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November 2012

Dear Colleague:

Time restraints prevented many of you from attending the 48th Annual Meeting of the European Association for the Study of Diabetes (EASD) which was held a few weeks ago in Berlin, Germany. Therefore, we developed Diabetes 2012 so that important information presented at the Conference could be shared with you on a timely basis.

Diabetes 2012, a newsletter CME program, is being offered to you by Yale University School of Medicine with the support of educational grants from Abbott Nutrition, Amylin Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk, Inc., and also supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc., which was made possible, in part, through a collaboration with Eli Lilly and Company. This booklet contains three Diabetes 2012 newsletters and a post-test. After successfully completing the test you will qualify for a maximum of 5.0 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

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

• Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
• Describe the evolving cellular mechanisms associated with 6-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 12 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

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

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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 B-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 EASD conference concludes, participants will receive a Diabetes 2012 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 2012 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 medical education activity for a maximum of 10 AMA PRA Category 1 Credits™ (5.0 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™.
# Table of Contents

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

**Issue One**

Banting's Best ................................................................................................................... 3
No Time to ‘Weight’ .......................................................................................................... 5
The Aging Brain of Diabetes ............................................................................................. 8

**Issue Two**

Diabetes: At the Heart of the Matter ................................................................................. 9
Update on DPP-4 Inhibitors ............................................................................................. 12
Diet Matters ....................................................................................................................... 13
So Many Posters, So Little Time... ................................................................................... 14

**Issue Three**

Advances in Type 1 Diabetes Care .................................................................................... 16
GLP-1 Agonists: What’s New? ...................................................................................... 17
Hypoglycemia: Implications and Associations ................................................................ 18
Diabetes Screening Methods .......................................................................................... 19
2012 Position Statement on T2DM Therapy ...................................................................... 20
Novel Therapies and Diagnostics ..................................................................................... 21
New Science Hot Off the Presses! .................................................................................... 22

Diabetes 2012 Test ........................................................................................................... 23
Diabetes 2012 Evaluation ................................................................................................. 24
Diabetes 2012 Answer Form ............................................................................................. 25
In this issue of the Diabetes 2012 monograph, we summarize important new diabetes information that was presented at the 48th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Berlin, Germany.

Groundbreaking data, with potential game-changing implications for the therapy of Type 2 diabetes, were presented by Talchai et al., Columbia University (abstract 141). Talchai asserted that beta cells may actually not die during the course of the disease, as had been previously thought. Instead, they may revert to an earlier, undifferentiated cell type that does not produce insulin. Mice bred without a specific transcription factor known as FOXO1 develop low levels of insulin when under physiological stress (pregnancy in the female mice, and aging in the male mice.) With the use of antibody tracers to explore the characteristics of these new stressed beta cells, the investigators were surprised to find new markers of undifferentiated, progenitor cells. FOXO1 is known to promote the differentiation and proliferation of beta cells, but this is the first time that FOXO1 was shown to be necessary for their ongoing identity. During chronic metabolic stress, beta cells can lose FOXO1, and begin to de-differentiate — possibly as a protective mechanism. These results indicate that de-differentiation — not apoptosis — may be the main cause of beta-cell failure in Type 2 diabetes. If the results are replicated in humans, diabetes management might shift toward resting the beta cells, perhaps with early exogenous insulin administration or insulin sensitizing drugs. Also, a future novel agent that stabilizes or promotes FOXO1 activity could potentially actually reverse the natural history of this disease.

The brain should be regarded as an organ predisposed to diabetes-related complications, not merely from acute injury related to hypoglycemia but of a chronic nature as well. In a 10-year, prospective, observational study of 1,334 Type 2 diabetes patients, Taton and Polish coworkers determined that age (p<0.001), fasting blood glucose level (p<0.02), albuminuria (p<0.001), atrial fibrillation (p<0.001), and smoking (p<0.04) were significant risk factors for stroke, and stroke-associated mortality, 11% second only to cardiac-related events (abstract 17). Following 1,290 persons aged 40 years or older, Spaunen and Dutch collaborators observed that patients with baseline diabetes showed greater cognitive impairment (decline in information processing, executive function, and delayed word recall) over 12 years follow-up, compared to non-diabetic subjects, after adjustment for demographic variables, history of smoking, alcohol intake, and comorbid conditions (abstract 18). Participants with incident diabetes, however, did not show a larger decline in any cognitive domain compared with non-diabetic subjects, indicating that there may be a window of opportunity for prevention and early treatment of diabetes-related brain dysfunction. And, in a related presentation, Selvarajah et al. from the UK found lower total grey matter volume in Type 1 patients with painful diabetic neuropathy (DN) (760 ml) and painless DN (767 ml) compared to those without DN (812 ml) and healthy non-diabetic subjects (798 ml), with no significant differences in white matter volume or ventricular cerebrospinal fluid volume across the study groups (abstract 45). It is unclear from these data whether these are simply two sequela of long-standing disease or whether neural tissue may be similarly sensitive to injury in both the central and peripheral nervous systems.

Diabetes educators and cardiologists converged to discuss the recent publication Diabetes and Acute Coronary Syndrome (ACS). The first speaker, Dr. Nikolaus Marx from the University of Aachen, Germany, carefully reviewed the combination of factors that place diabetic patients at very high risk for coronary events — the combination of the ‘vulnerable plaque’ (predisposed to plaque rupture), the ‘vulnerable blood’ (predisposed to hypercoagulability and platelet overactivity), and the ‘vulnerable myocardium’ (more apt to be injured from ischemic insults). Dr. Marx reminded the symposium attendees that silent myocardial ischemia is present in half of diabetic patients with coronary disease, making diagnosis particularly challenging. He then reviewed convincing data showing that, in the setting of diabetes, patients with ACS are prone to adverse clinical outcomes. However, studies have also demonstrated that these individuals benefit greatly from acute revascularization procedures, such as percutaneous coronary intervention (PCI). Next, Dr. Peter Gaede, lead investigator of the Steno-2 study from the University of Copenhagen, presented a historical overview of the approach to acute glycemic control in patients with ACS. Extensive epidemiologic evidence exists demonstrating an association between increased glucose levels in hospitalized patients with ACS and adverse outcomes, including mortality. Interestingly, this relationship is more apparent in non-diabetic versus diabetic individuals. This might reflect the acute, deleterious effects of hyperglycemia on endothelial function, coagulation, inflammatory markers, and cell apoptosis. However, the results from intervention studies which tested the hypothesis that controlling glucose levels in the critically ill reduces complications are conflicting, with some (DIGAMI-1, Leuven-1) showing a benefit from intensive insulin infusion to reduce glucose levels, but most others not confirming this (DIGAMI-2, Leuven-2, Hi-S, and NICE SUGAR). Based on these data, Gaede reviewed the new European Society of Cardiology guidelines, which emphasize good but not necessarily intensive glycemic control in acute cardiac patients (maintaining levels between 140-180 mg/dl). Hypoglycemia, which has also been associated with increased mortality in the ACS setting, should be avoided however. To end the symposium, Dr. Guy Rutten from the University of Utrecht, the Netherlands, discussed issues concerning medication compliance, disease treatment burden, and psychosocial well being of patients with both diabetes and coronary disease. With good evidence that adherence to evidence-based therapies, such as statins, blood pressure medications, and aspirin, can dramatically reduce recurrent event rates, monitoring all patients’ progress post-ACS is of extreme importance.

The recently published ADA-EASD position statement on management of hypoglycemia in Type 2 diabetes was the topic of a well-attended symposium at the EASD 48th Annual Meeting (Diabetes Care 2012;35:1364; Diabetologia 2012;55:1577). Key points of the Position Statement include:

- Glycemic targets and blood glucose-lowering therapies must be individualized.
- Diet, exercise, and education are the foundation of any Type 2 diabetes therapy program.
- Unless contraindicated, metformin is the optimal first-line drug. After metformin, data are limited.
- Combination therapy with one to two other oral/injectable agents is reasonable; minimize side effects.
- Ultimately, many patients will require insulin therapy alone/in combination with other agents to maintain blood glucose control.
- All treatment decisions should be made in conjunction with the patient (focus on his or her preferences, needs, and values).
- Comprehensive cardiovascular risk reduction should be a major focus of therapy.

With a focus on personalization of both treatment targets and anti-hyperglycemic strategies, the new Position Statement distinguishes itself from older guidelines, which were more algorithmic and more prescriptive.

Research continues to expand our understanding of currently available agents and uncover new agents of potential value in diabetes care. The role of DPP-4 inhibitors, on reducing albuminuria* (beyond the level expected by glucose lowering; abstract 36), beta-cell function* (vs. glipizide in patients with LADA; abstract 148), and CV outcomes* (vs. multiple comparator agents; abstract 1233) was discussed, as was a novel once-weekly DPP-4 inhibitor* (abstract 110). Preliminary analysis of data from the LEAD-5 and DURATION-3 trials suggest that glucagon-like protein-1 (GLP-1) receptor agonists are comparable, and possibly superior to, basal insulin for lowering Hba1c in Type 2 diabetes patients failing 1-2 oral agents (abstract 900). Innovations to rapid-acting insulin analogs to improve pharmacokinetics continue to be explored, for example the addition of recombinant human hyaluronidase* (abstract 41) and the addition of EDTA and/or citrate* (abstract 906). A formulation of insulin lispro covalently attached to polyethylene glycol — i.e., pegylated* (abstract 112). Pournaras and multinational associates reported a clinically significant (-1.1%) change in Hba1c 1 year following endoscopic placement of a removable duodenal jejunal bypass liner* in a small group of obese patients (BMI between 25 and 35 kg/m2; i.e., don’t qualify for bariatric surgery) with Type 2 diabetes and (abstract 9). Favorable effects on insulin sensitivity were also observed (as early as 1 week post-implantation). The SGLT-2 inhibitors and degludec are currently under consideration by the FDA.

More details on these and other topics are found in this volume of Diabetes 2012.

* The product is not labeled for the use under discussion or the product is still investigational.
New insulin analogs along with innovative ways to enhance the pharmacokinetic profiles of existing insulins were the subject of multiple presentations at the 48th EASD Annual Meeting in Berlin. Skyler and US colleagues examined the role of hyaluronidase to accelerate the absorption and onset of the rapid-acting insulins (i.e., aspart, glulisine, and lispro) and their impact on postprandial glycemic control (abstract 41). In a double-blind, 2-way crossover trial, 117 patients with Type 1 diabetes were randomized to receive aspart with recombinant human hyaluronidase (rHUPH20)* or lispro with rHUPH20* versus lispro alone for two, 12-week intensive management periods. This was preceded by a 4-6 week run-in with prandial glulisine and glargine twice daily. Primary endpoints included HbA1c (change from baseline), postprandial glucose excursions (measured by self-monitoring of blood glucose [SMBG] and continuous glucose monitoring [CGM], and self-reported hypoglycemia (SMBG ≤ 70 mg/dl). There were no significant differences in HbA1c changes from baseline between the 2 groups (-0.14% with analog-rHUPH20 and -0.19% with lispro alone; 95% CI -0.5 to 0.15). However, post-meal excursions (90 minutes) were significantly decreased in the analog-rHUPH20 group, with a greater percentage of patients achieving plasma glucose levels <180 mg/dl and <140 mg/dl after breakfast (70.5% vs. 54.0%, p = 0.003 and 21.4% vs. 10.6%, p = 0.007, respectively) and <180 mg/dl and <140 mg/dl at all meals (70.8% vs. 59.3%, p = 0.016 and 15.0% vs. 8.8%, p = 0.089, respectively). The analog-rHUPH20 group experienced no overall reduction in hypoglycemia, as defined by rates of blood glucose <70 mg/dl and <56 mg/dl, respectively (19.9 vs. 19.0 episodes per patient-month, p = 0.35 and 8.1 vs. 7.5 episodes per patient-month, p = 0.44, respectively). From this investigation, the researchers concluded that hyaluronidase enhances the pharmacokinetic profile of rapid-acting insulin, resulting in improved postprandial glycemic excursions. We note the same HbA1c control, however, and question how meaningful these modestly lower postprandial glucose excursions really are.

Other vehicles used to enhance insulin absorption and onset of action are EDTA and citrate*, which work by chelation of the zinc ions that are used to stabilize the insulin molecule. EDTA destabilizes insulin hexamers into monomers and citrate reduces the surface charge preventing their reassociation. These 2 excipients have previously been shown to enhance the rate of subcutaneous insulin absorption in an animal model. Pohl et al. from the US studied the impact of each excipient in combination at various concentrations and alone on the rate of subcutaneous absorption of lispro in miniature diabetic pigs (abstract 906). Blood glucose and plasma insulin were measured 30 minutes prior to and 360 minutes following each dose of each formulation. Calculations of time to maximal insulin concentration (Tmax) and half maximal concentration (T50) were calculated with results shown in Table 1.

Based on these findings, the investigators suggest that chelation of zinc ions with EDTA and citrate at full concentrations significantly enhances the rate of subcutaneous lispro absorption.

<table>
<thead>
<tr>
<th>Table 1. Times to Insulin Concentration with Varying Amounts of EDTA and Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tmax (minutes)</strong></td>
</tr>
<tr>
<td>Lispro alone (n=10)</td>
</tr>
<tr>
<td>Lispro +100% EDTA + 100% citrate (n=10)</td>
</tr>
<tr>
<td>Lispro + 0% EDTA + 100% citrate (n=9)</td>
</tr>
<tr>
<td>Lispro + 25% EDTA + 87% citrate (n=10)</td>
</tr>
<tr>
<td>Lispro + 25% EDTA + 43% citrate (n=4)</td>
</tr>
</tbody>
</table>

*Tmax= time to maximal concentration; T50= time to half maximal concentration.  
*p<0.05, †p<0.005 vs. insulin lispro alone.
We look forward to further studies in man. Whether this product or the one using hyaluronidase will provide any real benefits on more than biochemical outcomes remains unclear.

Basal insulins were also the subject of multiple presentations, with topics ranging from titration algorithms, comparisons between currently available basals, and the potential role of the ultra-long acting agent, degludec*, recently approved in Japan (and still under review in Europe and US).

Investigators from Canada and the US completed a pooled analysis of patient-level data to compare 3 different treatment algorithms for the initiation and intensification of insulin glargine (abstract 935). Aurand et al. pooled data from 8 randomized controlled trials in insulin-naïve patients with Type 1 diabetes. The algorithms initiate treatment with glargine 10 units daily and are adjusted as follows: (1) Algorithm 1: requires the addition of 1 unit daily when fasting plasma glucose (FPG) is above target; (2) Algorithm 2: requires the addition of 2 units every 3 days when FPG is above target; and (3) Algorithm 3: uses a treat-to-target approach, usually adding 2-8 units weekly based on a mean of 2-day FPG. Baseline oral antidiabetic drugs (OADs) differed across groups; patients on metformin and sulfonylureas made up 51% of 163 patients in algorithm 1, 70% of 117 patients in algorithm 2, and 71% of 1,100 patients in algorithm 3. Despite this, results were comparable, whether analyzed by baseline OAD or in the group as a whole (Table 2). After adjusting for baseline differences, the main significant difference was the change in baseline HbA1c, favoring algorithm 2. The researchers noted that hypoglycemia trended higher in the algorithm 3 group, suggesting that simpler regimens (e.g., algorithm 1 or 2) appear to achieve comparable glycemic control with less confirmed hypoglycemia than the more complex algorithm 3.

It is noted that firm conclusions cannot be made in the absence of a randomized controlled trial. We might also add that any adjustment of insulin based on glycemic results will eventually improve control. Clearly, the more conservative approaches are apt to result in reduced hypoglycemia risk.

Table 2. Comparison of Glargine Titration Algorithms in Insulin-naïve Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>(n=163)</th>
<th>(n=117)</th>
<th>(n=1,100)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>1 unit daily if FPG &gt; target</td>
<td>2 units every 3 days if FPG &gt; target</td>
<td>TTT; 2-8 units weekly based on mean of 2-day FPG</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c, %</td>
<td>8.6</td>
<td>8.8</td>
<td>8.8</td>
<td>p&lt;0.05 algorithm 1 vs. algorithm 3</td>
</tr>
<tr>
<td>% achieving HbA1c &lt;7%</td>
<td>53</td>
<td>61</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>% change in HbA1c</td>
<td>-1.54</td>
<td>-1.91</td>
<td>-1.81</td>
<td>p&lt;0.05 algorithm 1 vs. algorithm 2</td>
</tr>
<tr>
<td>Confirmed hypoglycemia &lt;56 mg/dl, n (%)</td>
<td>38 (23.3)</td>
<td>22 (18.8)</td>
<td>382 (34.7)</td>
<td></td>
</tr>
<tr>
<td>Confirmed hypoglycemia &lt;70 mg/dl, n (%)</td>
<td>68 (41.7)</td>
<td>31 (26.5)</td>
<td>560 (50.9)</td>
<td></td>
</tr>
<tr>
<td>Confirmed nocturnal hypoglycemia &lt;56 mg/dl, n (%)</td>
<td>12 (7.4)</td>
<td>7 (6.0)</td>
<td>214 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Final insulin doses, U/kg</td>
<td>0.43</td>
<td>0.60</td>
<td>0.44</td>
<td></td>
</tr>
</tbody>
</table>

From this investigation, the researchers concluded that aspart mix is associated with less glucose variability than degludec, primarily due to greater reductions in glucose excursions following breakfast. As mentioned previously, the importance of minimizing these glycemic spikes is, in the context of equal HbA1c, controversial. The researchers of RESOLUTE cite the data as an analysis of “real-life” conditions, supporting the consideration of a conversion to glargine in patients poorly controlled on degludec. We note that several studies have indicated that, per unit, glargine may have more glucose-lowering effect than degludec; accordingly, these results may not be surprising but should be tested in a more rigorously conducted study. Lastly, several investigations assessed the utility of the ultra long-acting investigational basal insulin, degludec.* Degludec forms soluble multihexamers following subcutaneous injection, resulting in a stable glucose-lowering effect.
Investigators from Germany and Denmark, Hovelfmann et al. evaluated the pharmacokinetic and pharmacodynamic properties of insulin degludec U-200 (a 2-fold concentrated formulation) in 16 Type 2 diabetes who received 0.6 units/kg once daily for 6 days (abstract 912). (The product is available experimentally in both U-100 and U-200 concentrations.) A 26-hour euglycemic glucose clamp was conducted on day 6. Results demonstrated a flat and stable dose response curve over the course of 24 hours. The terminal half-life at steady state was determined to be 26.2 hours. Doses were generally well tolerated.

In another clinical trial, degludec was compared with glargine in 493 patients with Type 1 diabetes over 52 weeks. The primary objective of this open-label, treat-to-target study by Cooper and co-investigators from Europe and the US was to evaluate whether flexible dosing of degludec might provide comparable safety and efficacy to degludec or glargine dosed at the same time each day (abstract 911). During the first 26 weeks, patients received once-daily degludec (with evening meal), glargine (at same time each day), or “flexible degludec” (alternating doses between mornings and evenings), each in combination with mealtime insulin aspart. In this manner, doses were given as close to 12 hours or as long as 36 hours from the last. In the second 26 weeks, all degludec patients utilized the flexible regimen (n=329), which was compared to glargine (n=164). At the 52-week mark, both degludec and glargine produced a comparable decrease in HbA1c from baseline control (D:-0.13 vs. G:-0.21; non-significant estimated treatment difference 0.07%; 95% CI: -0.05 to 0.19). Overall hypoglycemia rates were similar between groups, but nocturnal hypoglycemia (estimated relative risk [ERR] 0.75 [0.58-0.97] and severe hypo-
glycemia (ERR 0.74 [0.38-1.42]) were significantly lower in the degludec group. From these data, it appears the degludec dosed at any time of day provides comparable long-term glucose control with a lower risk of nocturnal and severe hypoglycemic episodes when compared with glargine. (The rationale for this study was to determine whether the new insulin is safe if taken irregularly during the course of the week by certain patients.)

Two additional presentations focused specifically on nocturnal hypoglycemia and the comparative effects of degludec and glargine. The first study by Zinman and North American and European colleagues randomized 1,030 insulin-naive patients with Type 2 diabetes inad
duately controlled on OADs to either degludec or glargine in a 3:1 ratio for 1 year (abstract 39). Patients were titrated to self-measured glucose targets of plasma glucose between 70–88 mg/dl. Long-term glycemic control was comparable with reductions in HbA1c values for degludec considered non-inferior to glargine (-1.06% vs. -1.19%). However, as in the Cooper study above, nocturnal rates of hypoglycemia were 36% lower in the degludec group compared with glargine (0.25 versus 0.39 episodes/patient-year; ERR 0.64 [0.42-0.98]; p=0.04). These results were confirmed in the 1-year extension trial conducted by Rodbard and colleagues, North America and Europe (abstract 920). In the extension trial, 725 entered from the original 1,030, with 659 patients completing. Similar to the initial study, the mean observed HbA1c was similar between groups, as were rates of overall hypoglycemia. However, confirmed nocturnal hypoglycemia was 43% lower in the degludec group: There were 0.27 versus 0.46 episodes per patient-year (ERR 0.57 [0.40-0.81]; p<0.001). Based on these and other studies, it appears that degludec may be a reasonable alternative basal insulin, providing flexible once-daily dosing, with similar overall glucose control and a lower risk of nocturnal hypoglycemia. Going forward, however, as the glargine patent expires and potential generic products (‘bio-equivalent versions’) become available, one question is whether the expected higher cost of degludec will be worth these modest improvements.

Not quite as close to market as degludec is the investigational pegylated basal insulin, LY2605541* (LY). LY is insulin lispro covalently attached to polyethylene glycol. The resulting 20 kDa size slows absorption and decreases clearance, creating a very long-acting insulin. Moore and American coworkers studied the pharmacodynamics of LY compared to regular insulin using euglycemic clamps in dogs (abstract 24). The net effect of the investigation demonstrated higher hepatic glucose uptake in the LY group versus regular insulin. Non-hepatic glucose uptake increased less (above basal) with LY than regular insulin. Although, incredibly preliminary, the investigators suggest that pegylated lispro insulin demonstrated a preferential hepatic effect similar to endogenous insulin, but different from regular insulin administered exogenously. We find this product of interest—one of the first attempts to dissect out the hepatic versus the peripheral (i.e., enhancing glucose uptake in skeletal muscle) effects of insulin. Such designer insulin formulations may allow for more refined glucose control in the future, with potential differential targeting of fasting and postprandial glucose levels.

These investigations and others on the science behind insulin therapy may advance our ability to better treat our patients. Whether these advances will be worth the price remains to be considered, however, given the relative safety of currently available formulations.

According to NHANES data from 2007-2008, 34% of US adults were obese (32% of men and 36% of women) (Flegal KM et al. JAMA 2010;303:235-41). The substantial (and increasing) prevalence of obesity significantly impacts public health. For example, the incidence of diabetes has doubled over the past 3 decades, primarily among individuals with a BMI >30 kg/m² (Fox CS et al. Circulation 2006;113:2914-8). In the Framingham Heart Study, the age-adjusted relative risk for cardiovascular events was increased by 46% in men and 64% in women among those who were obese (Wilson PW, et al. Arch Intern Med 2002;162:1867-72). In a recent meta-analysis of 15 prospective studies, obesity increased risk for Alzheimer disease or vascular dementia and any dementia by 2.0 and 1.6, respectively (Anstey KJ, et al. Obes Rev 2011;12:e426-37). An appreciation of the relationship between obesity and premature death is gained from NHANES 1978 to 2006 data, showing that the gains in life expectancy from smoking cessation are beginning to be outweighed by the loss of life expectancy from obesity (Stewart ST, et al. N Engl J Med 2009;361:2252-60). It therefore comes as no surprise that obesity has become the focus for research scientists worldwide. Some of the findings of this work in diabetics was presented this week at the 2012 Annual Meeting of the EASD and are summarized here.

Following on evidence from multiple studies showing successful weight loss and resolution of Type 2 diabetes after gastric bypass surgery for morbid obesity, Steven et al. from the UK conducted a study to determine if diabetes duration and the amount of weight loss achieved influence reversal
Diseases required greater weight loss to reverse 21.5 ± 9.4 kg compared to those who did not reverse their diabetes (Figure 1). In the long-duration group, average weight loss in those who reversed diabetes (duration, 12 years) did not reverse (median disease duration, 12 years). The majority of these (85% and 86%, respectively) did not reverse (median disease duration, 12 years). Type 2 diabetes have an irreversible decline in absolute weight loss (Rs = -0.307; p = 0.006). As diabetes duration 5 years (range 1 month - 22 years) treated with: metformin (76); sulfonylurea (32); GLP-1 receptor agonist (15); dipeptidyl peptidase-4 inhibitor (6). Insulin (18) thiazolidinedione (15) and dipalmitoyl phosphatidylcholine (32). Postoperative HbA1c was significantly correlated (by beta-cell function.)

![Figure 1. Diabetes Reversal as a Function of Weight Loss](image)

### Figure 1. Diabetes Reversal as a Function of Weight Loss

<table>
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<tr>
<th>Disease Duration</th>
<th>Weight Loss (kg)</th>
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<td>Percentage of patients with a history of short-duration (&lt; 4 years) and 38% in Type 2 diabetes patients (34 males, mean age 48.6 ± 4.3 years, BMI 36.9 ± 0.77 kg/m²) were influenced by pre-operative GLP-1 receptor agonist (15); dipeptidyl peptidase-4 inhibitor (6). The goal was to identify the role of GLP-1 in the improvement in insulin secretion after bariatric surgery. The investigators were able to decipher the role of GLP-1 in the improvement in insulin secretion after bariatric surgery. The level of the decrease in BMI pre-operatively was significantly lower (&lt; 10 kg/m², 53%; 10-15 kg/m², 74%; and &gt;15 kg/m², 82%). Postoperative HbA1c was significantly correlated (by beta-cell function.</td>
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### Table 3. Glucose Tolerance and B-cell Glucose Sensitivity Before and After RYG B

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In contrast, exendin (9-39) infusion decreased β-cell glucose sensitivity (vs. saline), which was increased as compared to the pre-surgical level. The investigators also measured the effects of bariatric surgery on incretin metabolism in 10 Type 2 diabetes patients (10). In the small intestine, GLP-1 receptors are activates by exendin (9-39) infusion. As a result, GLP-1 receptor-specific blockers were determined to be efficacious. The goal was to identify the role of GLP-1 in the improvement in insulin secretion after bariatric surgery. The level of the decrease in BMI pre-operatively was significantly lower (< 10 kg/m², 53%; 10-15 kg/m², 74%; and >15 kg/m², 82%). Postoperative HbA1c was significantly correlated (by beta-cell function. |

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Insulin secretion was enhanced in response to meals (21), and this increase is mediated through GLP-1 receptors. GLP-1 receptors are activated by exendin (9-39) infusion. As a result, GLP-1 receptor-specific blockers were determined to be efficacious. The goal was to identify the role of GLP-1 in the improvement in insulin secretion after bariatric surgery. The level of the decrease in BMI pre-operatively was significantly lower (< 10 kg/m², 53%; 10-15 kg/m², 74%; and >15 kg/m², 82%). Postoperative HbA1c was significantly correlated (by beta-cell function. |

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The Low-Down on Hypoglycemia

While successful weight loss and resolution of Type 2 diabetes have been demonstrated following gastric bypass surgery for morbid obesity, the intervention is not without risk of adverse consequences. These include short-term perioperative complications, long-term nutritional disorders, and reactive hypoglycemia. This latter concern was prospectively quantified by Brix and Austrian colleagues (abstract 624). The study cohort included 1,127 morbidly obese subjects (mean BMI 43.7±9.4 kg/m², age 38±11 years, 80.6% female). All were evaluated by oral glucose tolerance test (OGTT), and 314 of these had OGTT performed both before and 2 years after bariatric surgery.

A minority of the morbidly obese subjects (8/1127, 0.07%) experienced severe hypoglycemia (defined as blood glucose ≤50 mg/dl). In the subset that also underwent OGTT after bariatric surgery, the rate of post-surgical hypoglycemia (22.9%, 72/314) (blood glucose range 20-50 mg/dl) was, however, substantially higher than before surgery (0.02%). Interestingly, the rate of post-load hypoglycemia was different across the types of intervention: 32.6% of 175 who underwent gastric bypass; 19.4% of 72 patients who had sleeve gastrectomy; 1 patient (2.3% of 44 patients) who had gastric banding; and none of 23 patients who had vertical banded gastoplasty. These data are compatible with published reports of this sometimes severe metabolic derangement after bariatric procedures, being more common after RYGB.

Subjects with hypoglycemia lost more weight and had a greater reduction in BMI than those without hypoglycemia (Table 4). Statistically significant differences in glucose and insulin levels after OGTT between those who did versus did not develop hypoglycemia (Table 4) may help to identify patients at increased risk. The frequency of severe hypoglycemia was particularly high in those subjects with greater weight loss associated with low insulin resistance, but still presenting with high post-challenge insulin levels.

Definitive explanations for the mechanisms behind this syndrome remain elusive. It is not clear if the hypoglycemia results from altered incretin levels, dysregulated islet cells, or a dumping-like syndrome.

Less Invasive Procedures?

Further technical advancements are being made in the surgical treatment of obesity. For example, Pouraras and multinational associates reported glycemic control measures following endoscopic placement of a removable duodenal-jejunal bypass liner (Figure 2; DJBL.EndoBarrier™, GI Dynamics Inc., Lexington, MA) in 16 patients with Type 2 diabetes and BMI between 25 and 35 kg/m² (i.e., don’t qualify for bariatric surgery) (abstract 9). The device was designed to mimic the effects of bypassing the proximal gut as done with the RYGB and duodenal jejunal bypass, without the associated surgical risks.

One year post-implantation, fasting and 120 minute-glucose levels following a standard mixed-meal test were reduced (all p<0.001). Weight loss was -1 kg. The HbA1c change was clinically significant at -1.1% (p=0.001). Insulin sensitivity (as measured by the Matsuda Index and HOMA-IR) was significantly improved, as early as 1 week post-implantation (p<0.01). Fasting (p=0.053) and AUC (p=0.13) insulin, fasting (p=0.28) and AUC C-peptide (p=0.31), fasting (p=0.27) and total (p=0.81) insulin secretion rate, and insulinogenic index (p=0.43) remained unchanged over the 1-year period following device implantation, perhaps because of the reduction in glucose levels. Adverse effects included nausea and abdominal bloating in 3 patients during the first week.

New Obesity Drug

Rossner and Swedish and Canadian coworkers reported the results of a post-hoc analysis of data from 388 overweight/obese Type 2 diabetes patients with >2 weight-related comorbidities who were randomized to placebo (n=157) or 2 doses of the newly available combination anti-obesity drug, phentermine 7.5 mg/extended-release topiramate 46 mg (n=67) or phentermine 15 mg/extended-release topiramate 92 mg (n=164), in a phase 3, double-blind, 56-week study (CONQUER) (abstract 696). At week 56, weight loss among those who received active study drug exceeded that for those in the placebo group: Among the 347 patients with established weight-related chronic disease (i.e., score of 2 on Edmonton Obesity Staging System [E OSS]), least squares (LS) mean weight change from baseline was -6.9% and -8.5% for the lower and higher doses, respectively, vs. -1.9% for placebo (each p<0.0001 vs. placebo). Among the 41 patients with established end-organ damage (i.e., score of 3 on E OSS), LS mean weight change was -6.6% and -10.8% for the lower and higher doses, respectively, vs. -2.3% for placebo (p<0.05 for higher dose vs. placebo). Weight loss was associated with significant improvements in HbA1c (-0.1%, -0.4%, -0.4% for placebo, lower, and higher doses of active medications, respectively), with a minority of patients in the active treatment groups having a net change in their requirements for antihyperglycemic medications (i.e., percent of patients increasing-decreasing) (12.1%, 1.5%, and 0.6%, respectively). Discontinuation rate due to adverse events was 2-fold greater for the higher-
Several presentations at this year’s EASD meeting focused on our aging population with diabetes and their cognitive and neurological function.

In a randomized control trial, Olgaard et al. from the Steno Clinic in Denmark examined the effect of intensified multifactorial treatment on stroke risk reduction for patients with Type 2 diabetes and known microvascular disease (abstract 1223). The investigators randomized 160 patients with Type 2 diabetes and microalbuminuria to either conventional (according to national guidelines) or an aggressive multifactorial risk factor modification program involving both pharmacological and behavioral interventions. During a mean follow-up of 7.8 years during the intervention and 6 years of post-trial follow-up when all the patients were offered equal treatment, 6 patients in the intensive group experienced a total of 6 strokes, while 18 patients in the conventional arm experienced 30 strokes. Allocation to intensive treatment (p<0.05) and baseline systolic blood pressure (1% per mmHg, p=0.026) were identified as significant independent risk factors for stroke in a Cox regression analysis. Baseline fasting HDL-cholesterol levels were of borderline significance (p=0.09). At 3.8 and 7.7 years follow-up, the intensive group had significantly lower values of blood pressure, HbA1c, plasma glucose, total- and LDL-cholesterol, triglycerides, and microalbuminuria, whereas these risk factor levels were similar in the 2 groups at the post-trial assessment at 13.8 years. These findings further emphasize the importance of multifactorial intervention for significant cardiovascular protection in patients with Type 2 diabetes and microvascular disease.

Since diabetes is associated with an increased risk of cognitive impairment and dementia, Spauwen and Dutch collaborators followed 1,290 persons aged 40 years or older at baseline who participated in the Maastricht Aging Study (abstract 18). Patients received cognitive testing at baseline and after 6 years and 12 years. Changes in performance on tests of information processing speed, executive function, and verbal memory from baseline to 6- and 12- years were compared for patients with and without diabetes. Within the cohort, 68 had Type 2 diabetes at baseline, and another 54 and 57 developed incident diabetes at 6 years and 12 years follow-up, respectively. Patients with baseline diabetes showed a larger decline in information processing (Figure 3), executive function, and delayed word recall over the 12 years compared to non-diabetic subjects, after adjustment for demographic variables, history of smoking, alcohol intake, and comorbid conditions. No significant difference was observed, however, for immediate word recall (-1.88 [-5.28 to 1.52]). Of note, participants with incident diabetes did not show a larger decline in any cognitive domain compared with non-diabetic subjects, indicating that there may be a window of opportunity for prevention and early treatment of diabetes-related cognitive deficits.

In a corollary to assessing cognition, Selvarajah et al. from the UK quantified evidence of grey matter atrophy by brain MRI in 48 patients with Type 1 diabetes and 17 healthy volunteers (abstract 45). Patients with diabetes also had detailed clinical and neurophysiological assessment for diabetic neuropathy (DN), and fundus photography for diabetic retinopathy (DR). In an ANCOVA model controlling for age, gender, and DR score, the investigators found lower total grey matter volume in Type 1 patients with painful DN (760±388 ml) and painless DN (787±209 ml) compared to those without DN (812±471 ml) and healthy non-diabetic subjects (798±554 ml). The distribution of brain atrophy was mainly peripheral (p=0.02), with relative sparing of deep grey matter volume (p=0.14). There were no significant differences in white matter volume (p=0.90) or ventricular cerebrospinal fluid volume (p=0.40) across the study groups, or between painful and painless DN groups. The correlation between brain atrophy and diabetic neuropathy has, to our knowledge, not previously been explored. It remains unclear from these data whether these are simply two sequelae of long-standing disease or whether neural tissue may be similarly sensitive to injury in both the central and peripheral nervous systems.

The brain should be regarded as an organ predisposed to diabetes-related complications, not merely from acute injury related to hypoglycemia but of a chronic nature as well. The causes of neural dysfunction and grey matter atrophy in this disease are likely multifactorial, involving derangements in blood pressure, lipid and glucose metabolism, and perhaps other, yet unknown factors.

* The product is not labeled for the use under discussion or the product is still investigational.
Cardiovascular disease (CVD) remains the major, life-threatening complication of diabetes, with afflicted patients suffering 2- to 4-fold the rates of myocardial infarction, stroke, and congestive heart failure as compared to the non-diabetic population. Accordingly, there remains intense interest in CVD prevention, identification, and management in diabetes—as exemplified by the dozens of posters and oral presentations made on this topic this week in Berlin.

At a well-attended morning symposium on Wednesday, cardiologists and diabetologists convened to discuss Diabetes and Acute Coronary Syndrome (ACS). To begin the discussion, Dr. Nikolaus Marx from the University of Aachen in Germany addressed “The Role of the Cardiologist.” He carefully reviewed the combination of factors that place diabetic patients at very high risk for coronary events (Figure 4)—the combination of the ‘vulnerable plaque’ (predisposed to plaque rupture), the ‘vulnerable blood’ (predisposed to hypercoagulability and platelet overactivity), and the ‘vulnerable myocardium’ (more apt to be injured from ischemic insults).

Dr. Marx reminded the audience that silent myocardial ischemia is present in 50% of diabetic patients with coronary disease, making diagnosis particularly challenging. He then reviewed convincing data showing that, in the setting of diabetes, patients with ACS are prone to both morbid and mortal outcomes. However, studies have also demonstrated that these individuals benefit greatly from acute revascularization procedures, such as percutaneous coronary intervention (PCI). Next, Dr. Peter Gaede, lead investigator of the Steno-2 study from the University of Copenhagen, addressed “The Role of the Diabetologist.” He presented a historical overview of the approach to acute glycemic control in patients with ACS. Extensive epidemiological evidence exists demonstrating an association between increased glucose levels in hospitalized patients with ACS and adverse outcomes, including mortality. Interestingly, this relationship is more apparent in non-diabetic versus diabetic individuals. This might reflect the acute, deleterious effects of hyperglycemia on endothelial function, coagulation, inflammatory markers, and cell apoptosis. However, the results of intervention studies which have tested the hypothesis that controlling glucose levels in the critically ill reduces complications are conflicting, with some (DIGAMI 1, Leuven 1) showing a benefit from intensive insulin infusion to reduce glucose levels, but most others not confirming this (DIGAMI 2, Leuven 2, HI-5, and NICE SUGAR). Based on these, Dr. Gaede reviewed the European Society of Cardiology guidelines which emphasize good but not intensive glycemic control in acute cardiac patients (maintaining levels in the 140-180 mg/dl range). There should also be absolute avoidance of hypoglycemia, which has been associated with increased mortality as well in the setting of ACS.

To end the symposium, Dr. Guy Rutten from the University of Utrecht in the Netherlands focused on “Management after Discharge.” He devoted the bulk of his lecture on issues concerning medication compliance, disease treatment burden, and psychosocial well being of patients with both diabetes and coronary disease. With good evidence that adherence to evidence-based therapies, such as statins, blood pressure medications, and aspirin, can dramatically reduce recurrent event rates, monitoring patients’ progress after ACS is critically important.

Dozens of other presentations this week were dedicated to the diagnosis and management of cardiac disease in diabetes. Sultan et al. from France followed 703 high-risk patients with diabetes for a median of 5.8 years and attempted to determine predictors of both global and cardiovascular (CV) mortality (abstract 55). This cohort was comprised of 58% male patients, with mean age of 62 years, mean diabetes duration of nearly 14 years, and mean HbA1c of 8.4%. These patients had extensive CV risk factors. 14% had a creatinine clearance <60 ml/min and 29% had micro- or macroalbuminuria. 12% were determined to have
significant peripheral vascular disease (PVD) (i.e., obliterating arteriopathy) as assessed by absent pulses on clinical exam. Mean LDL-cholesterol was 110 mg/dl and HDL-cholesterol, 53 mg/dl; 54% were taking statins. 60% had hypertension and 43% were active smokers. During the follow-up period, 9.5% died—85% of this mortality was attributable to CVD. In multivariate analysis, lower extremity PVD, insulin therapy, the use of antiplatelet agents, and triglycerides >150 mg/dl were associated with all-cause mortality. The strongest mortality predictor was actually clinically detected PVD (RR=2.68; 95% CI 1.58-4.52). As for CV mortality, independent predictors proved to be PVD, decreased creatinine clearance, and high systolic blood pressure. Of these, PVD was the strongest, with a RR of 2.79 (1.68-4.64). The investigators concluded that a simple physical examination of the lower extremities could identify those patients at highest risk. They went on to suggest that this group should undergo more aggressive risk factor modification and, potentially, more invasive testing—conclusions that are not necessarily fully supported by their data.

Giorda and Italian colleagues presented interesting data from the left ventricular DYsfunction in DiAbetes (DYDA) study, a prospective, multicenter epidemiological study in 960 patients with Type 2 diabetes over 45 years old without overt heart disease (abstract 57). For this analysis of the study data, the group focused on structural assessment of cardiac function by echocardiography. At baseline, sonography, measuring midwall shortening (MFS) and transmitial flow pattern, demonstrated a relatively high prevalence of preclinical LV systolic (21%) and diastolic dysfunction (27%); 12% had evidence of both abnormalities. The investigators tracked clinical events over a 2-year follow-up period (data available for all but 3 patients). The primary endpoint was a composite of major events (all-cause death and hospitalizations); the secondary endpoint was development of new left ventricular dysfunction (LVD).

During follow-up, 15 deaths (1.6%, 3 CV, 11 non-CV, 1 unknown) and 181 hospital admissions occurred in 139 patients (48 CV cause, 133 non-CV). In multivariate analysis, independent predictors of a major event included older age (67 vs. 56 years: OR 2.45 [1.86-3.23]), high HbA1c (7.6 vs. 6.0%; OR 1.25 [1.01-1.54]), high baseline heart rate (80 vs. 68 bpm: OR 1.23 [1.03-1.47]), and high baseline diastolic blood pressure (90 vs. 78 mmHg: OR 2.29 [1.41-3.72]).

In contrast, systolic LVD was associated only with waist circumference (106 vs. 92 cm: OR 1.39 [1.05-1.84]). Incident systolic LVD was observed in 17% and diastolic LVD in 22% during follow-up. The investigators concluded that in those with diabetes but no overt cardiac disease at baseline, LVD is a frequent silent finding. All-cause death or hospitalization occurred in nearly 1 out of 6 of these patients, the great majority of events due to non-cardiac reasons. Independent predictors for these adverse clinical events included age, abnormal lipid profile, poor glycemic control, PVD, and, potentially, type of glucose-lowering therapy.

As discussed by Dr. Gaede in the Wednesday morning symposium, the management of glucose during acute coronary events has been a controversial issue for many years, with some studies showing a reduction in mortality extending out for at least 5 years, whereas more recent investigations not confirming this benefit. Using subcutaneous continuous glucose monitoring (CGM) devices (sensors), Mil et al. from China measured glycemic fluctuations early in the course of admission in 186 elderly ACS patients (abstract 229). The study patients were grouped into tertiles of several metrics of glycemic variability—mean amplitude of glycemic excursions (MAGE), absolute mean of daily differences (MODD), and postprandial glucose excursions (PPGE). The development of major adverse CV events (MACE) were tracked for 1 year after discharge.

Among all patients, and irrespective of diabetic status, higher MAGE, MODD, or PPGE (indicating greater variability) was associated with more advanced age, higher heart rate, admission blood glucose level, and HbA1c, reduced left ventricular ejection fraction, a higher GRACE (Global Registry of Acute Coronary Events) risk score (http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html), as well as an increased incidence of MACE.

MAGE (73±25 vs. 50±25 mg/dl, p<0.001), MODD (47.9±18 vs. 29±14 mg/dl, p<0.001), and PPGE (109±47 vs. 63±38 mg/dl, p<0.001) were significantly higher in patients who developed a MACE as opposed to those who did not. Multivariate analysis demonstrated that age, prior history of coronary disease, C-reactive protein, admission blood glucose, eGFR, MAGE, and MODD were independent determinants for MACE. After adjustments for several confounders, including GRACE risk score, diabetes history, and type of glucose-lowering therapy, MAGE (p=0.003) and MODD (p=0.052) levels retained a significant independent association with occurrence of MACE. This study suggests that glycemic variability in the setting of ACS may be important. Whether control of blood glucose in this setting using methods that minimize glucose excursions is advantageous remains an unknown.

In a similar vein, Pochinka and Russian collaborators reported on glucose variability as detected by CGM in patients with a different cardiac condition—heart failure (abstract 230). The group studied 80 Type 2 diabetes patients who had chronic heart failure, 60% having class III or IV illness based on the results of a 6-minute walk test and echocardiography. 50% were being treated with oral antihyperglycemic agents, 44% with insulin alone or with oral agents, and 6% managed with diet alone. Potentially dangerous ventricular arrhythmias were detected in 42 patients (51%) during 3 days of Holter monitoring. A blood glucose level <90 mg/dl increased the risk of dangerous arrhythmias by 4.8-fold (p=0.03, logistic regression). There was also a direct correlation between MAGE and the number of ventricular premature beats (r=0.54 Spearman; p=0.02). MAGE in patients with arrhythmias was 95 mg/dl vs. 43 mg/dl in those without arrhythmias (p=0.006, Mann-Whitney U-test). Prevalence of dangerous ventricular arrhythmias in cases with MAGE >90 mg/dl was a striking 43%, whereas it...
was only 8% in those with MAGE <90 mg/dl (p=0.02, Pearson Chi-square). These data underscore the emerging importance of glycemic variability in patients with diabetes and CVD.

The tendency for diabetic patients to experience thrombotic CV events has focused many scientists on the nature of platelet function in this disease. Years of study have determined that platelet aggregability is enhanced in diabetes and associated with some degree of aspirin resistance. Russo et al. from Italy sought to determine the prevalence of aspirin resistance in a population of diabetic patients and whether it is somehow linked to the quality of blood glucose control (abstract 232).

The study population included 37 men with Type 2 diabetes (mean age 61.6±1.2 years, diabetes duration 12.8±1.1 years, BMI 29.6±0.60 kg/m², HbA1c 8.9±0.14%). All were taking 100 mg/day of aspirin. They were entered into a 3-month anti-hyperglycemic therapy program designed to avoid hypoglycemia. No changes in anti-lipid or blood pressure therapy were allowed. Platelet sensitivity to aspirin was evaluated by Platelet Function Analyzer-100 (PFA-100): the cut-off for aspirin sensitivity was a ‘closure time’ of >200 seconds. To compare subjects within and between the two groups, 2-factor mix design ANOVA and Spearman correlation analysis were used, considering the following potential confounders: blood pressure, HbA1c, fasting and postprandial blood glucose, lipids, and von Willebrand Factor (vWF) concentrations.

At baseline, the patients were categorized as either aspirin sensitive (n=27, 73%) or aspirin resistant (n=10, 27%); the 2 groups did not differ significantly in terms of age, diabetes duration, BMI, systolic and diastolic pressures, HbA1c, blood glucose, HDL-cholesterol, triglycerides, or vWF. However, the aspirin-resistant patients had higher levels of total cholesterol (185.3±8.9 vs. 156.6±5.4 mg/dl, p<0.009), LDL-cholesterol (105.3±14.3 vs. 70.6±8.7 mg/dl, p<0.05), and apo B100 (93.0±4.9 vs. 77.2±3.0 mg/dl, p=0.009).

After the intervention, glycemic variables decreased in the aspirin-sensitive and aspirin-resistant groups:
- HbA1c, from 8.8%±2.0 to 7.6%±0.1% (p<0.0001) vs. from 9.2%±3.0 to 7.6%±0.2% (p<0.0001), respectively;
- fasting blood glucose, from 177.8±7.2 to 153.4±5.6 mg/dl (p<0.002) and from 181.7±11.9 to 134.3±9.1 mg/dl (p<0.0001);
- post-lunch blood glucose, from 182.1±9.3 to 144.4±6.9 mg/dl (p<0.0001) and from 186.3±15.3 to 148.0±11.3 mg/dl (p<0.009).

### Table 5. Aspirin for Primary and Secondary Prevention in Diabetes (Position Statement of the AHA, ADA and ACCF)

| Consider aspirin therapy (75-162 mg/day) as a primary prevention strategy in those with Type 1 or Type 2 diabetes at increased CV risk (10-year risk >10%) |
| Most men >50 years of age or women >60 years of age who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria) |
| Aspirin not recommended for CVD prevention for adults with diabetes at low CV risk (10-year CV risk <5%) |
| Men <50 years and women <60 years with no major additional CV risk factors, since the potential adverse effects from bleeding likely offset the potential benefits |
| In patients in these age groups with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment required. |
| Use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in those with diabetes + history of CVD. |
| For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used instead. |
| Combination therapy with ASA (75-162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to a year after ACS. |

Notably, PFA-100 values were unchanged from baseline to post-intervention in the aspirin-sensitive group but significantly improved in the aspirin-resistant cohort (149.2±10.4 to 228.5±15.0 sec [p=0.0001]). In addition, in aspirin-resistant patients, baseline PFA-100 time was negatively correlated with HbA1c (r=-0.835, p=0.003) and fasting blood glucose (r=-0.806, p=0.05). The investigators concluded that aspirin resistance is common in Type 2 diabetes and that aspirin-resistant patients tend to have higher lipid levels than those who are aspirin sensitive. Finally, platelet sensitivity to aspirin appears to correlate to changes in glycemic control. We would consider these data preliminary, given the small group of subjects and the lack of correlation with baseline HbA1c. Larger studies should be conducted for confirmation. We also need to better understand how glucose control affects the tendency for thrombosis that characterizes our diabetic patients. (See current AHA/ADA/ACCF aspirin guidelines in Table 5.)

Aignon et al. from France described screening for silent myocardial ischemia (SMI) in diabetic patients as an ‘appealing concept’, given their increased CV risk (abstract 1218). The identification of SMI might allow for more aggressive risk factor modification or, perhaps, for coronary arteriography in some, if indicated. The investigators retrospectively evaluated clinical outcomes in 913 high-risk patients with diabetes and normal baseline ECGs (706 Type 2, 207 Type 1) who had been screened at their institution with myocardial perfusion imaging. Of these, 171 patients (18%) were found to have SMI, 94 of whom underwent cardiac catheterization. There were no differences in risk factors, diabetic complications, or medical therapies in those who did versus did not undergo arteriography. All patients were then followed for a median of 6.5 years. During this time, a total of 79 patients (8.6%) died, predominately from CVD (84%). In univariate analysis, presence of SMI was not associated with either total (p=0.23) or CV (p=0.57) mortality. Coronary arteriography in patients with SMI was not associated with better survival in multivariate analysis. This observational study confirms the findings from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (Young et al. JAMA 2009;301:1547) which showed that, in a randomized design, indiscriminate screening for coronary artery disease in Type 2 diabetes detects disease in approximately 20% of individuals—but there appears to be no reduction in event rates over time as compared to unscreened patients under routine care. This may reflect aggressive risk factor modification that has become the standard-of-care for patients with diabetes over the past decade.

Despite more than a half century of investigation, we still don’t have a solid answer to the question, “Which glucose-lowering drug has a CV benefit?” The closest we’ve come is the finding of a modest benefit on MAGE from the thiazolidinedione, pioglitazone, in the PROactive trial (Dormandy et al. Lancet 2008;366:1279). Side effects of this medication have recently curtailed initial enthusiasm for its use, however. Yu and American colleagues performed a retrospective analysis through March 2012 within the i3 InVision Data Mart, a US claims database representing approximately 47 million covered lives (abstract 1231). Their specific question addressed...
the comparative association with mortality between patients initiating pioglitazone or insulin therapy for diabetes. Kaplan-Meier curves were generated for the occurrence of deaths in both groups, with adjustment of inverse probability weights derived from propensity scores. Hazard ratios (HR) were then estimated from Cox proportional hazards models, weighted by the propensity scores.

As with many database studies, this was a large sample including a total 56,536 patients over 45 years old with Type 2 diabetes (pioglitazone, 38,588; insulin, 17,948). The mean ages were 58.1 and 59.7 years, 59.6% and 53.0% male, and mean follow-up relatively short at 2.2 and 1.9 years, respectively. Overall, mortality occurred in 2,268 individuals (670 on pioglitazone and 1,598 on insulin). Kaplan-Meier curves for the 2 treatment groups are shown in Figure 5. The risk of all-cause mortality was significantly lower in the pioglitazone group compared with the insulin group: HR 0.334 (95% CI [0.306, 0.364]). In subgroup analyses by gender, age, the presence of congestive heart failure, pre-index glucose- and lipid-lowering medication, all-cause mortality was consistently and significantly lower in the pioglitazone group. Causes of mortality were not reported; one might presume that the differences were based on CV mortality.

We would comment that such retrospective studies should be interpreted cautiously, since they may not account for key confounding characteristics. That is, the use of these medications is not a random event—the groups are never equivalent. Insulin, for example, is traditionally used in more advanced patients, who might be expected to have greater mortality. While investigators attempt to control for such variables, such efforts are always imperfect.

Clearly, there continues to be great interest in the interplay between diabetes and vascular disease. Recent studies (ACCORD, ADVANCE, VADT) have taught us that glucose control itself may not be the best arbiter of which patients experience cardiac events—at least in the near term. There are suggestive data that long-term glucose control may be more important in this regard. In contrast, aggressive management of dyslipidemia, blood pressure, and platelet aggregability has much more substantive effects on CV risk than glucose lowering.

**Update on DPP-4 Inhibitors**

The role of the dipeptidyl peptidase-4 (DPP-4) inhibitors continues to evolve as further data accumulate relative to outcomes concerning and beyond glycemic control. In addition, newer agents within the class are under investigation. These drugs inhibit the degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), thereby increasing their activity profile. This, in turn, results in increased glucose-dependent insulin secretion and suppression of glucagon secretion. The levels of incretin hormones achieved after DPP-4 inhibition are not high enough to have any significant effect on gastric emptying or appetite suppression—as is seen with the injectable GLP-1 receptor analogues. Studies of their effects on renal and CV outcomes were presented this week at the EASD meeting.

Group and colleagues from Finland, Australia, and Germany examined the clinical effect of linagliptin on albuminuria in early diabetic nephropathy in patients with Type 2 diabetes (abstract 36). Seven double-blind, randomized, placebo-controlled trials with data available to determine urinary albumin-to-creatinine ratio (UACR) at baseline and after 24 weeks were pooled. Two groups were analyzed: (1) diabetic nephropathy in earlier stages of Type 2 diabetes; and (2) diabetic nephropathy in elderly patients with well-established diabetes. The former group was defined as persistent albuminuria at baseline, with an UACR between 30 and 3000 mg/g creatinine and stable treatment with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). The elderly group met the above criteria and was aged >65 years. The primary endpoint was percentage change in geometric mean UACR after 24 weeks. In the first group, linagliptin (n=168) significantly lowered UACR by 29% versus placebo (n=59) (95% CI: -3% to -48%; p<0.05). In the elderly group, linagliptin (n=232) lowered UACR by 25% versus placebo (n=145), although the difference did not reach the level of statistical significance (95% CI: -47% to 6%). However, if the decrease in the elderly group was compared to baseline, the decrease in UACR was significant (30%, p<0.05). In each of the 7 studies used for this pooled analysis, blood pressure and renal function were not impacted in a clinically meaningful manor.

The investigators propose that linagliptin reduced albuminuria* beyond the level one would expect from glucose lowering and suggest additional prospective clinical trials to examine the potential long-term renal benefits. Although we are intrigued by these results and wonder about the precise mechanism, it’s important to note that not all therapies that reduce urinary albumin excretion necessarily slow the progression to overt nephropathy. Clearly, more and longer-term studies are needed.

The impact of all available DPP-4 inhibitors (n=12,856) on CV outcomes* compared to sulfonylureas (n=12,856) was examined by Dworak and German co-investigators using a clinical practice database from general medical
practices representing 1,201 physicians in Germany (abstract 784). Data were retrospectively analyzed for macro- and microvascular endpoints via Cox regression after matching for age (67 ± 11 years) and gender (males 58%). Hazard ratios were adjusted for practice type, practice region, type of health insurance, concomitant antihyperglycemic medication, hypertension, hyperlipidemia, hypoglycemia episodes, and Charlson Comorbidity Index. A similar analysis was conducted in the UK, of 1,592 patients (796 each treated with a DPP-4 inhibitor or a sulfonylurea). Results from the German analysis demonstrated an overall 25% decreased risk of macrovascular events in patients treated with DPP-4 inhibitors when compared to sulfonylureas (p < 0.001). There was a trend toward decreased macrovascular events in the UK group; however, perhaps because of smaller numbers, statistical significance was not achieved (HR 0.77 [95% CI: 0.54-1.10]). The results from the German analysis were independent of insurance type and were further detailed as decreased risk of coronary heart disease (HR 0.75 [0.67-0.84]), stroke/transient ischemic attacks (HR 0.56 [0.47-0.68]), and peripheral arterial occlusive disease (HR 0.73 [0.64-0.84]). Myocardial infarction trended toward a decrease, but this outcome did not achieve statistical significance (HR 0.83 [0.69-1.01]). Additionally, higher rates of macrovascular complications were associated with number of hypoglycemic events (HR 1.6 [1.1-2.2]). In this study, there was, however, no differences between DPP-4 inhibitor therapy and sulfonylureas on the development of microvascular complications.

In a related (meta) analysis, Neubacher et al. (Germany and UK) reported reduced CV risk based on data from 8 phase 3 trials with linagliptin (abstract 1233). Using a Cox regression model, HRs for time to first occurrence of any component of the primary endpoint of CV death, myocardial infarction, stroke, and hospitalization from unstable angina were calculated for Type 2 diabetes patients receiving linagliptin (n=3,319) versus comparator (n=1,920), which included placebo (n=977), glibenpiride (n=781), or voglibose (an α-glucosidase inhibitor not available in the US) (n=162). Risk for the primary endpoint was significantly reduced with linagliptin (HR 0.36 [0.17-0.74]). There were no differences between groups based on cholesterol or blood pressure. Although significance was not reported, larger decreases were reported for linagliptin in HbA1c (-0.6 ± 0.9 vs. -0.3 ± 1.0%) and fasting triglycerides (-11 ± 136 vs. -6 ± 156 mg/dl), with no weight gain (0.01 ± 0.09 vs. 0.6 ± 3.42 kg). As with the previous investigation, this is very preliminary data showing that DPP-4 inhibitors may decrease CV risk. Ongoing prospective, randomized clinical trials formally testing this hypothesis are currently underway. If a benefit does exist, the mechanism remains arguable. Some have proposed that these agents augment levels of stromal cell derived factor 1-alpha (SDF1-α), which drives the movement of endothelial progenitor cells (EPCs) from the bone marrow to the endothelium, repairing sites of vascular injury.

Johansen and European colleagues compared the impact of linagliptin with glibenpiride on beta-cell function in adults retrospectively identified with latent autoimmune diabetes in adults (LADA) who were insufficiently controlled on metformin (abstract 148). LADA was defined as presence of one or more autoantibodies (GAD65, ICA, IA-2A, IAA) at baseline or any visit while on treatment. The study cohort included 1,519 patients with a LADA prevalence of 7.8% (n=118). The most common autoantibody was GAD65 (6.5%). Baseline characteristics between treatment groups of GAD 65+ patients were comparable (age 59 vs. 63 years; BMI 30.3 vs. 31.7 kg/m²; diabetes duration >5 years 62% vs. 59%). Overall, HbA1c reductions were of similar magnitude in each group. However, patients with LADA treated with linagliptin preserved C-peptide significantly better than those managed with glibenpiride over the 2-year study period (Table 6). Although comparable glycemic control was achieved, the investigators hypothesize that differences on long-term beta-cell function may be more favorable in patients on DPP-4 inhibitors.*

Finally, in addition to further investigation of existing DPP-4 inhibitors, a novel once-weekly agent, MK-3102*, is in development. Gantz and US co-investigators evaluated the efficacy and safety of MK-3102 as monotherapy in patients with Type 2 diabetes (mean HbA1c 8.1%) in a randomized, double-blind, placebo-controlled, dose-ranging study (abstract 110). The primary endpoint of the trial was change in HbA1c from baseline to week 12. A statically significant decrease in HbA1c was observed for doses ranging from 0.25 mg to 25 mg once weekly when compared to placebo. The lowest dose, 0.25 mg weekly, and the highest dose, 25 mg weekly, resulted in least squares (LS) mean decreases from baseline of -0.14 (-0.30 to 0.01; p<0.05 vs. placebo) and -0.57 (-0.73 to -0.42; p<0.001 vs. placebo), respectively.

MK-3012 was reported as well tolerated and associated with low incidence of hypoglycemia. The investigators noted that an oral antidiabetic medication administered once weekly may offer distinct advantages from a patient adherence perspective.

The DPP-4 inhibitors have been gaining in popularity since sitagliptin became available more than 5 years ago. While only modestly effective, they are well tolerated and associated with neither weight gain nor hypoglycemia. Data from ongoing studies on CV impact are awaited. At present their main role is as a second- or third-line therapy after metformin.

### Table 6. Change in Fasting C-Peptide in GAD65+ LADA Patients: Linagliptin Versus Glibenpiride

<table>
<thead>
<tr>
<th></th>
<th>28 weeks</th>
<th>52 weeks</th>
<th>104 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Glibenpiride</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Baseline C-peptide</td>
<td>821</td>
<td>1326</td>
<td>835</td>
</tr>
<tr>
<td>Change in C-peptide</td>
<td>96†</td>
<td>-105</td>
<td>143†</td>
</tr>
<tr>
<td>Change in HbA1c, %</td>
<td>-0.3</td>
<td>-0.8</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

* p<0.001 vs. baseline; † p<0.01 vs. glibenpiride.

**Diet Matters**

Type 2 diabetes is often referred to as a nutritional disease, given the significant rates of obesity associated with this condition. There are well-known benefits to dietary changes on both body weight and glycemia, but also on lipoprotein metabolism, blood pressure, and inflammation. At international diabetes meetings, while the bulk of the program involves pharmacological therapies, a number of presentations focus on nutritional...
Interventions and their impact on clinical and biochemical outcomes.

Kahleova et al. from the Czech Republic conducted a crossover study in which 54 patients with Type 2 diabetes were randomized to 12 weeks of a hypocaloric diet (baseline diet reduced by 500 kcal/day), consumed in either 6 meals per day or 2 meals per day (abstract 75). Importantly, the diet in both regimens had the same macronutrient and energy content. The investigators discovered favorable effects on body weight, HbA1c, and plasma C-peptide when the patients consumed their calories in 2 meals (Table 7). Plasma immunoreactive insulin, triglycerides, and LDL-cholesterol decreased comparably in both regimens. No significant changes in total cholesterol or HDL-cholesterol were observed with either diet regimen. Resting energy expenditure (as a percentage of predicted) decreased more so during the period when patients ate more versus less frequently (Table 7, p=0.08). These data suggest that larger, less frequent meals may be preferable to the standard teaching of smaller, more frequent meals in patients trying to lose weight. If this is correct, the explanation may lie in the adaptive response of basal metabolic rate to these two nutritional patterns.

Bozetto and Italian colleagues randomized 45 patients with well-controlled Type 2 diabetes (HbA1c 6.6±0.8%, age 35-70 years) to 12 weeks of either a high carbohydrate/high fiber/low glycemic index diet (CHO/fiber) or a diet high in monounsaturated fatty acids (MUFA). The goal was to investigate the effect of these two generally recommended diets on liver fat content and postprandial lipemia in the absence of weight loss (abstract 76). Liver fat, as measured by proton magnetic resonance spectroscopy, decreased significantly more in the MUFA-diet group than in the CHO/fiber group (-27% vs. -5%, p<0.05). Of note, the postprandial incremental AUC of triglycerides increased in the MUFA group, while decreasing in the CHO/fiber group (p<0.05). These results show a MUFA-rich diet leads to a clinically relevant reduction in hepatic fat in Type 2 diabetes patients, even in the absence of weight loss. The MUFA diet appears to decrease postprandial liver storage of triglycerides, but whether this resulted in an increase in subcutaneous fat stores was not measured. A long-term study, which would obviously be difficult to conduct, would be of great interest to assess the extended effects on CV risk from these nutritional interventions.

### Table 7. Mean Change from Baseline to Week 12 by Frequency of Meals

<table>
<thead>
<tr>
<th></th>
<th>2 Meals/Day</th>
<th>6 Meals/Day</th>
<th>p-value for Difference Between Groups by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>-3.7</td>
<td>-2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-4.1, -3.4</td>
<td>-2.7, -2.0</td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>-0.25</td>
<td>-0.23</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>-0.29, -0.20</td>
<td>-0.27, -0.19</td>
<td></td>
</tr>
<tr>
<td>Fasting C-peptide, nmol/l</td>
<td>-0.14</td>
<td>-0.05</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>-0.18, -0.10</td>
<td>-0.09, -0.01</td>
<td></td>
</tr>
<tr>
<td>Predicted REE, %</td>
<td>-3.0</td>
<td>-4.6</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>-3.9, -2.1</td>
<td>-5.6, -3.7</td>
<td></td>
</tr>
</tbody>
</table>

REE= resting energy expenditure (according to Harris Benedict equation).

### A New Meaning to “Sugar Coma”?

The prevalence of obstructive sleep apnea (OSA) is ~25% in patients with Type 2 diabetes, and substantially higher (approaching 90%) in those who are also obese. Lecube and Spanish coworkers conducted a case-control study, evaluating nocturnal oxygen desaturation index (ODI) at baseline and 5 days after rapid intensification of glucose control in 30 Type 2 diabetes patients and also in 10 non-diabetic subjects over the same time period (abstract 1267). The patients were matched by age, gender, and BMI. ODI was distinguished into 4 event periods, based on progressive decreases in oxygen saturation from baseline as follows: ODI-3%, ODI-4%, ODI-6%, and ODI-8%. At baseline, nocturnal oximetry was impaired (i.e., significantly higher ODI-6% in all categories in the diabetic patients [Figure 6]). There was also positive correlation between the cumulative percentage of time spent with oxygen saturation <90% and both fasting plasma glucose and HbA1c. In multiple linear regression analyses, HbA1c was independently associated with ODI-3%, ODI-4%, and ODI-6%. Importantly, statistically significant reductions in ODI were observed 5 days after blood glucose optimization (fasting plasma glucose reduced from 157±74 mg/dl to 121±38 mg/dl [p=0.035]) in the diabetic patients, with (as expected) no change in the normal control subjects. The rapid effect of improved glycemic control on ODI, without changes in body weight, suggests a central mechanism on the respiratory center.

### Figure 6. Changes in Percentage of Patients Experiencing Oxygenation Desaturation Indices

*p<0.05 between baseline and follow-up.
Putting the 'D' in Diabetes

Wium and Norwegian coworkers reported baseline results of insulin sensitivity and insulin secretion in relation to 25-hydroxyvitamin D (25-OH D) levels from DIVINE, an ongoing intervention trial with vitamin D in patients with Type 2 diabetes and vitamin D deficiency (abstract 571). The study population included 28 men and 14 women of Nordic origin, and 9 men and 10 women of South Asian ethnicity, with confirmed Type 2 diabetes and 25-OH D levels <20 pg/ml.

In this biethnic group of patients with Type 2 diabetes and hypovitaminosis D, the investigators found no correlation between 25-OH D and insulin resistance or first-phase insulin secretion, measured by euglycemic clamp and IV glucose tolerance test. Despite selecting subjects with levels <20 pg/ml, there were still marked ethnic differences in 25-OH D levels (Nordic: 16.8±4.0 pg/ml vs. South Asian: 14.4±5.6 pg/ml p=0.015) and anthropometrical measurements, but these differences did not influence insulin sensitivity or insulin secretion. The investigators concluded that their results do not disprove a relationship between vitamin D and diabetes, but such a relationship, if it exists, is probably more complex than a direct effect on insulin sensitivity or secretion. We await the full results of their trial to see whether a high-dose vitamin D intervention will improve insulin secretion and/or insulin sensitivity in these patients.

Mind the Gap

Banu and French coworkers evaluated the potential association between ‘glycation gap’ and complications in Type 2 diabetic patients (abstract 32). Glycation gap is the term used to describe the difference between the measured HbA1c and that predicted by an actual assessment of mean ambient glucose. Originally, the latter was measured through an averaging of frequent blood glucose tests—clearly a suboptimal method. The gap has been theorized to arise from altered access of glucose from the extra-cellular to the intra-cellular compartment, since hemoglobin is mainly an intra-erythrocytic protein. For this investigation, the investigators compared the difference between HbA1c (representing glycation within the intra-erythrocyte compartment) to level of fructosamine (as a measure of glycation in extracellular space). They assessed predicted HbA1c (HbA1c-F) from the correlation between fructosamine and measured HbA1c (HbA1cF = 0.021 x fructosamine + 2.025; r=0.72; p<0.001). They then determined glycation gap—the difference between measured HbA1c and HbA1c-F—in 925 Type 2 diabetes patients (mean age 58 years, 53% male, BMI 31 kg/m², diabetes duration 12 years, HbA1c 8.3%), including 486 at high CV risk (who underwent CV examinations, including the detection of silent myocardial ischemia by stress scintigraphy) and 459 Type 2 diabetes patients at low CV risk. The patients were next separated into 3 glycation gap groups: high and low defined as the 5% of patients with the highest and lowest measured HbA1c as compared to the predicted value (i.e., HbA1cF), respectively, and normal, defined as the 90% intermediate group.

The prevalence of nephropathy (23.1%/28.0%/33.2% for low/normal/high glycation gap; p<0.05) and macroproteinuria (2.9%/6.2%/11.0%; p<0.001) were significantly different across the glycation gap groups, but not so for retinopathy (p=0.057), peripheral neuropathy (0.06), cardiac autonomic neuropathy, or silent myocardial ischemia. In an analysis of 200 patients without proteinuria and 54 patients with macroproteinuria who were matched for HbA1c (8.3%), 33.5% and 51.9%, respectively, were in the high glycation gap group (p<0.05 by univariate analysis). In multi-variate analysis controlling for HbA1c and other potential confounders, the OR was 2.3 (95% CI 1.2-4.4), indicating that glycation gap is associated with macroproteinuria, independently of glycemia and other confounding factors, in patients with Type 2 diabetes and suggesting a specific role of glycation susceptibility on kidney glomerulus. These data give support to the theory that some individuals simply glycate at lower or higher levels than others and this may itself have some implications for the development and progression of diabetic complications. The broader suggestion is that measured HbA1c values may not necessarily faithfully reflect ambient glucose levels. A higher HbA1c than might be suggested by examining blood glucose levels and trends themselves may have very important intrinsic value.

Breakfast is Ready!

Wainstein and colleagues from Israel randomized 60 lean women with polycystic ovary syndrome (PCOS) (mean age 29.4±6.5 years, mean BMI 22.7±0.64 kg/m²) to 1 of 2 isocaloric (1500 kcal/day) diets, with a high-calorie meal (700 kcal with 50:30:20 carbohydrate:protein:fat) consumed at breakfast vs. dinner (abstract 567). Insulin and glucose response to an oral glucose tolerance test (OGTT) and free testosterone level were measured at baseline and after 90 days of the dietary intervention. High caloric protein and carbohydrate intake at breakfast, with reduced intake at dinner, resulted in improved insulin sensitivity and decreased hyperandrogenism. In patients randomized to the high-calorie breakfast diet, area under the curve (AUC) for glucose during the OGTT decreased from 708.8±145.8 mg/dl/hr at baseline to 582.6±134.3 mg/dl/hr at day 90 (p<0.0001), and AUC for insulin decreased from 335.3±161.0 to 102.4±55.2 µU/L/hr (p<0.0001). Additionally, serum testosterone levels decreased from 3.8±1.0 to 1.3±0.7 ng/ml (p<0.0001). In contrast, these values did not change in the group that was randomized to a high-calorie dinner diet. BMI was unchanged in both groups. These results suggest that the timing of meals and composition of calories may have a role in the therapeutic management of women with PCOS, including those who do not require weight loss. If these data hold up after similar investigations by other groups, it would be of extreme interest to determine the biological explanation for this effect, which currently escapes us.

A New CV Risk Marker?

Copeptin, a proximate marker for vasopressin secretion, has been reported to be of diagnostic and prognostic value in acute heart failure and myocardial infarction. If this is also the case for patients with Type 2 diabetes, copeptin could be useful as a CV risk marker and, perhaps, targeted by vasopressin antagonist therapy for CV risk reduction.

Using data from 1,265 Type 2 diabetes patients (44% male, age 67±11.6 years) participating in the Zwolle Outpatient Project Integrating Available Care (ZODIAC-31) study, Riphagen et al. from The Netherlands and Germany prospectively investigated whether copeptin is associated with CV and all-cause mortality (abstract 135). Copeptin concentrations were higher in men than in women (median: 7.4 vs. 4.1 pmol/l; p<0.001). After a median follow-up of 6.4 years, 365 patients died (29%), with 154 deaths (12%) attributable to CV causes. After adjustments for potential confounders (age, sex, BMI, smoking, systolic blood pressure, total cholesterol-HDL ratio, duration of diabetes, HbA1c, use of RAAS-inhibitors, history of CVD, serum creatinine, urinary albumin-to-creatinine ratio) in Cox regression analyses, copeptin was associated with both CV mortality (HR 1.18 [1.00-1.39]; p<0.05) and all-cause mortality (HR 1.22 [1.10-1.35]; p<0.001). While further study may be of interest, the very modest changes observed suggest it unlikely that this line of investigation will lead to useful CV therapeutics in diabetes.

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

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New Haven, Connecticut
McGill and American investigators utilized the Type 1 Diabetes Exchange registry to identify distinguishing patient characteristics that may be predictive of improved control in Type 1 diabetes (abstract 186). The Type 1 Diabetes Exchange is a network of 67 clinics representing over 25,000 patients. Patients ≥18 years of age were categorized into 2 groups of glycemic control: HbA1c < 6.5% and HbA1c ≥8.5%. Patient demographics and diabetes management techniques were compared between groups. Race, marital status, education, income, and insurance influenced diabetes control, as did method of insulin delivery and dosing and glucose monitoring (Table 8). While observational only, these data provide some insights into characteristics of those Type 1 patients able to successfully manage their disease.

Progress on the Artificial Pancreas

An issue that continues to plague intensively managed Type 1 patients is hypoglycemia. Even those on insulin pumps suffer frequent episodes. The first step to the development of a fully automatic pump—where an indwelling subcutaneous continuous glucose monitor (CGM) actually directs the pump’s insulin infusion—is a ‘shut-off’ feature whereby detected hypoglycemia results in temporary cessation of insulin infusion. In a study of 50 insulin pump users (56% male, mean age 34.3±12.4 years, BMI 26.9±4.3 kg/m², HbA1c 7.9±0.6%) who were asked to exercise with a CGM device in place after an overnight fast, Garg and ASPIRE investigators randomized the patients to 2 groups. They were to exercise until their plasma glucose value was <85 mg/dl with a new ‘low-glucose suspend’ feature ON (set to suspend insulin for 2 hours at CGM sensor glucose values ≤70 mg/dl) or OFF (abstract 627).

The patients were then observed for up to 4 hours or until a plasma glucose value of 50 mg/dl was reached or if symptomatic hypoglycemia occurred. Patients were then crossed-over to the opposite group, with a minimum 3-day washout between periods.

Of the 134 experiments, 98 were successful (48 ON and 50 OFF). Of the 36 unsuccessful experiments, 17 were due to plasma glucose values falling below 50 mg/dl, 14 were due to plasma

Table 8. Characteristics* Associated with Improved Glycemic Control in Patients with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HbA1c &lt;6.5% (n=889)</th>
<th>HbA1c ≥8.5% (n=2,314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>94%</td>
<td>81%</td>
</tr>
<tr>
<td>Education: Bachelor’s or higher</td>
<td>63%</td>
<td>24%</td>
</tr>
<tr>
<td>Annual income ≥$75,000</td>
<td>63%</td>
<td>36%</td>
</tr>
<tr>
<td>Married</td>
<td>58%</td>
<td>29%</td>
</tr>
<tr>
<td>Working full time</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>Private insurance</td>
<td>86%</td>
<td>70%</td>
</tr>
<tr>
<td>Using insulin pump</td>
<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>Gives insulin bolus before (versus after) starting meal</td>
<td>67%</td>
<td>47%</td>
</tr>
<tr>
<td>Varies insulin to carbohydrate ratio for each meal</td>
<td>37%</td>
<td>21%</td>
</tr>
<tr>
<td>Monitors blood glucose &gt;6 times daily</td>
<td>53%</td>
<td>18%</td>
</tr>
<tr>
<td>Monitors blood glucose prior to bolus dose</td>
<td>52%</td>
<td>25%</td>
</tr>
<tr>
<td>Total daily insulin dose (units/kg/day)</td>
<td>0.6±0.3</td>
<td>0.8±0.4</td>
</tr>
</tbody>
</table>

*Each characteristic associated with a statistically significant difference between groups: p<0.001.
GLP-1, an endogenous peptide hormone released by the intestines in response to meal ingestion, augments pancreatic insulin secretion in a glucose-dependent fashion. It also suppresses pancreatic glucagon secretion, slows gastric emptying, and promotes satiety at the level of the central nervous system. Thus, GLP-1 receptor agonists (RAs), approved for glucose lowering in Type 2 diabetes, are starting to be used after primary failure of metformin. The main beneficial attribute distinguishing these drugs from other antihyperglycemic agents is weight loss. They are injectables, however, and more expensive than other agents.

Many presentations this week focused on this incretin-based therapy. Gallwitz and European and North American colleagues reported results from the EUREXA clinical study (abstract 5). This longest-term study (up to 54 months) thus far with GLP-1 RAs compared exenatide twice daily (n=490) to glimepiride once-daily (n=487) as add-on therapy in patients not adequately controlled with metformin (mean age 56 years, BMI 32.5 kg/m², diabetes duration 6 years, HbA1c 7.4%). The primary endpoint was time to inadequate glycemic control, defined as HbA1c >9% at any visit or >7% at 2 consecutive visits. Those meeting the endpoint were recruited and re-randomized to receive add-on therapy with glimepiride or thiazolidinedione (TZD), if previously prescribed. Those meeting the endpoint were recruited and re-randomized to receive add-on therapy with glimepiride or TZD (if previously prescribed). In the initial phase of the study, the estimated hazard ratio (HR) for time to inadequate control favored exenatide over glimepiride (HR 0.748 [95% CI 0.623, 0.899], p=0.002; exenatide/glimepiride Cox regression adjusted for baseline HbA1c). Comparing patients who received a TZD in addition to exenatide, HbA1c decreased further (-0.22±0.03%), whereas those who received glimepiride as the add-on had an increase in HbA1c (+0.16±0.99%), with a significant difference between months 18 and 30 (statistics not provided). Percentages of patients with HbA1c values <6.5% and <7% did not differ between the 3 groups. However, lower rates of hypoglycemia occurred in the group receiving exenatide and TZD versus exenatide and glimepiride (p<0.001), with significantly greater weight gain (from 24 months on) in the TZD group. The investigators concluded that this study supports initial addition of exenatide (versus glimepiride) and, when needed, the addition of a TZD, but not glimepiride, to patients inadequately controlled on metformin and exenatide.

Diamant et al. from Europe and the US posed the question whether GLP-1 RAs may be superior to insulin as an injectable Type 2 diabetes therapy (abstract 800). Using data from the LEAD-5 and DURATION-3 trials, the investigators compared patients receiving either liraglutide once daily, long-acting exenatide once weekly, or insulin glargine, by quartiles of baseline HbA1c values (Table 10). For either GLP-1 RA, change in HbA1c was equivalent or greater in all quartiles versus baseline. From this preliminary analysis, the investigators propose that in patients with Type 2 diabetes failing 1-2 oral agents, GLP-1 RAs are comparable, and possibly superior to basal insulin for HbA1c lowering. We find this to be an interesting approach, and certainly apt to lead to very different effects on body weight. Nonetheless, the much higher cost of any GLP-1-based drug must be considered.

A new GLP-1 RA under investigation, semaglutide*, was evaluated for its HbA1c lowering efficacy in addition to safety and tolerability. Nauck and co-investigators from Europe performed a 12-week, randomized, double-blind trial comparing semaglutide at 5 increasing doses compared to liraglutide 1.2-1.8 mg weekly or to placebo (abstract 2). Semaglutide demonstrated a dose-dependent reduction in HbA1c and in body weight compared to baseline and to placebo. Higher doses (0.2 to 1.6 mg) provided statistically significant reductions in HbA1c compared with placebo (p<0.05-p<0.001). The highest dose of semaglutide (1.6 mg weekly) was superior to that of liraglutide 1.2 mg and 1.8 mg daily relative to HbA1c reduction. Body weight reduction from baseline was 4.8 kg versus 1.2 kg with placebo (p<0.01 for doses ≥0.8 mg). Overall, semaglutide was well tolerated, with dose-dependent increases in nausea and vomiting, as seen with other GLP-1 RAs.

In fact, gastrointestinal side effects, specifically nausea, are the most commonly reported adverse events in patients receiving GLP-1 RAs. To better predict those patients predisposed to GLP-1 RA-induced nausea, Umematsu and Japanese coworkers investigated clinical
parameters and incidence of nausea among patients with Type 2 diabetes managed with these agents while hospitalized in a case-control study (abstract 734). Patients on GLP-1 RAs were retrospectively identified from September 2010 to January 2012 and categorized by those experiencing versus not experiencing nausea. Microvascular complications and clinical parameters were evaluated for each group and compared via chi-square analysis and student t-test. Multivariate analysis in a stepwise multiple logistic-regression model was performed to assess significant predictors of nausea. A total of 66 patients received either liraglutide 0.3 mg daily or exenatide 5 μg twice daily (36 males, age 59±12 years, diabetes duration 11.7±7.8 years, HbA1c 9.0±1.6%, BMI 30.5±6.9 kg/m²). Nausea occurred in 26 (39%) patients. In the patients experiencing nausea, urine albumin to creatinine ratios were significantly higher (p=0.009) and HbA1c values and estimated GFRs were significantly lower (p=0.014 and p=0.017). There were no differences based on gender, BMI, duration of diabetes, waist circumference, and the specific GLP-1 RA utilized. Presence of microalbuminuria was significantly associated with nausea via multivariate logistic regression analysis (p=0.0058) even when adjusted for co-variables. Those with albuminuria (microalbuminuria [n=22] or proteinuria [n=14]) had a significant increase in the rate of nausea (OR 2.50 [1.10-5.73]; p=0.048), however, there was no difference between the two. The investigators recommend that clinicians carefully monitor gastrointestinal symptoms when prescribing GLP-1 RAs to patients with microalbuminuria. It is unclear to us why this association might exist—perhaps low-level of autonomic neuropathy (in conjunction with early nephropathy, another microvascular complication) is playing a role.

### Hypoglycemia: Implications and Associations

Hypoglycemia is the primary limiting factor to intensive glycemic management, and its frequency tends to increase with longer duration of diabetes. The ACCORD, ADVANCE, and VADT trials highlighted the concern of hypoglycemia as potentially associated with cardiovascular events and mortality. Since the publication of these studies, many investigators have attempted to further elucidate this link.

In a symposium on Wednesday, the most feared consequence of nocturnal hypoglycemia, the “dead in bed” syndrome, was discussed. Dr Brian Frier from the University of Edinburgh, Scotland presented a summary of the data regarding potential causes of sudden death as a result of hypoglycemia. Hypoglycemia-related mortality may be cardiac (myocardial infarction, cardiac arrhythmias, cardiac failure), cerebral (prolonged coma, seizures, stroke), or accidental (fall, trauma, motor vehicle accidents) in nature. However, the brain is very resilient to hypoglycemic stress, and Dr. Frier estimates that sustained hypoglycemia of <1.5 mmol/L (or about 25-30 mg/dl) for over 6 hours may be the level required for coma and death to occur. The frequency of hypoglycemia-related seizures in people with diabetes is not known.

The most likely cause of sudden death in the setting of hypoglycemia is cardiac arrhythmias, especially in the context of diabetic patients with underlying coronary artery disease. Dr. Simon Heller from the United Kingdom described the effect of hypoglycemia on the QTc interval. Both insulin and increased sympathetic activity lower serum potassium, prolonging cardiac repolarization. This delayed repolarization, characterized by increased QTc interval on ECG, is a set-up for ventricular tachycardia and potential sudden death. The presence of autonomic neuropathy may be an additional risk factor. Nevertheless, clinical hypoglycemia is common but sudden death is rare, so most individuals are thankfully afforded a level of protection from this tragic cascade of events. Specific genetic mutations may make someone more vulnerable to the cardiac consequences of hypoglycemia, such as a mutation in the SCN5A gene, which codes for the cardiac sodium channel and is associated with a prolonged QTc. However, the most important risk identifier remains the presence of repeated severe hypoglycemic episodes.

Recent clinical trial data provide us with risk factors for severe hypoglycemia in our diabetic population, and these risk factors were discussed by Sophia Zoungas, PhD, a co-investigator of the ADVANCE Trial from Melbourne, Australia. From an assessment of the ADVANCE trial, independent risk factors for severe hypoglycemia are listed in Table 11 (Zoungas, NEJM 2010;363:1400-1418). The most frequent antecedents are variation in food intake (missed or delayed food, less than usual carbohydrates, 48%), unexpected or more rigorous exercise (15%), and incorrect insulin dosing (9%).

Even children with Type 1 diabetes, who are otherwise healthy with normal vasculature, may be at risk for arrhythmias in the setting of hypoglycemia. Laptev and Russian collaborators determined the effect of hypoglycemia on QT interval, heart rate variability (HRV) parameters, and frequency of arrhythmias in 107 children and adolescents (age 6-18 years) with diabetes (abstract 623). Participants were continuous and simultaneous ECG Holter and glucose (CGM) monitors for a period of 24 hours. Cardiac rhythm characteristics were compared between participants with or without hypoglycemia (blood glucose <63 mg/dl). There were 24 episodes of nocturnal hypoglycemia in 17 participants (15.6%) and 45 episodes of daytime hypoglycemia in 34 participants (31.8%). During episodes of nocturnal hypoglycemia, QTc intervals were longer (439 vs. 424 ms, p<0.05) and HRV parameters were reduced (standard deviation of all normal to normal RR-intervals [SDNN] 68 vs. 90 ms and square root of the mean squared difference of successive normal RR-intervals [RMSSD] 48 vs. 79 ms, p<0.05) without a significant increase in heart rate (69 vs. 68 beats/min, p=0.29). Similar changes in cardiac rhythm characteristics also occurred during daytime hypoglycemia, as compared to rhythm characteristics from participants whose blood glucose remained within or above the normal range. These data suggest significant effects on cardiac conduction can occur in children during insulin-induced hypoglycemia.

Singh and colleagues from the US reported an estimated annual incidence of hospitalizations for hypoglycemia in people with Type 2 diabetes, and the related medical care costs (abstract 628). The investigators analyzed all inpatient hospitalizations with a primary or secondary diagnosis of Type 2 diabetes and hypoglycemia in adults within the Nationwide Inpatient Sample database, a

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**Table 11. Independent Risk Factors for Severe Hypoglycemia**

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Duration of diabetes mellitus</td>
</tr>
<tr>
<td>Increased creatinine level</td>
</tr>
<tr>
<td>Lower BMI</td>
</tr>
<tr>
<td>Abnormal cognitive function</td>
</tr>
<tr>
<td>Use of ≥2 oral hypoglycemic agents</td>
</tr>
<tr>
<td>History of smoking</td>
</tr>
<tr>
<td>History of major microvascular disease</td>
</tr>
<tr>
<td>Undergoing intensive glucose control</td>
</tr>
</tbody>
</table>

*Hypoglycemia defined as glucose <50 mg/dl, p<0.05 for all risk factors. From supplementary material in Zoungas et al. NEJM 2010;363:1410-1418.*
stratified random sample of all US community hospitals, for a 1-year period (2009). The investigators found 248,422 hospitalizations for hypoglycemia (mean age of affected patients was 67.3 years, with even distribution between genders). These accounted for 3.5% of all hospitalizations in these patients. The resulting 1.9 million hospitalization days (average, 7.58 days) cost a total of $12.07 billion dollars (average $48,569). Medicare and Medicaid programs were responsible for 76.1% of these costs. The case-fatality rate was 3.7%, resulting in 9,274 deaths. While glycemic control remains important in our patients with diabetes, the clinical and financial implications of therapy-induced hypoglycemia are considerable. Individualization of treatment targets, with an emphasis on glucose control strategies that minimize the risk of hypoglycemia, is important.

**Table 12. Criteria for Diagnosis of Diabetes**

| A1c ≥6.5% | The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*  
| FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*  
| 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*  
| In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).  

* In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

**Figure 7. Cumulative Incidence of Death in Screening and No Screening (Control) Groups in the ADDITION-Cambridge Trial**

The ADA recommends a much more aggressive approach—screening all adults by age 45 and then at least every 3 years. According to the ADA, screening should occur earlier in overweight individuals with additional risk factors. The main question of any screening recommendation is whether identifying affected individuals actually improves their outcomes. Interesting data were presented by Simmons et al. from the UK, who assessed the impact of a population-based step-wise screening program for diabetes on mortality, using a cluster-randomized trial design (abstract 183).

A total of 33 general practices in eastern England were allocated to (1) screening followed by intensive multifactorial treatment for detected diabetes (IT, n=15), (2) screening plus routine care according to national guidelines (RC, n=13), or (3) a no-screening control group (n=5). In all, the study population consisted of 20,184 individuals aged 40–69 years, at high risk for diabetes, based on a previously validated risk score involving clinical characteristics. In those screening practices, individuals were invited to a stepwise program...
The management of Type 2 diabetes has become increasingly complex over the past decade and a half, with an explosion in the number and types of anti-hyperglycemic agents available. Several guidelines and algorithms have been published over the past 5 years, attempting to provide a roadmap for clinicians to optimally implement these therapies. The latest iteration is an official Position Statement from 2 major diabetes professional organizations, the ADA and the European Association for the Study of Diabetes (EASD). Please see Diabetes 2012, Volume 25, Edition 1 for a full discussion of the statement, based on a presentation at the ADA’s Scientific Sessions earlier this year in Philadelphia. On Thursday, the statement was the topic of a major symposium in Berlin.

Professor David Matthews of Oxford, UK, co-chair of the statement’s writing committee, began, with a discussion of “A New Approach to Individualized Treatment.” He underscored the growing need for personalized medicine and patient-centered care, which accounts not only for variable pathophysiological defects of the disease, but also those important patient factors of age, disease duration, comorbidity, adherence, motivation, and socio-economic context. These concerns help guide the determination of individualized treatment targets (i.e., HbA1c) for a specific individual. More aggressive approaches are warranted in younger and healthier patients, but more conservative ones are necessary in the elderly and more infirm. A ‘one-size-fits-all’ approach is no longer justifiable, especially given the results of the major cardiovascular studies from 3 years ago. These taught us that overly aggressive glucose-lowering approaches in older, high-risk patients may be counter-productive.

Dr. Silvio Inzucchi from Yale, the committee’s other co-chair, next addressed “Drugs—Which and When?” Reviewing the unique mechanisms of action of the various agents available to reduce glucose, as well as their unique side effect profiles and risks, Dr. Inzucchi emphasized the use of an equally individualized approach to constructing the best treatment program for each patient. He presented the main figure from the statement (Figure 8), which describes the key features of each

Diabetes 2012

European Association for the Study of Diabetes  ▪ Berlin, Germany  ▪ Volume 26 ▪ October 4, 2012

2012 Position Statement on T2DM Therapy

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drug class and in which sequence they might be used. In most patients, initial therapy with metformin is warranted. Five effective drug classes, if combination therapy is then needed, include the sulfonylureas, the TZDs (mainly, pioglitazone), the DPP-4 inhibitors, GLP-1 receptor agonists, and basal insulin. He cautioned the audience to try to minimize treatment burden on patients, especially those confronting multiple other comorbidities.

In all, the new Position Statement represents something of a departure from earlier guidelines. The focus is now on the rational and safe use of the numerous treatment strategies available to us—incorporating the patient's preferences, needs, and values into all decision making.

### Novel Therapies and Diagnostics

Over the past 2 decades, the number of oral and injectable antihyperglycemic agents has increased more than 5-fold. Yet, the perfect diabetes drug remains elusive. Each current class, from traditional sulfonylureas, to metformin, to the latest GLP-1 agonists, has both its benefits and risks. Moreover, most patients with Type 2 diabetes will require more than one agent to attain glucose control, because few—other than for perhaps insulin—are either completely and durably effective. Accordingly, there remains great interest in the development of new drugs, often with very novel therapeutic targets. On Wednesday, global experts gathered to discuss "Oral Therapies: Novel Agents" to an interested audience comprised of clinicians, scientists, and industry developers. Attendees were reminded that the pathophysiology of diabetes is complex and that ideal, individualized treatment requires advancements in agents that target both the glycemic and myriad of associated non-glycemic derangements of the disease. To this end, over 150 new chemical entities are currently in some phase of development for Type 2 diabetes, which reminds us that knowledge of today’s "pipeline" will better prepare us to incorporate newly approved agents of the future into our clinical practices.

The first speaker, Dr. Richard DiMarchi of Indiana University, discussed “Glucagon-Incretin Hybrids: An Improvement Over GLP-1 Receptor Agonists?” A pioneer in the search for translational medicines, DiMarchi highlighted work from his and other groups that have used ‘chemical biotechnology’ to devise biologically relevant molecules (bringing function to molecules that don’t actually exist in nature). He summarized two fronts of research involving poly-pharmacy in a single molecule: 1) glucagon/glucagon-like receptor (GLP)-1 co-agonism*, made possible by chemical manipulations that stabilize the “forgotten hormone” so it can be administered at physiological conditions, and 2) glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 co-agonism*. In each case, preclinical pharmacology has seemed superior to a GLP-1 agonist. As compared to exendin-4 (the original GLP-1 homolog discovered in the salivary secretions of the gila monster), DiMarchi indicated that weight loss (and fat mass reduction) with a glucagon/GLP-1 co-agonist is comparable in diet-induced obese mice. Furthermore, glycemia and lipids improved and resting metabolic rate increased. Altering the ratio of GLP-1 to glucagon properties of the molecule impacts the glycemia relative to weight loss effects. GIP/GLP-1 co-agonists have also been shown superior to a pure GLP-1 agonist with similar benefits (e.g., weight loss, fat mass reduction, improvements in glycemia, lipids and liver fat content) in preclinical testing.

The second speaker, Dr. Andre Scheen from the University of Liege, Belgium, addressed “Targeting the Glucocorticoid Pathway.” Attendees were reminded of the phenotypic similarities between metabolic syndrome/diabetes and Cushing syndrome, suggesting a role for cortisol in the pathophysiology of diabetes, and sparking interest in targeting 11α-hydroxysteroid dehydrogenase-1 (11B-HSD-1). This enzyme reduces the conversion of less active cortisone to more potent cortisol in the liver and adipose tissue. Knock-out of the enzyme in rodents reduces insulin resistance, improves glucose tolerance, and enhances insulin secretory response. Scheen mentioned that, to date, 11B-HSD-1 inhibitors (INC813739*, MK-0916*, MK-0736*, LY2523199*) have had favorable, albeit modest, pleiotropic effects on weight, glucose, lipids, and blood pressure. Advances will require greater potency and specificity for the enzyme. Safety concerns include potential deleterious effects on the hypothalamic-pituitary-adrenal axis and also the potential to increase androgenic hormone levels in women. We await the results of several phase 2 trials involving these compounds.

### Glucagon Antagonists

Kazda et al. from France, the US, and Singapore conducted a double-blind, phase 2 study in which they randomized Type 2 diabetes patients (aged 18-70 years, mean HbA1c 7.7%), either naïve to antidiabetic medications or taking a stable metformin dose, to treatment with the glucagon receptor antagonist LY2409021* (10 mg (n=17), 30 mg (n=34), 60 mg (n=26), or placebo (n=10) once a day (abstract 112). Failure to suppress glucagon secretion is a known postprandial phenomenon in this disease, which may contribute to meal-time glucose spikes in our patients. At 12 weeks, a (least squares mean) decrease from baseline in HbA1c was observed in each dose group compared to placebo: 10 mg: -0.83%, p=0.030; 30 mg: -0.65%, p=0.042; 60 mg: -0.66%, p=0.051; placebo: 0.11%. Increases in transaminase values were observed at the higher doses (+3.7 to 19.9 U/L in the 30 mg and 60 mg groups), with no elevated bilirubin or other signs or symptoms of liver injury. No significant changes in triglycerides, LDL-cholesterol, HDL-cholesterol, weight, or blood pressure were observed. The incidence of hypoglycemia (<5%) was not dose-dependent; no severe events were reported. This study shows modest glycemic benefit with glucagon receptor blockade in patients with Type 2 diabetes, although the effects on liver function will clearly require further study.

### Sodium-Glucose co-Transporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors* are a novel class of oral antihyperglycemic drugs that lower blood glucose via inhibition of glucose reabsorption in the renal tubule, thereby removing glucose from the body through the urine. This novel mechanism—lowering of the renal glucose threshold—complements those of currently available antidiabetic agents, making SGLT2 inhibitors potential partners to not only metformin and other oral drugs, but also conceivably to insulin. Tsapas et al. from Greece and England performed a meta-analysis of 16 randomized trials of more than 12 weeks duration (duration 12-104 weeks) that compared an SGLT2 inhibitor with placebo or any other antihyperglycemic medication for Type 2 diabetes (n=5,030) (abstract 241). SGLT2 inhibitors were associated with a greater decline in HbA1c compared with placebo, when used either as first-line or as add-on treatment (Table 13). They also compared favorably to placebo and to other antihyperglycemic agents based on decreases in weight and systolic blood pressure. Risks (risk ratio, RR) of hypoglycemia or urinary tract infections with SGLT2 inhibitors were each similar to that of placebo. Risk of genitourinary mycotic infections with these drugs, however, was much higher as compared to placebo (RR 3.3, 95% CI 2.2 to 4.9) or other agents (RR 4.6, 95% CI 2.8 to 7.5).

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* Data from abstracts presented at the oral sessions of the European Association for the Study of Diabetes (EASD) meeting, Berlin, Germany, September 28-October 1, 2012.

** Evidence from preclinical and clinical studies.**
Hach et al. from Germany and The Netherlands conducted a study to further explore the blood pressure lowering effect of SGLT2 inhibitors and to determine whether it could be independent of their changes on weight or HbA1c (abstract 770). The investigators pooled data from 2 randomized, double-blind, placebo-controlled, dose-finding phase 2 trials in which empagliflozin was used as monotherapy (n=408) or as add-on to metformin (n=495) in patients with Type 2 diabetes. Mean changes from baseline in systolic blood pressure (4-5 mm Hg) were consistent with those reported by Tsapas et al. (above). The Pearson correlation coefficients between change in weight and change in systolic blood pressure were 0.10 (empagliflozin 10 mg), 0.04 (empagliflozin 25 mg), and 0.12 (placebo). None of the correlations reached statistical significance (p>0.14 for each). These data suggest that any effect of this drug class on blood pressure is, at least in part, independent of effects on weight or glycemia, perhaps related to a mild natriuretic effect. In addition, placebo-adjusted effects on blood pressure were not affected when the number of antihypertensive medications used at baseline was included in an ANCOVA analysis.

So, these agents appear to have modest efficacy, with the advantage of slight weight loss, and a blood pressure lowering effect that is potentially noteworthy. One drug, dapagliflozin, has received preliminary approval in Europe but no SGLT2 inhibitor is yet available in the US. The issue of fungal infections of the genital tract, especially in women, might be an impediment to their use. Their overall role in the future diabetes pharmacopeia remains to be determined.

### Table 13. Change from Baseline in HbA1c, Weight, and Blood Pressure with SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. Patients</th>
<th>Mean* (95% CI)</th>
<th>No. Patients</th>
<th>Mean* (95% CI)</th>
<th>No. Patients</th>
<th>Mean* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors vs. placebo, first-line therapy</td>
<td>4/532</td>
<td>-0.8 (-1.0 to -0.6)</td>
<td>4/532</td>
<td>-1.5 (-2.4 to -0.5)</td>
<td>3/396</td>
<td>-6.7 (-9.8 to -3.5)</td>
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<tr>
<td>SGLT2 inhibitors vs. placebo, add-on therapy</td>
<td>10/2,338</td>
<td>-0.6 (-0.7 to -0.5)</td>
<td>10/2,440</td>
<td>-1.9 (-2.2 to -1.7)</td>
<td>7/1,752</td>
<td>-3.0 (-4.3 to -1.6)</td>
</tr>
<tr>
<td>SGLT2 inhibitors vs. other antihyperglycemic agent, first-line or add-on treatment</td>
<td>6/1,792</td>
<td>-0.1 (-0.2 to 0.1)</td>
<td>6/1,838</td>
<td>-2.0 (-3.5 to -0.5)</td>
<td>5/1,536</td>
<td>-3.3 (-4.6 to -2.0)</td>
</tr>
</tbody>
</table>

BP = blood pressure, *Weighted mean difference.

### Implantable Glucose Sensor With Smartphone Interface!

Whitehurst et al. from Maryland presented the results of a 28-day pilot study (18 patients) showing feasibility of a fluorescence-based glucose sensor, which is intended to be implanted (subcutaneous) for a 6-month period (abstract 1030). An external body-worn reader provides power to and communicates with the sensor via a wireless link. The reader includes a Bluetooth communications link with a smartphone as well as a USB port for charging and data exchange. In this context, the smartphone operates as a user interface device for the reader, displaying data and providing user input, but does not process or store sensor data. Patients can use the smartphone app to view sensor glucose data and enter data on daily events (e.g., meals, insulin bolus administration, exercise), with entered data immediately transmitted to the reader. Two reader prototypes were evaluated in the pilot study: a wristwatch designed for use with a sensor inserted subcutaneously in the dorsal wrist and an armband reader designed for use with a sensor in the upper arm. The readers were programmed to display essentially continuous glucose information, with a new result every 2 minutes. In this era of a new smartphone launched seemingly every month, we find it timely that an investigational glucose sensor is now being designed with such an interface. Current intermittent capillary blood glucose testing using fingerstick lancets may seem medieval by comparison! Of course, there are many concerns about any such new device—cost, accuracy, local complications, etc. It's interesting to reflect back over our 12 years of bringing to you this newsletter—many of the medicines in common use today were actually introduced as ‘novel’ compounds at these very international diabetes meetings. Accordingly, looking into the future, we’d expect at least one or two of these compound/devices to eventually make it to the clinic. What advantages they will bring to the treatment of our patients remains to be seen.

### New Science Hot Off the Presses!

Beta cells may actually not die during the course of Type 2 diabetes but may instead revert to an earlier, undifferentiated cell type that does not produce insulin. Talchai et al. from Columbia University in New York presented the groundbreaking results today in a well-attended forum (abstract 141). Mice bred without a specific transcription factor known as FOXO1 develop low levels of insulin when under physiological stress, pregnancy in the female mice, and aging in the male mice. With the use of antibody tracers to explore the characteristics of the stressed beta cells, the investigators were surprised to find markers of uncommitted, progenitor cells. FOXO1 is known to promote the differentiation and proliferation of beta cells, but this is the first time that FOXO1 is shown to be necessary for the ongoing identity of beta cells. During chronic metabolic stress, beta cells can lose FOXO1, and begin to de-differentiate, possibly as a protective mechanism. These results indicate that de-differentiation, not apoptosis, may be the main cause of beta-cell failure in Type 2 diabetes. If the results are replicated in humans, the implications of this research could be immense for the therapy of Type 2 diabetes. Management might shift toward resting the beta cells, perhaps with early exogenous insulin administration or oral insulin sensitizers, instead of pushing the beta cell to work harder with secretagogues. Also, a future novel agent that stabilizes or promotes FOXO1 activity could reverse the natural history of Type 2 diabetes. These results were simultaneously published in the journal Cell 2012; 150:1223.

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

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Diabetes 2012 Test
Volume 26

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

1. Diabetes reversal following bariatric surgery is observed in patients with a history of short-duration disease (<4 years), but not long-duration (>8 years) disease, regardless of the amount of weight loss following the procedure.
   a. true
   b. false

2. The incidence of hypoglycemia following bariatric surgery is particularly high among patients with substantial weight loss, low insulin resistance, but who maintain high post-challenge insulin levels.
   a. true
   b. false

3. Compared to glargine, which of the following advantages has not been observed with degludec?
   a. lower post-meal excursions
   b. lower rate of nocturnal hypoglycemia
   c. longer half-life
   d. possibility for more flexible dosing schedule

4. Select the false statement from the following about effects of Type 2 diabetes on the brain.
   a. Diabetes is associated with an increased risk of cognitive impairment.
   b. Based on brain MRI, grey matter atrophy is increased in Type 1 diabetes patients with peripheral neuropathy vs. those with no neuropathy.
   c. According to results from Maastricht Aging Study, decline in cognition over 12 years was similar between participants with new-onset diabetes and non-diabetic subjects.
   d. Diabetes patients are at lower risk of dementia than those without diabetes.

5. The risk of cardiovascular mortality in diabetes is increased almost 3-fold in those with clinically apparent peripheral vascular disease.
   a. true
   b. false

6. Indiscriminate screening for silent coronary artery disease in Type 2 diabetes detects disease in approximately 20% of individuals, with a substantial reduction in event rates over time as compared to unscreened patients under routine care.
   a. true
   b. false

   a. true
   b. false

8. Investigation of various screening strategies, as presented at the EASD, showed that a combined fasting plasma glucose (FPG)-HbA1c screening approach, with the additional but selected use of an oral glucose tolerance test (OGTT), increases the diabetes detection rate by ~40%, as compared to screening with either FPG-HbA1c alone or FPG supplemented by OGTT in those with impaired fasting glucose.
   a. true
   b. false

9. Favorable effects on nocturnal oxygenation desaturation index can be seen within days of blood glucose optimization in Type 2 diabetes patients.
   a. true
   b. false

10. Given the impact of glycemia on thrombosis, current ADA/AHA/AACF guidelines recommend low-dose aspirin (75-162 mg) once daily for all of the following subgroups of diabetes patients, except ______.
    a. most men >50 years and women > 60 years of age who have at least one additional major cardiovascular disease risk factor
    b. patient with history of cardiovascular disease
    c. any patient with diabetes over age 40
    d. in combination with clopidogrel (75 mg/ day) for up to a year after acute coronary syndrome

11. The prevalence of dangerous ventricular arrhythmias is ~5-fold higher in Type 2 diabetes patients with substantial glycemic variability.
    a. true
    b. false

12. Data from the DIVINE study, presented at the 2012 EASD Annual Meeting, show that low vitamin D level in patients with Type 2 diabetes is associated with insulin resistance and decreased insulin secretion.
    a. true
    b. false

13. Which of the following is not a risk factor for severe hypoglycemia.
    a. duration of diabetes
    b. lower BMI
    c. abnormal cognitive function
    d. female

14. Which of the following is recommended as first-line therapy in the 2012 ADA/EASD Position Statement on Management of Type 2 Diabetes?
    a. sulfonylureas
    b. basal insulin
    c. metformin
    d. thiazolidinediones

Based on the following patient characteristics, all other things being equal, select the best antihyperglycemic agent from the choices below to add to metformin in the described patient with Type 2 diabetes who has not yet achieved his/her glycemic target. (Each answer may be used only once.)
    a. dipeptidyl peptidase 4 (DPP-4) inhibitor
    b. insulin
    c. glucagon-like peptide 1 (GLP-1) receptor agonist

15. _____ The patient is also extremely obese
16. _____ The patient also has a strong history of GI side effects
17. _____ The patient has HbA1c of 12.9%

18. Each of the following may be expected during treatment with sodium-glucose transporter-2 (SGLT-2) inhibitors except ______.
    a. decreased HbA1c
    b. glucosuria
    c. blood pressure reduction
    d. increased weight

19. Each of the following may be expected during treatment with GLP-1 receptor agonists, when added to metformin, except ______?
    a. glucose-dependent increase in insulin secretion
    b. weight loss
    c. hypoglycemia
    d. nausea

20. Which of the following have been shown to improve the pharmacokinetics of insulin?
    a. recombinant human hyaluronidase
    b. calcium
    c. bicarbonate
    d. glucagon
Please mark your answers on the Evaluation Questionnaire Form on page twenty-five.

1. How would you rate Diabetes 2012 for content?
   a. very relevant to my practice
   b. interesting but not relevant
   c. uninteresting

2. How would you rate Diabetes 2012 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 2012 in meeting the educational objectives of the CME program?
   a. the objectives of CME program were met
   b. some of the program objectives were met
   c. the program content did not satisfy the objectives

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

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

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

8. Additional comments: ________________________________________________________________
   ________________________________________________________________________________

Thank you for your participation.
Diabetes 2012 Answer Form
Volume 26

To receive 5.0 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 2012 to July 31, 2013.

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 2012 Test - Volume 26

1. (a) (b) 11. (a) (b)
2. (a) (b) 12. (a) (b)
3. (a) (b) (c) (d) 13. (a) (b) (c) (d)
4. (a) (b) (c) (d) 14. (a) (b) (c) (d)
5. (a) (b) 15. (a) (b) (c)
6. (a) (b) 16. (a) (b) (c)
7. (a) (b) 17. (a) (b) (c)
8. (a) (b) 18. (a) (b) (c) (d)
9. (a) (b) 19. (a) (b) (c) (d)
10. (a) (b) (c) (d) 20. (a) (b) (c) (d)

Please indicate the number of hours actually spent in this educational activity, up to a maximum of 5.0 hours: __________

Diabetes 2012 Evaluation - Volume 26

1. (a) (b) (c)
2. (a) (b) (c)
3. (a) (b) (c) (d) (e)
4. (a) (b) (c)
5. (a) yes / no (b) yes / no (c) yes / no (d) yes / no (e) yes / no (f) yes / no (g) yes / no (h) yes / no
   (i) yes / no (j) yes / no
6. Will you make changes that will benefit patient care as a result of information received? If yes, please describe: __________
7. Do you anticipate any barriers to making these changes? If yes, please describe: __________________________________________________________________________________________
8. Additional comments: __________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________
____________________________________________________________________________________________________________

☑ If you currently receive the Diabetes 2012 newsletters by fax and would like to receive them by e-mail instead, please mark this box with an “X”.

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