is still thought to be a ‘coronary artery disease risk equivalent’, in this study, Type 2 diabetes patients without CAD had a significantly lower event rate than their non-diabetic peers with established coronary heart disease (p=0.017). Importantly, the decision to perform angiography may differ based upon diabetes status and could not be taken into account in this study. However, these data, and others, suggest that, in the context of aggressive, modern risk factor reduction strategies, the rate of appearance of coronary risk in our diabetic patients may actually be slowing.

Asymptomatic patients with diabetes are felt to be at higher risk for cardiovascular events. Screening asymptomatic patients for CAD remains controversial, with some investigators showing no benefit on clinical outcomes (DIAD Study, Young et al., JAMA 2009). Several small studies at the EASD meeting assessed the presence of sub-clinical CV events in patients with diabetes. Mokan and colleagues from Slovakia examined 47 patients (20 with Type 1 diabetes, 27 with Type 2 diabetes) without a history of CVD for the presence of cardiomyopathy, hypoperfusion, and cardiac autonomic neuropathy (abstract 1142). Treadmill testing was negative in all patients. Echocardiography showed diastolic dysfunction in 10% and 11% of patients with Type 1 and Type 2 diabetes, respectively. Hypoperfusion by 99mTc-tetrofosmin-gated SPECT was found in 35% and 60% of the respective cohorts. Cardiac autonomic dysfunction (based
on heart rate variability, spectral analysis, and a battery of tests developed originally by Ewing) was diagnosed in 60% and 77%, respectively. Overall, the investigators found that a large proportion of patients with diabetes had hypoperfusion by SPECT and cardiac autonomic dysfunction, whereas more conventional testing with treadmill and echocardiography identified few patients with abnormal findings, although this study did not contain a control group.

In another study, Valensi and French colleagues evaluated 263 asymptomatic patients with at least one cardiovascular risk factor who had silent myocardial ischemia (SMI, here defined as an abnormal stress myocardial scintigraphy) (abstract 1257). These patients subsequently underwent coronary angiography: 93 individuals had CAD (defined as a stenosis >70%) on angiography. Of these individuals, 29 had percutaneous coronary intervention, 7 coronary artery bypass (CABG), and 56 were treated medically. After a mean follow-up of 5.5 years, 8 cardiac deaths occurred, 23 acute coronary syndromes, 3 revascularizations, 1 cardiac failure, and 1 ventricular fibrillation. The incidence of events was lowest in patients with SMI but no CAD on angiography, intermediate in the group treated with revascularization, and highest in those with CAD who were subsequently treated medically. In the subgroup of patients with 3-vessel disease (n=17), the incidence of events was lower in those who underwent CABG than in those treated medically. This study adds to the recognition of poor prognosis in patients with SMI, but because of its retrospective, non-randomized design, specific recommendations regarding revascularization cannot yet be made. In the DIAD study noted above, which was randomized and involved more than 1,000 patients, no difference in morbidity and mortality was found between a screened and unscreened group, with cardiac event rate in the entire study being very low at <1% per year.

Although SMI has long been associated with diabetes, its relationship to pre-diabetic states is less clear. Intzilakis and colleagues from Denmark studied 596 non-diabetic individuals (age 55-75) without known CVD or cancer for the presence of SMI (defined as ST depression ≥1mm for at least 1 minute during 48-hour continuous ECG monitoring) and prediabetes (based upon fasting plasma glucose [FPG] 100-125 mg/dl) at baseline (abstract 1236). During follow-up (median 6.3 years), 77 individuals developed the primary endpoint of acute myocardial infarction and/or death. This occurred in 36% of individuals with prediabetes and SMI at baseline, 15% with prediabetes but no SMI, 12% with normal glucose and SMI, and 10% with neither abnormal glucose nor SMI. Subjects in the combined prediabetes/SMI cohort had a higher risk for the primary endpoint (HR 4.0, 95% CI 2.0-8.1) compared to those with normoglycemia/no SMI, even after adjustment for many cardiovascular risk factors, although the risk was attenuated (HR 2.5, 95% CI 1.2-5.2).

Prediabetes may raise the risk of cardiovascular events in patients with silent ischemia. Finally, although there is consensus regarding high cardiovascular risk in patients with diabetes, the optimal treatment targets in these patients remain controversial. Hemmingsen and colleagues from Denmark conducted a meta-analysis of 19 randomized clinical trials evaluating intensive vs. conventional glycemic control in patients with Type 2 diabetes (abstract 1250). To be included, trials had to pre-specify different targets of blood glucose control in patients. Data on 29,977 patients with a duration of intervention up to 12.5 years were analyzed. The primary outcomes of all-cause mortality and CVD mortality did not differ between the two groups (RR 1.00, 95% CI 0.93-1.08 and RR 1.05, 95% CI 0.95-1.17, respectively). The risk for all-cause mortality did not differ by disease duration, HbA1c, or fasting glucose at baseline. For secondary endpoints, intensive therapy was associated with a reduced risk of non-fatal myocardial infarction (RR 0.86, 95% CI 0.78-0.93), amputation of lower extremity (RR 0.64, 95% CI 0.44-0.95), nephropathy (RR 0.80, 95% CI 0.70-0.91), retinal photocoagulation (RR 0.79, 95% CI 0.69-0.91), and all microvascular complications combined (RR 0.85, 95% CI 0.78-0.93), but not of non-fatal stroke, cardiac or peripheral revascularization. Serious adverse events were more frequent in the intensively-treated patients and the risk for severe hypoglycemia was increased (RR 2.71, 95% CI 2.42-3.02).

It remains unclear how to weigh the potential risks and benefits of intensive glucose control in everyday clinical practice, and more work is needed to define which patients derive more benefit than harm from intensive control. As has been emphasized in the latest guidelines, individualization of therapeutic targets in diabetes is of increasing importance.

Insulin – An Oldie but Goodie

Multiple studies presented at the EASD this week focused on optimizing insulin therapy with currently available formulations in a variety of combinations and dosing regimens. UK investigators, Hope et al. (abstract 995) inquired whether patients with a long history of Type 2 diabetes develop absolute insulin deficiency, which in turn would alter the therapeutic approach for them. Urinary C-peptide:creatinine ratio (UCPCR) from a single urine sample has been previously shown to be a non-invasive indicator of endogenous insulin production. UCPCR values in patients with Type 2 diabetes (n=171) who started insulin at least one year post-diagnosis were evaluated. Subjects with a UCPCR of ≤0.2 nmol/mmol were considered to have an absolute insulin deficiency. This occurred in 13.5% (23/171) of patients. Characteristics of these patients included longer
diabetes duration (18 vs. 12 years, p=0.02) and higher daily insulin dose (0.77 vs. 0.5 units/kg/24 hours, p=0.01). There was no association with age at diagnosis (median 58 vs. 58 years, p=0.27), BMI (29 vs. 29 kg/m², p=0.87), HbA1c (8.0 vs. 7.8%, p=0.76), time from diagnosis to insulin initiation (6.0 vs. 5.5 years, p=0.31), or concomitant treatment with oral agents (52% vs. 62%, p=0.36). In the insulin deficient, 17% (4/23) and 34.8% (8/23) were managed with basal-bolus and basal only regimens, respectively. The investigators pointed out that a proportion of patients with long-standing Type 2 diabetes on higher doses of insulin may indeed be insulin deficient, and these individuals demonstrate certain clinical differences when compared to their non-insulin deficient counterparts. UCPCR as a diagnostic tool, along with recognition of the potential for insulin deficiency, may play a significant role in optimizing their therapeutic management.

How do advanced insulin strategies compare beyond the simple, basal-only approach? This was the question asked by Storms and researchers from The Netherlands and Belgium. The group conducted a 6-month, prospective observational study evaluating the efficacy and safety of switching patients to glargine plus gluculoline (The Netherlands) or glargine and any rapid-acting insulin (Belgium) from premixed insulin, dosed twice daily (abstract 962). Described as a “real world” clinical trial setting, patients with Type 2 diabetes (n=214) were enrolled if their insulin regimen was being converted from twice daily premixed to a basal-bolus regimen. The primary aim was to determine the proportion of patients at goal HbA1c (<7%) 6 months following the conversion. Additional measures such as changes in mean HbA1c, FPG, self-monitoring results, weight, insulin dose, hypoglycemia rates, and patient satisfaction were also assessed. The percent of patients achieving goal HbA1c significantly improved at month 6 upon switch to basal-bolus, as did other measures (Table 4). Weight did not differ significantly, yet the incidence of nocturnal and severe hypoglycemia was reduced. Patient satisfaction scores also improved (p<0.0001), as measured by diabetes treatment satisfaction questionnaires. The researchers concluded that conversion to basal-bolus insulin dosing from a pre-mixed regimen in a real-world setting improves glycemic control and enhances patient satisfaction, without increasing weight or hypoglycemia. These data are of some interest, but we would caution over interpretation, given the open-label, non-randomized design of the study.

Combined insulin-oral agent therapy was the topic addressed by Pfutzner and German colleagues. These investigators conducted an interim analysis of the PIOcomb study, assessing the metabolic benefits of insulin plus pioglitazone versus insulin plus metformin (abstract 899). Type 2 diabetes patients (n=78) on prior insulin therapy were transitioned to an individualized and optimized regimen of glargine, then randomized to additionally receive pioglitazone 30 mg/day, metformin 1700 mg/day, or a combination of both oral agents. Baseline and 6-month measures of various parameters were measured (Table 5). HbA1c was stable in the two drug groups, but improved with the triple combination. There were no differences in hypoglycemic event rates among the three treatment arms. The pioglitazone combinations resulted in increased insulin sensitivity, reduced insulin dose, and improved biomarkers of cardiometabolic syndrome (e.g., adiponectin, CRP).

While the standard approach with the newer analogs (i.e., detemir, glargine) is generally once daily dosing, Dhatriya and co-investigators from the UK examined whether twice daily dosing would provide better glycemic control (abstract 977). In a retrospective case analysis, HbA1c data were collected from 206 patients with Type 1 or Type 2 diabetes; 38% (78/206) taking glargine once daily and 62% (128/206) on twice daily at baseline. Those who switched from another insulin regimen to once daily glargine had a 0.27% reduction in HbA1c; a mean decrease of 0.49% occurred when they were switched to bid glargine. Based on these findings, the investigators suggested that twice daily* dosed glargine may confer additional HbA1c benefit over once daily administration in selected patients.

Detemir, the other long-acting basal insulin, was the subject of an investigation by Zachariah and UK colleagues (abstract 981). Noting that detemir has been associated with less weight gain than other insulins, these investigators sought to determine the potential mechanism. In a 32-week, open-label crossover study, 23 patients with Type 1 diabetes managed with a basal-bolus (aspart) regimen were randomized to receive either detemir or NPH as their basal insulin for 16 weeks, then crossed over to receive the other basal for

**Table 4. Patient Parameters Upon Conversion from Pre-Mixed Insulin Dosing to Basal-Bolus Regimens**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Month 6</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with HbA1c &lt; 7% (95% CI)</td>
<td>3.3 (1.6-6.7)</td>
<td>24.9 (19.0-31.8)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.2 ± 4.5</td>
<td>7.5 ± 0.9</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>187 ± 73</td>
<td>140 ± 48</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>7-point SMBG (mg/dl)</td>
<td>195 ± 48</td>
<td>153 ± 36</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Basal dose (glargine, units/day)</td>
<td>28.1 ± 17.4</td>
<td>34.7 ± 22.1</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Bolus dose (rapid-acting insulins, units/day)</td>
<td>35.7 ± 17.5</td>
<td>43.8 ± 20.9</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Hypoglycemia: patient-reported reduction from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal: 33.9% decrease</td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Severe: 27.8% decrease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SMBG=self-monitored blood glucose.

**Table 5. Parameters at Baseline and Endpoint with 3 Insulin-Based Regimens**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metformin + Glargine (n=25)</th>
<th>Pioglitazone + Glargine (n=28)</th>
<th>Metformin + Pioglitazone + Glargine (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.3 ± 0.6</td>
<td>7.4 ± 0.6</td>
<td>7.3 ± 0.5</td>
</tr>
<tr>
<td>Daily insulin dose (units)</td>
<td>37 ± 17</td>
<td>37 ± 17</td>
<td>36 ± 21</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.5 ± 2.6</td>
<td>4.4 ± 2.1</td>
<td>3.3 ± 2.9</td>
</tr>
<tr>
<td>Adiponectin (mg/l)</td>
<td>4.2 ± 2.4</td>
<td>4.0 ± 2.5</td>
<td>4.7 ± 3.2</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>3.6 ± 2.7</td>
<td>3.3 ± 2.7</td>
<td>2.6 ± 1.9</td>
</tr>
</tbody>
</table>

*p<0.05 vs. baseline (HOMA-IR, a measure of insulin resistance.)
an additional 16 weeks. Measures of energy intake/expenditure along with glycemic control parameters and satiety hormones were collected at various intervals. After the first treatment period, the impact on weight with detemir was -0.69 vs. +1.7 kg with NPH (p=0.0006). Total energy expenditure (measured by double-labeled water) was not significantly different between groups, whereas energy intake (measured by 7-day food diary) was significantly lower in detemir patients (2,016 vs. 2,181 kcal/day, p=0.026).

Finally, these days many patients require very high-dose insulin therapy. In such circumstances, human regular U500 has been useful to maintain the total dose needed, but with minimization of injection volume. U500 is 5-times as concentrated as U100, so that 10 ‘units’ on an insulin syringe (i.e., 0.1 ml) actually comprises 50 units of insulin. Its time course of action is somewhere between Regular U100 and NPH, with dosing typically 2-3 times per day. Despite being on the US market since 1997, there are few studies characterizing the pharmacokinetic (PK)/pharmacodynamic (PD) properties of this insulin. Linnebjerg and US researchers evaluated 24 healthy obese subjects (weight 98.1 kg, BMI 34.4 kg/m²) in a randomized, double-blind, crossover, euglycemic clamp study of U500 and U100, each given at two fixed doses, 50 and 100 units. Serum immunoreactive insulin and glucose infusion rates were measured for PK/PD analyses, respectively. Area-under-the-curve (AUC) concentrations were similar for both doses of either insulin. However, with U500, peak concentrations were lower (p<0.05) and duration of effect was longer at both doses. U500 also had a longer time-to-peak concentration and time-to-peak effect (p<0.05), but at the higher dose (100 units) only. The clinical implication of these findings is that in patients who require high-dose insulin therapy, the longer duration of action/time to peak may favor use of U500 injections in multiple daily doses, negating the need for an additional basal insulin. However, randomized clinical trials are needed to assess the efficacy and safety of this approach.

To optimally manage both Type 1 and Type 2 diabetes, a sound knowledge base about the various available insulin formulations is important. We look forward to similar investigations at our international diabetes meetings, bringing you the very latest information to help optimize the use of this very important therapy.

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

**Implications of Islet Autoimmunity at Diagnosis in T1DM**

In a large cohort of children with Type 1 diabetes prospectively followed, Holl et al. from Germany and Austria assessed the association between measured islet autoimmunity at disease onset and future insulin requirements and metabolic control (abstract 139). Of 3,302 patients who had onset of Type 1 diabetes prior to age 12 and continuous follow-up from diagnosis for 5 years (age at onset: 7.1±3.1 years, 50.4% male), islet antibodies (ICA, IA2, GAD or IAA) were absent at diagnosis in 263 patients (8%). One antibody only proved positive in 790 patients (24%) and ≥2 antibodies in 2,249 patients (68%). There were no differences among the groups based on gender, age at onset, initial BMI, rate of diabetic ketoacidosis, or HbA1c at diagnosis. Concomitant thyroid autoimmunity was more common in the group with multiple antibodies (24.1% vs. 17.6% and 16.7% in patients with 1 and 0 antibodies, respectively, p<0.001). Mean daily insulin requirement, adjusted for age at onset, gender, BMI, and insulin regimen, was slightly, but significantly higher in patients with multiple antibodies vs. antibody-negative patients during the first 3 years of diabetes (1st year: 0.55 vs. 0.52 U/kg, respectively, p<0.05). However, these trends disappeared thereafter (by year 5, 0.85 U/kg in those with single or multiple antibodies vs. 0.83 in antibody-negative patients, p=NS). Throughout the 5-year period, adjusted HbA1c values were similar among the 3 groups (7.5-7.6%).

**Gut Microbiota and Metabolism**

In animal models, obesity has been shown to be associated with alterations in the microbiology of the gut. Vrieze et al. from the Netherlands and Finland conducted a double-blind study in which 18 male subjects with newly diagnosed and untreated metabolic syndrome (BMI ≥30 kg/m², FPG >100 mg/dl, triglycerides >142 mg/dl) underwent bowel lavage through a duodenal tube followed by randomization to either allogenic fecal transplantation (from lean males, n=9) or autologous fecal transplantation (reinfusion of own collected feces, n=9) (abstract 90). At 12 weeks after the procedure, fasting triglycerides (as measured by TG/ApoB ratio) were significantly reduced (1.43±0.21 to 1.11±0.18, p<0.01) among the subjects who received allogenic donor feces (from lean subjects), but not after autologous feces infusion. Likewise, there was improvement in both peripheral insulin sensitivity as measured by clamp (from 26.2 to 45.3 µmol/kg/min, p=0.02) and hepatic insulin sensitivity (suppression of endogenous glucose production; from 51.5% to 61.6%, p=0.08) at 6 weeks after the procedure in the allogenic group, but not in the autologous group. These results suggest a potential role of gut flora in the disturbances of glucose and lipid metabolism in obesity and could provide pathophysiological insights into their origins. The therapeutic technique will require a bit more refinement, however!

**Less Stringent Targets in the Aged?**

Van Hateren et al. from The Netherlands determined the impact of glucose control on cardiovascular mortality over a 10-year period in a prospective, observational study of Type 2 diabetes patients older than 75 years (abstract 398). In patients with diabetes for less than 5 years, each 1% increase in HbA1c was associated with an increase in all-cause and cardiovascular mortality risk of 40% and 66%, respectively. According to results of a Cox proportional hazard model, including age, gender, smoking status, BMI, diabetes duration, serum creatinine, overt macrovascular complications, albuminuria, systolic blood pressure, total cholesterol/HDL ratio, and insulin use as potential confounders, glycemic control (HbA1c <7%) was associated with decreased risks of all-cause mortality (HR 0.56, 95% CI 0.33-0.95) and cardiovascular mortality (HR 0.28, 95% CI 0.11-0.69), compared to poor control, in elderly patients with diabetes for less than 5 years, but not among those with diabetes for a longer period of time. These data are consistent with several large, randomized clinical trials that were presented in 2008 (ACCORD, ADVANCE, VADT, see Diabetes 2008, volume 17). Based on these, there are increasing calls for less rigid targets in the elderly, particularly those with established vascular complications.

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

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University,
New Haven, Connecticut
The American Diabetes Association (ADA) recently endorsed HbA1c (≥6.5%) for diagnosis of diabetes and prediabetes (Table 1), but it has become clear that this change in the diagnostic criteria will have an important impact on the epidemiology of the dysglycemic states around the world. Advantages and disadvantages of the HbA1c test are noted in Table 2.

Table 1. 2010 ADA Criteria for Diagnosis of Diabetes and Pre-Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Prediabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>100-125</td>
<td>≥126</td>
</tr>
<tr>
<td>2-hour plasma glucose (mg/dl)</td>
<td>140-199</td>
<td>≥200</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.7-6.4</td>
<td>≥6.5</td>
</tr>
</tbody>
</table>

Cabrera and colleagues from Spain and Finland examined concordance of the conventional 2-hour plasma glucose (PG) during OGTT and/or fasting plasma glucose (FPG) criteria with the new HbA1c criteria for diabetes and prediabetes using data from an active public health program (DE-PLAN) in Catalonia (abstract 194). They screened 1,144 non-diabetic subjects (ages 45-75 years) annually and obtained 2,287 blood tests for glucose and HbA1c. The demographics of the sample were: 65% women, mean age 61.4 years, BMI 29.9 kg/m², and 68% were deemed to be at moderate to very high risk for diabetes (by FINDRISC score). Individuals were categorized as normoglycemic (64.8% when using 2-hour PG, 68.7% using FPG, and 83.4% using HbA1c), prediabetic (26.6% when using 2-hour PG, 28.5% using FPG, and 15.3% using HbA1c), and diabetic (8.6% using 2-hour PG, 2.8% using FPG, and 1.3% using HbA1c). Among individuals diagnosed with diabetes either by 2-hour PG or HbA1c, only 12.9% were identified by both criteria, underscoring the large proportion of discordant cases. Likewise, among those individuals diagnosed with diabetes either by FPG or HbA1c, only 25.3% met both criteria. The investigators did not find differences in age, sex, BMI, waist circumference, or the FINDRISC score between those diagnosed by both criteria and by one alone. They concluded that application of the new HbA1c criteria for dysglycemic states in this population was not advisable given the poor concordance with standard glucose-based testing.

Similarly, Midthjell and colleagues from Australia screened over 50,000 individuals for diabetes risk between years 2006-2008 also using the FINDRISC score (abstract 195). They

Table 2. Advantages & Disadvantages of the HbA1c (vs. Fasting Plasma Glucose) for Diabetes Diagnosis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Convenience—fasting not required</td>
<td>◆ Misleading results in patients with high/low red cell turnover</td>
</tr>
<tr>
<td>◆ Globally standardized</td>
<td>◆ High (false low HbA1c) in hemolysis, hemoglobinopathy, treatment for iron/B12/folate deficiency, or pregnancy</td>
</tr>
<tr>
<td>◆ Low coefficient of variation, excellent reproducibility</td>
<td>◆ Low (false high HbA1c) in iron/B12/folate deficiency</td>
</tr>
<tr>
<td>◆ Better pre-analytic stability</td>
<td>◆ Altered in chronic kidney disease, erythropoietin therapy</td>
</tr>
<tr>
<td>◆ Excellent correlation with diabetic complications</td>
<td>◆ Imperfect correlation with fasting and post-challenge glucose (particularly in African-American and older individuals)</td>
</tr>
<tr>
<td></td>
<td>◆ Higher cost than measurement of glucose</td>
</tr>
</tbody>
</table>
invited only high-risk individuals (FINIDRISC score ≥15) for follow-up OGTT and HbA1c testing, resulting in 2,645 study participants. Using OGTT results, they identified 9.6% as having diabetes, 16.9% as IGT, and 8.2% as IFG. In contrast, HbA1c identified fewer subjects with diabetes (6.5%) and classified an additional 17% as high risk for diabetes, using HbA1c 6.0-6.4%. Among those classified as diabetic by glucose criteria, the majority (60.7%) had an HbA1c below 6.5%. As in the Catalonias study, the concordance between glucose and HbA1c criteria was poor, signaling that adoption of the HbA1c criteria worldwide may not gain rapid acceptance.

Slightly different results were reported by Cosson and colleagues from France, who examined 1,157 individuals at risk for diabetes (abstract 196). All subjects underwent an OGTT, and HbA1c was also obtained. In this study, fewer patients met the criteria for diabetes based upon OGTT (n=76) than HbA1c (n=113). A similar number of individuals met criteria for prediabetes, however, based upon the tests (n=307 and 299, respectively). Consistent with prior studies, the concordance between the tests remained poor—a third of individuals with HbA1c ≥6.5% had a normal OGTT result. Further analysis showed that individuals with both an abnormal OGTT and increased HbA1c (≥5.7%) were at the highest diabetes and cardiovascular risk.

Finally, a very large retrospective study by Kim and colleagues from Korea compared the concordance of FPG and HbA1c for diabetes in 35,624 individuals (abstract 198). Those patients with known diabetes, significant anemia, or hemoglobinopathy were excluded. Although roughly similar proportions were identified as diabetic (3.2% by FPG and 2.9% by HbA1c), the tests classified different individuals with the disease. Thus, among those meeting either criteria, about a third (31.6%) were diagnosed by FPG only, about a quarter (23.5%) were diagnosed by HbA1c only, and the remainder (44.9%) by both tests. Those identified only by HbA1c were older, had lower hemoglobin concentration, lower blood pressure, lower fasting insulin, and lower HOMA-IR compared to those identified only by FPG. Thus, the metabolic derangements in both groups may indeed be quite different.

While of great interest with regard to the epidemiology of diabetes based on various tests, these studies are predicated on the illusion that prior criteria were ‘gold standards.’ Indeed, all 3 criteria—HbA1c, FPG, and 2-hour PG—correlate well with microvascular complications in diabetic patients and with the risk of developing diabetes in those in high-risk categories (i.e., ‘pre-diabetes’). Which is the best test is arguable and, in part, dependent on local availability and experience. The good news is that a variety of screening methods are now available, so that affected individuals can be easily identified, lifestyle changed, and when necessary, pharmacotherapy can be instituted as soon as possible.

### Table 3. Meta-Analysis of Incretin-Based Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Studiest</th>
<th>No. of Subjects†</th>
<th>HbA1c (%)</th>
<th>FPG (mg/dl)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1 Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide 2 mg weekly*</td>
<td>3</td>
<td>323</td>
<td>-1.7</td>
<td>[-2.0, -1.4]</td>
<td>-36.0 [-43.2, -28.8]</td>
</tr>
<tr>
<td>Exenatide 10 µg twice daily</td>
<td>12</td>
<td>2,216</td>
<td>-1.0</td>
<td>[-1.2, -0.9]</td>
<td>-19.8 [-23.4, -16.2]</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg daily</td>
<td>6</td>
<td>1,345</td>
<td>-1.2</td>
<td>[-1.3, -1.1]</td>
<td>-30.6 [-36.0, -25.2]</td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin* 25 mg daily</td>
<td>5</td>
<td>902</td>
<td>-0.7</td>
<td>[-0.9, -0.5]</td>
<td>-18.0 [-23.4, -12.6]</td>
</tr>
<tr>
<td>Saxagliptin 5 mg daily</td>
<td>4</td>
<td>581</td>
<td>-0.7</td>
<td>[-0.8, -0.5]</td>
<td>-16.2 [-23.4, -9.0]</td>
</tr>
<tr>
<td>Sitagliptin 100 mg daily</td>
<td>13</td>
<td>2,689</td>
<td>-0.7</td>
<td>[-0.7, -0.6]</td>
<td>-16.2 [-18.0, -12.6]</td>
</tr>
<tr>
<td>Vildagliptin 100 mg daily</td>
<td>17</td>
<td>5,210</td>
<td>-0.9</td>
<td>[-1.0, -0.8]</td>
<td>-19.8 [-21.6, -18.0]</td>
</tr>
</tbody>
</table>

*Investigational. †For HbA1c analysis.

219 studies identified (all in Type 2 diabetes), 63 were randomized controlled trials (12-52 weeks duration) with the desired primary endpoints: change in HbA1c, FPG, and weight from baseline. Results with the highest doses of each compound studied were then tallied (Table 3). Overall, each class significantly reduced HbA1c, FPG, and weight, as compared to baseline, but the greatest magnitude of reduction was seen with the GLP-1 agonists. As noted above in the meta-analysis, the vast majority of data related to the incretin-based therapies are derived from patients with Type 2 diabetes, reflected in the FDA-labeling for each of the approved agents. Two posters at the EASD assessed the role of liraglutide and sitagliptin in the management of patients with Type 1 diabetes*. Kielgast and Danish investigators, examined the impact of daily liraglutide in Type 1 patients with residual beta-cell function (n=8) following 4 weeks of treatment in addition to their basal-bolus insulin regimen (abstract 853). Measures of glycemic control (i.e., HbA1c) and weight were analyzed during the 3 days prior to initiation of liraglutide...
and last 3 days of treatment. Two of the 8 patients actually discontinued insulin while receiving the GLP-1 agonist, without loss of glycemic control. Mean HbA1c decreased during liraglutide treatment from 6.6 to 6.2% (p = 0.05). The percentage of patients with glucose values <70 mg/dL decreased from 12.0% to 5.1% (p = 0.03). Weight loss occurred in all patients (on average of -2.6 kg; range -1.5 to -3.6). While response rates were promising, all patients experienced gastrointestinal (GI) side effects, most transient, with 2 requiring lower doses (0.9 mg). Results from this small, uncontrolled study will need to be validated in larger trials, but suggest that GLP-1 agonists may be successfully used to maintain glycemic control and reduce insulin requirements in Type 1 diabetes patients with residual beta-cell function.

In a related trial, Ellis and researchers from the US conducted a pilot study investigating the effect of the DPP-4 inhibitor, sitagliptin, on glycemia in poorly controlled (HbA1c 8.5–12%) patients with Type 1 diabetes (abstract 77). A continuous glucose monitor (CGM) was used to monitor glycemic control in this double-blind, randomized, crossover trial of 20 patients who received sitagliptin 100 mg or placebo for 1 month each. While receiving sitagliptin, patients had their insulin doses significantly reduced (p = 0.02). Downloads from CGM demonstrated a decrease in mean blood glucose values during DPP-4 inhibitor treatment (mean = -10.9 mg/dL, p = 0.012) as well as greater periods of time in the euglycemic range (+0.46 hour, p = 0.046) and less, although not significant, time in the hyperglycemic range (-0.55 hour, p = 0.17). Additionally, there was a significant reduction in HbA1c with sitagliptin during both periods within groups (we note that placebo also had an apparent beneficial effect during month 1—this was not addressed during the presentation). These data suggest successful use of DPP-4 inhibitors in patients with Type 1 diabetes. However, the researchers noted that larger trials of longer duration are needed to truly determine their utility.

Another area of interest in the incretin field is manipulation of existing GLP-1 agonists to develop agents of longer duration that can be administered less frequently than the prototype compound, twice daily exenatide. The longer-acting compounds appear to be better tolerated and may have a more favorable impact on some glycemic measures. Pullman et al. from the US compared an extended duration formulation of exenatide, permitting weekly delivery,* with the traditional twice daily agent in a 24-week, randomized, open-label study of 252 Type 2 diabetes patients (abstract 843). Patients were either drug naïve (18.7%) or were taking one (46.8%) or multiple coconcurrent oral agents (34.5%). All measures of glycemic control improved with the weekly formulation of exenatide: HbA1c (-1.6% on weekly vs. -0.9% on twice daily, p < 0.0001), FPG (-34.1 mg/dl on weekly vs. -12.6 mg/dl on twice daily, p = 0.0008), and proportion of patients achieving goal HbA1c < 6.5% (41.1% on weekly vs. 16.3% on twice daily, p < 0.0001). Improvements were independent of other concurrent therapies. Patients on the weekly formulation also experienced a lower incidence of GI side effects, although injection site reactions occurred with greater frequency. Weight loss was observed in both groups. Overall, the weekly formulation appears to offer more favorable glycemic control and is better tolerated than twice daily exenatide.

Another method of prolonging exenatide dosing, which also provides consistent drug delivery, is the use of ITCA 650; a continuous subcutaneous delivery device that uses DUROS technology. DUROS is a subcutaneous osmotic delivery system allowing for one time administration of exenatide that provides drug for up to 12 months. Henry and co-investigators from the US examined ITCA 650 in a phase 2 study of poorly controlled Type 2 diabetes patients comparing it to twice daily exenatide (abstract 78). Patients were randomized to receive a single dose of exenatide by ITCA 650, delivering 20 or 40 µg/day for 12 weeks or twice daily dosed exenatide (5 µg bid x 4 weeks, then 10 µg bid x 8 weeks). Following the initial 12 weeks, patients were then randomized to receive ITCA 650, delivering doses of 20, 40, 60, or 80 µg/day for 12 additional weeks. All treatment groups experienced weight loss and decreased HbA1c values at the 12-week mark (p < 0.001). Additional HbA1c reductions and continued weight loss occurred at week 16 with further exenatide dose escalation (60-80 µg/day). Nausea occurred less frequently in the group dosed at 20 µg/day of ITCA 650 versus those on injection therapy. This may be a promising delivery mode for exenatide, which might allow for enhanced compliance and improved tolerability without multiple daily injections. Further research is, of course, needed.

Data on the clinical utility, dosing optimization, and method of delivery continue to evolve in the incretin field, with additional compounds and formulations on the horizon. Certainly, these agents have an important niche in the antihyperglycemic therapy of Type 2 diabetes. We obviously need more data going forward on cardiovascular effects, glycemic durability, and long-term safety.

Kidney Kronicles

Nephropathy is a common complication of diabetes. Patients with early stage diabetic nephropathy often have persistent microalbuminuria, now also recognized as a marker for cardiovascular disease risk. Glycemic and blood pressure control and blockade of the renin-angiotensin system all reduce the development and/or progression of diabetic nephropathy. Results of presentations made this week further our understanding in this area.

Interested in progression of nephropathy in diabetic patients and associated demographic/clinical characteristics, Vuppuru et al. from the US conducted a population-based study involving 11,562 members with Type 2 diabetes and hypertension from a managed care organization (abstract 111). The mean age was 59.4 ± 11.3 years, 50% were male, 18% African-American, and the mean HbA1c was 8.1%. All participants had a urine albumin-to-creatinine ratio (UACR) measurement in 2001-2003, and at least 1 follow-up determination. At baseline, 59% had normal UACR (<3.4 mg/mmol), 30% had microalbuminuria (3.4-33.9 mg/mmol), and 11% had macroalbuminuria (≥33.9 mg/mmol). A review of the medical records during 2008 showed significant progression from baseline to a higher stage of nephropathy across all subgroups. 68% of all patients had

![Figure 1. Impact of Sitagliptin vs. Placebo on HbA1c in Type 1 Diabetes](image-url)
developed micro- or macro-albuminuria by the end of the follow-up period (Figure 2). At this time, most patients were on antihypertensive therapy; approximately two-thirds of patients were taking an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), except patients with macroalbuminuria at follow-up. Age, diabetes duration, and HbA1c were significant predictors of progression. These results suggest that the lifetime risk of renal disease and its progression among adults with diabetes and hypertension may be greater than previously reported and that modulators of the renin-angiotensin axis may be underutilized for its slowing and/or prevention.

Albuminuria and renal impairment are traditionally linked in patients with Type 2 diabetes. In a cross-sectional study conducted by Afghahi et al. from Sweden, however, the prevalence of non-albuminuric renal impairment in Type 2 diabetic patients was determined, along with associated clinical characteristics, in a large nation-wide, population-based diabetes register (n=62,661; aged 30-80 years) (abstract 110). 15% of all patients (n=9,308) had renal dysfunction (as defined by an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m² by the MDRD equation). Among these individuals, 56% were non-albuminuric and 42% were albuminuric (urinary albumin excretion rate > 20 µg/min). In multivariate analyses, patients with non-albuminuric renal impairment had significantly and independently shorter diabetes duration (adjusted OR [95% CI] = 0.73 [0.70-0.76]), higher total cholesterol (1.05 [1.01-1.10]), lower levels of triglycerides (0.83 [0.80-0.87]), lower systolic blood pressure (0.81 [0.78-0.84]), better glycemic control (HbA1c% (0.86 [0.82-0.91]), lower BMI (0.88 [0.84-0.93]), and were more often female and non-smokers, as compared with patients with albuminuric renal impairment. Taken together, these findings demonstrate that the majority of patients with Type 2 diabetes and renal impairment do not exhibit albuminuria and that this cohort has fewer features of the metabolic syndrome than those with more classical diabetic renal disease. Markers and methods that accurately estimate renal function are needed for screening, follow-up, and treatment of patients with Type 2 diabetes, even when albuminuria is absent.

Brovodovc et al. from Wales and the US quantified the risk of acute renal failure (ARF) in Type 2 diabetes using a large general practice database from the United Kingdom (2,834,927 patients without and 148,963 with diabetes) (abstract 401). Between 2003 and 2007, the incidence of ARF was 192 per 100,000 person-years in patients with diabetes compared to 24 per 100,000 person-years among those without diabetes (crude HR 8.3 [95% CI 7.7, 8.9]). The risk of ARF for the diabetic patients remained significant, but attenuated, in multivariate analyses adjusting for various potentially confounding factors (age, obesity, prior ARF, heart failure, CKD, hypertension, and Charlson comorbidity index) (adjusted HR 2.4 [2.2, 2.5]). Of note, CKD alone was not associated with an increased risk of ARF diagnosis (adjusted HR 1.25 [0.97 - 1.59]). The combination of Type 2 diabetes, heart failure, and hypertension further increased the risk for ARF relative to patients without diabetes (Figure 3). Physicians should remember this increased risk of ARF in Type 2 diabetes patients, and the additional risk associated with the presence of comorbidities.

Zoungas and international co-investigators determined the effects of intensive glucose lowering (HbA1c ≤6.5%) on renal outcomes among 11,140 Type 2 diabetes patients who participated in the Action in Diabetes and Vascular disease: preterAx and diamicron-MR Controlled Evaluation (ADVANCE) study (abstract 221). Patients were randomly assigned to intensive glucose control based on the use of glargiide MR* (a sulfonylurea not available in the US) and other medications as required to achieve the target HbA1c level of ≤6.5% or standard glucose control (defined on the basis of local guidelines). After a median follow-up of 5.0 years, the mean HbA1c level achieved was 6.5% in the intensive control group and 7.3% in the standard control group. Intensive glucose control led to significantly reduced risk for (1) total renal events (by 11% [95% CI, 5%-17%]; p<0.001), (2) new or worsening nephropathy (by 21% [7%-34%]; p=0.006), (3) new-onset microalbuminuria (defined as UACR 30 to 300 g/mg) (by 9% [CI 2%-5%]; p=0.018), (4) new-onset macroalbuminuria (defined as UACR >300 g/mg) (by 30% [15%-43%]; p<0.001), and (5) progression of albuminuria by at least one
Hypoglycemia is the event that limits insulin dosing and tight glycemic control in many patients with diabetes. It is also well recognized to have both immediate and long-term adverse effects, and its potential relationship to cardiovascular (CV) events was highlighted in the ACCORD, VADT, and ADVANCE trials for higher risk patients with Type 2 diabetes. Several poster presentations this week addressed this important clinical concern.

Galan et al. presented data on risk factors that predict severe hypoglycemia in a sub-study of the ADVANCE trial (abstract 589). The collaborators found that 231 of 11,140 patients (2.1%) experienced severe hypoglycemia (defined as needing assistance of another) over a 5-year follow-up. This was statistically associated (p<0.05) with multiple baseline characteristics such as age, diabetes duration, renal dysfunction, smoking, BMI, HbA1c, assignment to the intensive glucose control arm of the trial, and use of combination anti-hyperglycemic therapy. However, since the mean time interval between the first severe hypoglycemic event and a major CV event was 1.56 years (IQR=0.84, 2.41 years), and that between the event and death was 1.05 years (IQR=0.34, 2.41 years), the researchers concluded that there was no temporal relationship, making causality between hypoglycemia and cardiac ischemia less likely. We would note that repeat hypoglycemic episodes or unrecognized hypoglycemic may make causality difficult to recognize.

Vespasiani et al. also assessed risk factors for hypoglycemia in their multi-national prospective study of 2,510 patients with Type 2 diabetes initiated on insulin therapy (abstract 577). 504 (20.1%) patients had at least one documented episode of symptomatic hypoglycemia between 6 and 12 months after starting insulin. In a multi-variable analysis, higher HbA1c levels and BMI were associated with a reduced risk of symptomatic hypoglycemia. For every 1% increase in higher HbA1c at 1 year, there was a 25% risk reduction. Also, each 1 kg/m² higher increment in BMI at insulin initiation was associated with a 3% reduction in symptomatic hypoglycemia. Risk of hypoglycemia was also significantly lower with basal insulin alone than with other insulin strategies, including premixed insulin and short-acting insulin alone (OR 1.42, 95% CI 1.11-1.83).

In contrast to Vespasiani’s findings for people with Type 2 diabetes, A’Campo and Danish colleagues determined that there was no association between severe hypoglycemia and HbA1c or the use of insulin analogues in persons with Type 1 diabetes (abstract 592). In their cohort of 486 patients with a mean diabetes duration of 25 years and average HbA1c of 7.9%, severe hypoglycemia was independently associated with the presence of autonomic neuropathy (OR 3.62, 95% CI 1.65-7.94) and the use of benzodiazepines (OR 4.59, 95% CI 1.80-11.73). However, hypoglycemia unawareness, as assessed by the Clarke questionnaire, was associated with lower HbA1c (OR per %, 1.03, 95% CI 1.01-1.05), and estimated GFR <60 ml/min (OR 3.30, 95% CI 1.20-9.10).

Since hypoglycemia unawareness might prevent appropriate intervention prior to a severe episode, a therapeutic strategy to reinstate hypoglycemia awareness would be invaluable, particularly for those with longstanding disease.

### Table 4. Stages of Chronic Kidney Disease Based on GFR

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular Filtration Rate (ml/min/1.73 m² BSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Kidney damage and mildly decreased GFR</td>
<td>60 to 89</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderately decreased GFR</td>
<td>30 to 59</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severely decreased GFR</td>
<td>15 to 29</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Kidney failure</td>
<td>&lt;15 or on dialysis</td>
</tr>
</tbody>
</table>

BSA = body surface area, GFR = glomerular filtration rate.

Source: National Kidney Foundation. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm
Thomacos et al. from the United Kingdom evaluated modafinil, an oral drug that reduces the release of the inhibitory brain neurotransmitter GABA and improves adrenergic sensitivity, in 8 patients with Type 1 diabetes and documented hypoglycemia unawareness (abstract 590). After receiving 2-100 mg doses of modafinil or placebo, in random order, each subject had a paired hypoglycemic clamp study in which plasma glucose was reduced in a stepwise progression from 90 to 43 mg/dl. Neuroglycopenic symptoms (difficulty speaking, confusion, dizziness, irritability, blurred vision, drowsiness) were experienced at higher glucose levels with modafinil than placebo (mean 46 ± 11 vs. 41 ± 7 mg/dl, p = 0.025), to a greater degree (area under the curve for neuroglycopenic symptoms; see Figure 4).

![Figure 4. Change in Neuroglycopenic Symptom Score Over Time](image)

**Does It Add Up?**

**Results of the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) trial were presented on Wednesday by Drs. Lauritsen of Denmark and Griffin of the UK. The primary aim of the study was to evaluate whether screen-detected patients with Type 2 diabetes would benefit from a subsequent multifactorial risk factor intervention regimen. Inclusion criteria were patients age 40-69 years from general practices in 3 countries. They were screened for potential diabetes by a combination of postal questionnaires, medical record review, and random glucose levels. Diagnosis of diabetes was confirmed by 2-hour OGTT using WHO diagnostic criteria. From the original patient cohort, the prevalence of previously unrecognized diabetes was 3.5%. A total of 3,057 screen-positive patients participated: 1,379 (representing 156 practices) and 1,678 (161 practices) were randomized to receive routine care and intensive treatment, respectively. Targets for routine care were based on national guidelines, which became more intensified over the course of the study (2001-2006). Treatments in the intensive care arm were as follows: (1) lifestyle modification recommendations included diet, physical activity, and smoking cessation; (2) if HbA1c > 6.5%, intensified antihyperglycemic drug regimens; (3) if blood pressure (BP) ≥ 120/80 mmHg, addition of an ACE inhibitor and if BP ≥ 135/85 mmHg, further intensification with medications; (4) if baseline cholesterol ≥ 174 mg/dl (or ≥ 193 mg/dl and existing cardiovascular disease), additional diet management and a statin; and (5) low-dose aspirin to all patients receiving BP therapy. The primary endpoint was a composite of first cardiovascular event: cardiovascular mortality, non-fatal MI, non-fatal stroke, revascularization, or non-traumatic amputation. The mean follow-up was 5.3 years. All 3 intervention parameters (HbA1c, blood pressure, and cholesterol) improved in both groups, however, the magnitude of improvement, not unexpectedly, was greatest in the intensive treatment arm. Neither arm demonstrated significant overall weight loss.

With respect to the primary endpoint of the study, the composite cardiovascular outcome, the intensive arm demonstrated a non-significant 17% risk reduction (0.83 [0.65-1.05]). Although the risk curves appeared to begin to diverge after 4 years, this was not statistically significant (p = 0.12). In an invited commentary, US epidemiologist Dr. William Herman noted that ADDITION was, in part, successful to the extent that it demonstrated that primary care-based diabetes screening programs are feasible, identify patients with modifiable risk, and can positively impact risk factors. Also, despite the overall neutral findings from intensive therapy, the observed rates of adverse clinical outcomes were lower than predicted in both treatment arms. Moreover, employing a simulation model for long-term outcomes based on previously published data, Herman predicted a 5-year risk reduction of 50% for the composite cardiovascular event endpoint.

**Novel Therapies in T2DM**

If one includes insulin, the various classes of antihyperglycemic medications available in the US now number 11—most with unique mechanisms of action. With so much variety, an important question that arises is whether additional drug types are needed? Clearly, many believe so. At this week’s meeting, results from investigations of many new drug compounds were revealed.

One class garnering a lot of attention is the sodium glucose cotransporter (SGLT)-2 inhibitors. These agents have a unique manner in which they lower plasma glucose concentrations—namely, the inhibition of a transporter that is responsible for glucose reclamation in the nephron. The net result is increased urinary excretion of glucose. One advantage of this mechanism is that the drugs work regardless of the underlying cause of diabetes. That is, their action is somewhat independent of insulin secretory status, insulin resistance, diet, comorbidities, etc. Modest weight loss may also be induced. One concern, however, is a possible increase in urinary and genital infections.
Parikh and US colleagues reported on the SGLT-2 inhibitor, dapagliflozin,* in Type 2 diabetes patients (abstract 869). In a series of double-blind, randomized studies, they tested three doses (2.5, 5, and 10 mg) versus placebo in monotherapy, as add-on to metformin, and in combination with insulin (n=807). The main outcomes for the highest dose are shown in Table 5. There were significant improvements in fasting plasma glucose and HbA1c in each active therapy arm versus placebo. Adverse events included signs and symptoms of genital and urinary tract infections (UTI). To better quantify this potential risk, Nauck et al. reported a 10.5% UTI rate vs. 6.4% in a sulfonylurea-treated control group; corresponding rates for symptoms of genital infection were 12.3% vs. 2.7%, respectively (abstract 241). Parikh et al. proposed that, due to its insulin-independent mechanism, dapagliflozin is a potential oral therapy to improve glucose control and body weight in patients with Type 2 diabetes across various stages of the disease process.

Two other SGLT-2 inhibitors were reported on this week: canagliflozin† (abstract 874) and BI 10773* (abstract 877). In the first study, a ~3 kg loss of body weight was noted in otherwise healthy, obese subjects over just 2 weeks vs. ~1 kg with placebo. In the second study, efficacy comparable to metformin (HbA1c ~0.7%, FPG ~30 mg/dl) was reported in a mildly diabetic cohort (baseline HbA1c 7.9%) over 12 weeks. The future of the ‘flozin’ class remains to be established, particularly with regard to the risk of genitourinary infections.

In a small, preliminary study, the novel class of glimin drugs was introduced. Their mechanism of action is not fully understood, but may involve beneficial effects on both insulin sensitivity (liver, muscle) and insulin secretion (glucose dependent). One such agent, imeglimin,* was tested over 1 month at a dose of 2,000 mg once daily (n=20) and 1,000 mg twice daily (n=19) versus metformin 850 mg twice daily (n=19) in Type 2 diabetes patients (abstract 884). Baseline-adjusted changes in the area-under-the-curve (AUC) for glucose concentrations during an OGTT were -33% with twice-daily dosing (p<0.0001), -30% for metformin (p<0.001), and -10% for once-daily dosing (p<0.05). In a second study of 1,500 mg twice daily for 2 months, HbA1c was reduced by ~0.4% vs. placebo and comparable to metformin 850 mg twice daily.

<table>
<thead>
<tr>
<th>Table 5. Glycemia and Weight Changes With Dapagliflozin Alone or Combined with Metformin or Insulin</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>HbA1c* (% ± SE)</td>
</tr>
<tr>
<td>FPG* (mg/dl ± SE)</td>
</tr>
<tr>
<td>Body weight* (kg ± SE)</td>
</tr>
<tr>
<td>% reaching HbA1c</td>
</tr>
<tr>
<td>&lt;7.0% at week 24</td>
</tr>
</tbody>
</table>

*Adjusted mean change from baseline to week 24 (Last Observation Carried Forward, LOCF).
†Primary endpoint, p<0.0001 vs. placebo.
‡Statistically significant based on sequential testing for secondary endpoints at α = 0.05.
§p=0.0003 vs. placebo+insulin.
DAPA = dapagliflozin, INS = insulin, MET = metformin, PLA = placebo.

So Many Posters, So Little Time....
Owing to recent controversies regarding the impact of antihyperglycemic agents on cardiac risk, substantial interest was demonstrated at this week’s Scientific Sessions on the cardiovascular (CV) effect of both established and emerging diabetes medications.

In a well-attended symposium on Monday afternoon, diabetes experts from around the world convened to discuss Glucose Lowering: Is It Safe for the Heart? Dr. Hertzel Gerstein from McMaster University in Canada first addressed the question, “Insulin: Cardiovascular Friend or Foe?” Dr. Gerstein defined Type 2 diabetes as a disease of insulin deficiency, irrespective of earlier pathophysiological defects, such as insulin resistance. He presented data from the UKPDS follow-up study, which revealed a 15% reduction in myocardial infarction (MI) in the group of patients initially randomized to more intensive therapy with sulfonylureas or insulin. This was despite nearly equal HbA1c levels between the two groups during most of the post-randomized study follow-up period. He then presented the results from a meta-analysis that incorporated data from the largest diabetes/CV clinical trials focusing on overall glycemic targets (UKPDS, ACCORD, ADVANCE, and VA DT), not any specific drug regimen. This study found a 9% relative risk reduction in major CV events and a 15% reduction in MI as compared to the standard therapy arms of the trials. No overall benefit on all-cause mortality was demonstrated, and in one study, ACCORD, the hazard ratio (HR) for mortality was actually increased (1.22) in the intensive group. Dr. Gerstein next listed the benefits (universal effectiveness, titratable, no recognized drug toxicities, and extensive experience dating back nearly 9 decades) and risks (hypoglycemia, weight gain, new concerns about cancer) of insulin. He concluded his comments by reviewing the design of the ORIGIN trial, now underway. In this clinical trial, persons with pre-diabetes or early Type 2 diabetes at high CV risk are being randomized to a single injection of glargine insulin vs. no insulin, with a variety of outcomes being tracked, including CV endpoints.

Dr. Rury Holman from Oxford, England next tackled “Metformin and Sulfonylureas: Good or Bad for CVD Risk?” First, the benefits of metformin were extolled. Dr. Holman reviewed the CV effects of metformin from the UKPDS, a study for which he served as principal investigator. 753 overweight patients were randomized to metformin (342) vs. conventional diet therapy (411). Over a 10-year median follow-up, with an average HbA1c difference of just 0.6%, the metformin group experienced a relative 39% reduction in MI (p=0.01) and a 36% reduction in all-cause mortality (p=0.01) vs. standard (diet) therapy. In the non-randomized follow-up to this landmark study, benefits persisted with the HR for MI being 0.67 (p=0.005) after nearly 20 years. Dr. Holman also observed that even in a group of patients in whom it was previously felt that metformin was contraindicated, namely those with heart failure, a mortality benefit has been suggested by several observational studies.

In shifting his discussion to sulfonylureas, Dr. Holman remarked that these older agents appear to be neutral with regard to CV outcomes. Their relative safety has been confirmed in the UKPDS as well as the ADVANCE trials. He did note that in a substudy within the UKPDS, the addition of metformin to failing sulfonylurea therapy was associated with a 96% relative increase in diabetes related deaths (p=0.039) and a 60% increase in all-cause mortality (p=0.041) vs. continued sulfonylurea monotherapy. Dr. Holman suggested that these were chance findings, since the expected mortality in the sulfonylurea group was predicted to be nearly two-fold higher than that observed. The Oxford group is now coordinating a large metformin CV trial in prediabetic patients.

Dr. Curt Furberg from Wake Forest University next took the stage to discuss the safety of thiazolidinediones (TZDs). He reviewed the history of this controversial drug class, beginning in 1997 with the approval of the ill-fated troglitazone. The currently available drugs of this class, pioglitazone and rosiglitazone, were associated with an increased risk of edema and heart failure soon after they became available. Observational studies suggest that the risk of heart failure may be greater with
the latter compound. A now famous meta-analysis of rosiglitazone clinical trials (n=42) was published by Cleveland Clinic investigators in 2007, reporting a relative 43% increase in MI events in patients randomized to the drug vs. placebo or other diabetic agent. This finding was later supported by a separate meta-analysis conducted by the Wake Forest group.

Very recently, rosiglitazone was removed from the market in Europe and now has significant restrictions in the US. Such a CV risk has not been ascribed to pioglitazone, however. (Indeed, a pioglitazone meta-analysis and a secondary outcome from a large randomized clinical trial [PROactive] actually suggested a potential CV protective effect.*) Nonetheless, Dr. Furberg felt that a cloud has been cast over the entire drug class. He suggested that the TZD experience should encourage drug regulatory authorities to be more selective in the drugs they approve and to shy away from approval based on surrogate endpoints, such as inflammatory markers, markers of insulin resistance, etc.

Dr. Silvio Inzucchi from Yale next presented on “New Kids on the Block: DPP-4 Inhibitors and GLP-1 Analogs.” The relative lack of clinical trial data on CV endpoints with these relatively newer incretin-based therapies was acknowledged. The speaker reviewed incretin physiology and the metabolic effects of these related drug classes. The injectable GLP-1 receptor agonists have been associated with improvement in several CV risk factors, including (in addition to glucose) weight, blood pressure, and lipids. Moreover, preliminary data from both animal models and small human trials have suggested a potential direct effect on cardiac tissue (reduction in infarct size, improvement in left ventricular function).* The oral DPP-4 inhibitors, which raise endogenous GLP-1 levels, are weight neutral and, to date, appear to be generally well tolerated. The ultimate effects on CV outcomes from incretin-based therapies is completely unknown however. To address this knowledge void, several large clinical trials, such as TECOS (sitagliptin) and LEADER (liraglutide), are now underway, as recently encouraged by the US Food & Drug Administration (FDA).

Finally, Dr. Kausik Ray from Cambridge, UK presented his own meta-analyses of the largest diabetes/CV clinical trials, including UKPDS, ADVANCE, ACCORD, VADT, and PROactive. He found that more intensive therapy was associated with a HR for non-fatal MI of 0.83 (0.75-0.93) and for fatal/non-fatal MI of 0.85 (0.77-0.93), but with no effect on overall mortality, as compared to less intensive therapy. Dr. Ray noted that most older diabetes medicines, with the exception of metformin, result in HbA1c lowering, but with weight gain. He wondered if some of the newer compounds, such as the GLP-1 agonists, which tend to reduce both HbA1c and body weight, might hold greater promise. Clearly, well-designed, long-term clinical trials will be required to answer this question.

In related presentations this week, Marsø et al. from the US reported on CV safety findings of the GLP-1 receptor agonist, liraglutide, in pooled data from all completed phase 2 and 3 clinical trials in Type 2 diabetes patients (aged 18-80 years, baseline HbA1c 7-11%, BMI <45 kg/m2) (abstract 16904). Classical major adverse cardiovascular events (MACE; defined as death, MI, or stroke) were identified retrospectively using three standardized search criteria of trial records. Serious MACE, as reported by the site investigators, were then adjudicated on a post hoc basis by an independent outcomes committee, blinded to treatment assignment. In all, 15 trials were analyzed, consisting of 6,638 patients, almost two-thirds of whom were exposed to liraglutide. There were a total of 32-44 serious MACE identified using variable search criteria. After adjudication, 31-39, serious MACE were confirmed. For each search criterion, the incidence ratio for MACE was <1.0 for liraglutide patients, with the upper limit of the 95% CI less than the 1.8 threshold that has been determined by the FDA to preliminarily suggest CV safety (Figure 1).

As mentioned, the LEADER trial will better address this issue.

The risk of CV events in patients treated with the first GLP-1 receptor agonist, exenatide, was investigated by Hoogwerf and American collaborators (abstract 13242). In this ‘real world’ study, the LifeLink™ healthcare database was used. Patients who initiated a new prescription for any glucose-lowering drug between 2005 and 2009 were identified and followed until a CV event occurred (MI, stroke, or coronary revascularization). Results were adjusted for differences in clinical and demographic characteristics and compared using propensity-score-weighted methods. With the exception of the comparison to those treated with either metformin or sitagliptin, exenatide-treated patients experienced fewer CV events than those using other agents, including sulfonylureas, TZDs, and insulin (Figure 2). More extensive data on this drug class’s CV effects are needed.

Despite decades of clinical investigation into diabetes drugs, we are still in something of an infancy in our understanding of their CV impact. We look forward to learning more in coming years, as the results of these trials unfold.

**Aspirin as Primary Prevention**

Previously, the ADA and the AHA jointly recommended that diabetes patients at increased cardiovascular disease (CVD) risk take daily aspirin (75-162 mg) for primary prevention. Recently, however, questions about efficacy were raised from two randomized, controlled clinical trials—the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial (RR, 95% CI for CVD events in aspirin treated subjects = 0.87, 0.40-1.87) and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial (1.09, 0.82-1.44). The ADA, AHA, and the American
The results of subgroup analyses of the JPAD study were presented this week, shedding some light on which subgroups of diabetic patients might derive the most benefit from aspirin prophylaxis. The JPAD trial was a randomized, controlled, open-label blinded-endpoint study that was conducted to examine the efficacy of low-dose aspirin therapy for primary prevention of atherosclerotic events. A total of 2,539 Japanese patients with Type 2 diabetes were enrolled and followed for a median 4.4 years.

In one post-hoc analysis, Okada et al. analyzed risk of atherosclerotic events (HR, 95% CI) by therapeutic regimen for diabetes, as a surrogate for diabetes severity (abstract 12166). The regimens used at baseline included insulin (n=326), oral hypoglycemic agent (OHA) (n=1750), and diet (n=463). The insulin group had the longest duration of diabetes, the highest level of HbA1c and fasting plasma glucose, and the highest prevalence of diabetic microvascular disease; in contrast, the diet group had characteristics consistent with the lowest disease severity. The incidence of atherosclerotic events was 26.6, 14.6, and 10.4 cases per 1,000 person-years in the insulin, OHA, and diet groups, respectively. Aspirin therapy significantly reduced events in the subgroup of patients with early-stage illness being treated with diet, despite their having the lowest event rates (Figure 3; 0.21, 0.05-0.64; p<0.01), but did not affect outcomes in patients on insulin (1.19, 0.60-2.40) or OHA (0.84, 0.57-1.24).

In a second post-hoc analysis of JPAD, Soejima et al. analyzed risk of stroke events (HR, 95% CI) by level of blood pressure control (uncontrolled defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg in one analysis and systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg in another analysis) (abstract 12906). At a cutoff of ≥140/≥90 mmHg, the incidence of stroke events was significantly higher in the uncontrolled versus controlled blood pressure group (2.18, 1.37-3.50; p=0.0008), whereas there was no between-group difference for incidence of coronary events (p=0.9751). There was a difference in the incidence of stroke events between the uncontrolled and controlled blood pressure groups in those not assigned to aspirin prophylaxis (2.84, 1.52-5.11; p=0.0008). In contrast, in those taking aspirin, patients with either controlled or uncontrolled blood pressure had similar (relatively low) stroke rates (Figure 4). When the blood pressure cutpoint was made more stringent, however (uncontrolled defined as ≥130/≥80 mmHg), there was no significant difference between the uncontrolled and controlled blood pressure groups, regardless of aspirin use status.

In summary, these post-hoc analyses of JPAD identified potential benefit from low-dose aspirin in reducing the risk of: 1) atherosclerotic events in patients with early stage (vs. more advanced) diabetes, and 2) cerebrovascular events in diabetes patients with poorly controlled blood pressure. We find these results a bit perplexing. In the hypertension analysis, it would appear that aspirin may provide a benefit in the more “diseased” patients—that individuals substantially not at target. Yet, in the diabetes treatment analysis, it was the more mildly affected patients that appeared to benefit from aspirin prophylaxis. Perhaps more advanced diabetes nullifies the effect of anti-platelet therapy—it is difficult to say. Subgroup analyses, we would point out, are sometimes not entirely consistent and should be considered merely hypothesis generating.
ST Changes on ECG: Really Nonspecific?

Siu et al. from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study conducted a post-hoc analysis of their Type 2 diabetes patients with no symptoms of CVD. DIAD randomly assigned participants to screening or no screening with adenosine-stress myocardial perfusion imaging (MPI) and, then, routine care by their primary provider (abstract 12642). The study's main finding was that silent ischemia was present in 22% of screened patients but that this information did not ultimately affect cardiac outcomes. The current analysis focused on those patients with mild ECG changes at baseline. The prevalence of nonspecific ST and T wave abnormalities (NSSTTA) was 18.2% (204/1119 patients with complete outcomes data). NSSTTAs were associated with a higher incidence of abnormal stress MPI (31% vs. 20%, p = 0.03), primary cardiac events (i.e., MI and cardiac death; 6.4% vs. 2.1%, p<0.01), and all-cause mortality (5.9% vs. 2.3%, p < 0.01), compared with those without NSSTTA. Moreover, patients with NSSTTA who were initially screened with MPI had improved cardiac outcomes during follow-up (3.6% vs. 9.7% for primary endpoint, p<0.01; Table 2). Thus, asymptomatic diabetic patients with NSSTTA on ECG may constitute a high-risk sub-group, and screening them with nuclear stress testing may improve their CV outcomes. Prospective studies are needed to confirm these post-hoc results.

Table 2. Cardiac Outcomes by Screening Status Among DIAD Patients with Mild ECG Abnormalities

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<tr>
<th>Endpoint</th>
<th>Not Screened (n=93)</th>
<th>Screened (n=111)</th>
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<td>Primary</td>
<td>9 (9.7%)</td>
<td>4 (3.6%)</td>
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<td>Non-fatal MI</td>
<td>7 (7.5%)</td>
<td>2 (1.8%)</td>
<td>&lt;0.01</td>
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<td>Cardiac death</td>
<td>3 (3.2%)</td>
<td>2 (1.8%)</td>
<td>0.44</td>
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<tr>
<td>Secondary</td>
<td>4 (4.3%)</td>
<td>2 (1.8%)</td>
<td>0.34</td>
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<td>Unstable angina</td>
<td>1 (1.1%)</td>
<td>1 (0.9%)</td>
<td>0.88</td>
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<tr>
<td>Heart failure</td>
<td>3 (3.2%)</td>
<td>1 (0.9%)</td>
<td>0.49</td>
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<tr>
<td>All-cause death</td>
<td>6 (6.5%)</td>
<td>6 (5.4%)</td>
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Treatment of Pre-Diabetes & Major Cardiovascular Events

Hopper and Australian colleagues performed a meta-analysis of 10 prospective, randomized controlled trials (RCTs), which enrolled ~23,000 patients (mean age 52 years, 47% male) with impaired glucose tolerance (IGT), reported all-cause mortality rates (at a minimum), recruited at least 100 patients, and had a follow-up period of at least 1 year (abstract 15435). Over a mean study period of ~3 years, the investigators determined that drug and/or lifestyle interventions delayed or prevented progression to diabetes quite significantly (risk ratio [RR] 0.66, 95% CI 0.55-0.80 vs. control), with drug-based (n=20,872) superior to lifestyle interventions (n=3,495). There was no difference, however, between the intervention group versus control group in risks of all-cause mortality (0.96, 0.84-1.10), CV death (1.04, 0.61-1.78), or MI (0.59, 0.23-1.50), whereas stroke death was reduced by 24% (0.76, 0.58-0.99).

Endo fibrates and Peripheral Neuropathy

The results of a post-hoc analysis of FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), a 5-year randomized trial of fenofibrate 200 mg/day or matching placebo in patients with Type 2 diabetes (Lancet 2005;366:1849-61), were presented this week at the AHA Scientific Sessions. Rajamani and Australian collaborators assessed peripheral neuropathy progression, as determined by presence of neuropathy symptoms and sensation tested by a standard monofilament technique, 2 years, and study ended (abstract 18897). At baseline, 5.6% of participants (564/9795) had documented monofilament neuropathy. According to logistic regression, neuropathy was increased with female sex, history of prior CVD, diabetes duration (per 10 years), insulin use, and height (all p<0.01). Additional factors associated with incident neuropathy included prior retinopathy, age, glycemia (elevated HbA1c), and hypertriglyceridemia (all p<0.03). By study close, neuropathy was present in 8.0% of placebo patients, compared with 6.6% of fenofibrate-treated patients (between-group difference, adjusted for baseline neuropathy; p=0.003). This difference was based on an 18% reduction in new neuropathy (OR 0.82, 95% CI 0.67-1.01; p=0.06) and a greater reversal of baseline neuropathy with treatment (OR 1.67, 95% CI 1.14-2.38; p=0.009).*

Neuropathy was one of the strongest predictors of amputation, increasing the risk of a first amputation by ~3-fold (HR 2.7, 95% CI 1.8-4.1; p<0.001). We find these data to be provocative, in the context of previously disclosed benefits of this fibrate derivative on both retinopathy and albuminuria endpoints from FIELD. All these data obviously need to be interpreted cautiously given that the trial was neither initially designed nor powered to investigate microvascular outcomes. (FIELD was primarily designed to assess the effect of fenofibrate, and, by inference, triglyceride lowering and HDL raising, on macrovascular outcomes. No overall benefit was found from the treatment strategy on the composite CV primary outcome.) In addition, there have been few biologically plausible explanations for these findings. Clearly, more study is needed on the potential effect of this lipid-lowering medication on microvascular disease.

CVD Risk Factors are Poorly Controlled in Type 2 Diabetes

Using the cross-sectional National Health and Nutrition Examination Survey (NHANES 2003-2006) database, Glovac et al. from California and New Jersey found that insulin-treated patients were more likely than otherwise-treated Type 2 diabetes patients to be obese, have poorly controlled glycemia and triglycerides, and have pre-existing CVD, chronic kidney disease, or macroalbuminuria (abstract 18450). Only a minority (10%) of all patients was at goal for HbA1c (<7%), blood pressure (<130/80 mmHg), and LDL-C (<100 mg/dl), with a lower proportion of insulin-treated versus non-insulin-treated patients at this composite target. The differences might reflect the impact of comorbidities and the complexities of polypharmacy in a population with more advanced diabetes. These data underscore the need for increased efforts targeting risk-factor control in Type 2 diabetes patients, in particular insulin users, to prevent CVD-related complications.

* 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
Diabetes 2010 Test

Choose the one most correct answer and record your responses on the Answer Form on page twenty-nine

1. Which of the following is incorrect?
   a. Injectable GLP-1 agonists have been shown to improve cardiovascular (CV) risk factors but definitive clinical trials data on hard CV endpoints are lacking.
   b. Women diagnosed with gestational diabetes mellitus (GDM) are at substantially increased risk of CV events during pregnancy.
   c. Screening for silent ischemia has been shown to improve CV outcomes.
   d. Lifestyle interventions delay or prevent the progression from prediabetes to diabetes, but have not yet been associated with improvement in CV outcomes.

2. Low-dose aspirin for primary prevention of CV events is reasonable for men >50 years and women >60 years with diabetes, no previous history of vascular disease, at increased risk of CV disease, and having at least 1 additional risk factor. Which of the following is NOT a risk factor.
   a. smoking
   b. high HDL-cholesterol
   c. hypertension
   d. albuminuria

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

4. The ADA now recommends an HbA1c target of <7.0% in all patients, irrespective of age or other comorbidities.
   a. true
   b. false

5. Select the false statement from the following about diabetes and its renal complications.
   a. Bariatric surgery has beneficial effects on metabolic derangements of diabetes and has also been shown to improve renal outcomes.
   b. A substantial proportion of diabetes patients with renal impairment do not have albuminuria.
   c. ADVANCE investigators observed that more intensive glucose control reduced the risk of new or worsening nephropathy (-21%) vs. standard therapy.
   d. Risk of acute renal failure is increased in patients with Type 2 diabetes, especially in those with coexisting hypertension and heart failure.

6. Select the false statement from among the following about peripheral neuropathy following long-standing diabetes.
   a. The prevalence of diabetic neuropathy appears to be increased in patients with obstructive sleep apnea.
   b. Glycemic control has no bearing on the risk of diabetic patients developing peripheral neuropathy.
   c. Several drugs (amitriptyline, pregabalin, duloxetine) significantly decrease patient-rated pain severity of diabetic neuropathy, as compared to placebo.
   d. Peripheral neuropathy is a strong predictor of amputation risk.

7. Data from the NHANES (National Health and Nutrition Examination Survey) 2003-2006 database showed that which of the below percentages of Type 2 diabetes patients have achieved HbA1c <7%, blood pressure <130/80 mmHg, and LDL-cholesterol <100 mg/dl.
   a. > 90%
   b. 75%
   c. 50%
   d. 10%

Numerous new antihyperglycemic agents/technologies are currently in development. Match the antihyperglycemic agent with its action.

8. _____ increases tissue permeability of insulin, accelerating insulin absorption.
9. _____ may increase insulin sensitivity and insulin secretion.
10. _____ is being studied in a continuous subcutaneous delivery device.
11. _____ decreases pancreatic glucagon secretion.
12. _____ increase urinary excretion of glucose.
13. _____ is a very long-acting basal insulin under investigation.

   a. Sodium glucose cotransporter (SGLT)-2 inhibitors
   b. Alogliptin
   c. Hyaluronidase
   d. GLP-1 agonists
   e. Exenatide
   f. Digludec

14. In the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, there was a linear relationship between maternal blood glucose levels and risk for both neonatal and maternal complications.
   a. true
   b. false

15. Which of the following is not a complication associated with gestational diabetes mellitus?
   a. higher C-section rate
   b. larger babies
   c. offspring at greater risk of childhood obesity and Type 2 diabetes
   d. post-term delivery

16. In patients with Type 1 diabetes, continuous glucose monitoring has high specificity and good negative predictive value for hypoglycemia (each >90%), but poor positive predictive value (42%) and sensitivity (30%).
   a. true
   b. false

17. One group of investigators determined that the risk of symptomatic hypoglycemia in insulin-treated Type 2 diabetes patients decreased by 3% for each 1 kg/m² higher increment in BMI.
   a. true
   b. false

18. Which of the following anti-hyperglycemic drugs, previously contraindicated in this group of patients, has been linked to improved clinical outcomes in patients with heart failure in retrospective studies?
   a. metformin
   b. sulfonylureas
   c. insulin
   d. sitagliptin

19. Which lipid-lowering drug was recently associated with reduced risk of microvascular complications in Type 2 diabetes?
   a. rosuvastatin
   b. ezetimibe
   c. niacin
   d. fenofibrate

20. Which liver condition is associated with Type 2 diabetes and prediabetes?
   a. Budd-Chiari syndrome
   b. primary biliary cirrhosis
   c. steatohepatitis
   d. autoimmune hepatitis
Dia be te s 2010 Evaluation
Volume 22

Please mark your answers on the Evaluation Questionnaire Form on page twenty-nine.

1. How would you rate Diabetes 2010 for content?
   a. very relevant to my practice
   b. interesting but not relevant
   c. uninteresting

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

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

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

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

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

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

8. Additional comments: ________________________________  
   ________________________________________________________________________________
   ________________________________________________________________________________

Thank you for your participation.
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: December 2010 to July 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 2010 Test - Volume 22

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

### Diabetes 2010 Evaluation - Volume 22

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| 6. | Will you make changes that will benefit patient care as a result of information received? If yes, please describe: ________________
| 7. | Do you anticipate any barriers to making these changes? If yes, please describe: ________________________________
| 8. | Additional comments: ____________________________________________________________
|   | __________________________________________________________

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