Volume 25

Highlights from the 72nd Annual Scientific Sessions of the American Diabetes Association

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July 2012

Dear Colleague:

Time restraints prevented many of you from attending the 72nd Annual Scientific Sessions of the American Diabetes Association (ADA) which was held a few weeks ago in Philadelphia, PA. 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 four 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 β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of actions of the various pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

Given the recent explosion of information on diabetes, as well as its relationship to cardiovascular diseases, we began publishing this newsletter series 12 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

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**Educational Needs**

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

**Learning Objectives**

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

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Describe the evolving cellular mechanisms associated with β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
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- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on the healthcare system.

**Target Audience**

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

**Educational Methods**

At the end of each conference day, a newsletter will be available on-line at www.cme.yale.edu or faxed or sent by e-mail to the office of participating physicians. Shortly after the ADA conference concludes, participants will receive a *Diabetes 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™.
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Editors' Summary

In this volume of the Diabetes 2012 monograph, we summarize important new diabetes information that was presented at the 72nd Annual Scientific Sessions of the American Diabetes Association (ADA).

At an opening day symposium, a capacity crowd attended the meeting's first State-of-the-Art Lecture, entitled, "The New ADA-EASD Position Statement on Management of Hyperglycemia in Type 2 Diabetes" (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.

To the extent that the severity of diabetes tends to progress and a patient's status may change over time, treatment strategies may need to be revised—individualizing to the patients' current needs at various points of their disease. 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 prescriptive.

Trial results for the NIH/NIDDK-supported “Targeting Inflammation using SALSalate for Type 2 Diabetes” (TINSAL) study were presented at the ADA 2012 Scientific Sessions. On the basis that Type 2 diabetes and its underlying insulin resistance (via TNFα and IL-6) as well as pancreatic β-cell failure (via IL-1) are associated with increased systemic inflammation, TINSAL was designed to determine if anti-inflammatory treatment improves glycemia in diabetes. This multicenter trial randomized 286 people with uncontrolled Type 2 diabetes to salsalate 3.5 grams per day or placebo. Most participants were on metformin (88%) and/or a secretagogue (82%), while 6% were on insulin (87% of placebo patients who required an increase in medication dosing). Other findings in the anti-inflammatory group included the following statistically significant changes from baseline: decreased WBCs, neutrophils, lymphocytes, uric acid, and triglycerides and increased adiponectin, total cholesterol, and LDL-cholesterol. An increase in microalbuminuria (mean change 1.8 µg albumin/mg creatinine) was found in the salsalate-treated group by 12 weeks into the trial, and then decreased after stopping it. Taken together, this study appears to give some support to the notion that inflammation may be an underlying cause of hyperglycemia; overall, the results of TINSAL were disappointing.

Results of the much-anticipated ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial were also presented at the ADA 2012 Scientific Sessions. The primary objective of this landmark study, which involved 12,537 patients from 573 centers in 40 countries, was to determine whether basal insulin-mediated normoglycemia or the use of omega-3 fatty acids could reduce cardiovascular morbidity and/or mortality in people at high risk for vascular disease—with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or early Type 2 diabetes. The primary endpoint in the glargine arm was cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (a second co-primary endpoint expanded this to include revascularization and heart failure); in the omega-3 fatty acid arm, the primary endpoint was cardiovascular death. Several secondary endpoints included a variety of other cardiovascular disease composites. Consistent with the findings of previously conducted studies (ACCORD, ADVANCE, and VADT), early control of glycaemia with insulin conferred no cardiovascular benefit after a median follow-up of 6.2 years in ORIGIN. Although not a pre-specified endpoint of the study, <10% of participants developed cancer (HR=1.0; 95% CI 0.88-1.13 for glargine), indicating no effect of glargine on malignancy risk over 6 years.

About a year ago, the Food and Drug Administration (FDA) published an FDA Safety Alert suggesting that the thiazolidinedione (TZD), pioglitazone, may increase the risk of bladder cancer and required the manufacturer to include this information in the package labeling. Studies are ongoing to further inform this potential relationship. For example, 74% of patients (n=3599) from the PROactive study—a double-blind placebo-controlled trial that assesses from the blood vessels into the retina, have potent effects on retinal neovascularization, and down-regulate the expression of retinopathic factors (VEGF and ICAM-1) in the retina of rats (abstract 258-OR), setting the stage for study in humans. Which of these agents, if any, will eventually be approved for clinical use is unclear. The SGLT-2 inhibitors and degludec are closest to market.

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.
At the opening day of the 72nd Scientific Sessions of the American Diabetes Association in Philadelphia, a capacity crowd attended the meeting’s first “State of the Art” Lecture, entitled, “The New ADA-EASD Position Statement on Management of Hyperglycemia in Type 2 Diabetes”—which was simultaneously published in this month’s *Diabetes Care* (35:1364) and *Diabetologia* (55:1577), the flagship clinical journals of both organizations. The address was given by Dr. Silvio Inzucchi from Yale University, who, along with Professor David Matthews of Oxford, England, co-chaired the Position Statement writing group.

The management of Type 2 diabetes has become enormously complex over the past decade with the introduction of many new classes of glucose-lowering drugs, each with unique mechanisms of action. There are now 11 separate categories of pharmacological agents, including insulin. These each address one or more of the recognized pathophysiological defects that characterize the disease: impaired insulin secretion, peripheral insulin resistance (mainly manifested in skeletal muscle), inappropriately augmented hepatic glucose production, failure to suppress glucagon secretion in the post-prandial state, derangements in the incretin axis, and, in the obese, aberrant regulation of appetite.

**Older Guidelines**

Prior guidelines and algorithms were reviewed. Beginning in 2006, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released similar statements, incorporating the best available evidence and expert opinion, in order to assist primary care physicians to provide the best care for their diabetic patients. Other organizations, such as the American Association of Clinical Endocrinologists (AACE) and the National Institute for Health & Clinical Excellence (NICE) in the UK followed suit. All guidelines tend to emphasize the importance of lifestyle modification, including weight reduction (or maintenance), healthy food choices, and increased physical activity. Metformin is almost universally endorsed as the best first-line therapy. We have extensive experience with this drug—it is known to be safe and effective and is inexpensive. Generally weight neutral, metformin, as monotherapy, is not associated with hypoglycemia and may have some cardiovascular and anti-cancer benefits as well. Side effects are mainly gastrointestinal in origin.

**Figure 1. Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↔†</td>
<td>↔†</td>
</tr>
<tr>
<td>DCCT/EDIC (Type 1)</td>
<td>↓</td>
<td>↔†</td>
<td>↔</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

* Effects appeared to be sustained during long-term follow-up after randomized component of the trial.
† Beneficial effects appeared to emerge during long-term follow-up after randomized component of the trial.


The most concerning one, lactic acidosis, is extremely rare and mainly occurs if the drug is prescribed incorrectly to those in renal failure.

The controversy typically begins after metformin, however! The majority of patients will at some point require combination therapy, usually metformin plus another drug from a different class. Previously, the ADA-EASD guidelines had recommended either a sulfonylurea or basal insulin as preferred second-line therapies. However, in an update to the 2006 guidelines, in 2008, the options expanded to pioglitazone, a thiazolidinedione (TZD), or a GLP-1 receptor agonist (RA) (e.g., exenatide, liraglutide). These newer agents were more or less directed to patients under specific situations — such as where the avoidance of hypoglycemia (consider a TZD or a GLP-1 RA) or the need for weight loss (consider a GLP-1 RA) dominates the clinical picture. Ultimately, most patients were then channeled to aggressive insulin regimens. While constituting a major step forward in the management of Type 2 diabetes, this algorithm has been criticized for its more restrictive drug choices, with an emphasis on insulin therapy. The ADA and EASD recently assembled a group of experts to update the guidelines because of several changes over the intervening four years. There are new drug classes, such as the DPP-4 inhibitors; new evidence about the risks and benefits from tight glycemic control in older patients with Type 2 diabetes (predominantly from the ACCORD, ADVANCE, and VADT trials); increasing concerns about drug safety from clinicians, patients, and regulatory bodies; and increasing discourse in the medical community — emanating initially from primary care — about the need to make chronic disease management more ‘patient-centered’.

**The Patient at the Center**

Dr. Inzucchi reviewed some of the tenets of patient-centered care: to provide care that is respectful of, and responsive to, individual patient preferences, needs, and values, ensuring that patient values guide all clinical decisions. First, his or her preferred level of involvement should be explored. Then, where possible, shared decision-making should be emphasized, exploring all relevant therapeutic choices. Decision aids may be helpful in this regard. Of course, in diabetes, final decisions regarding lifestyle choices ultimately lie with the patient. The concept of ‘minimally disruptive medicine’ (see May, Montori, & May, BMJ 2009) was also discussed — the important notion that both disease and treatment burden must be balanced, especially in those faced with multiple chronic diseases. With an aging population, the role of these comorbidities in overall patient management must be acknowledged, with careful prioritization of interventions in conjunction with the patient.

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**Figure 2. Approach to Management of Hyperglycemia: An Overview**

<table>
<thead>
<tr>
<th>Efforts to Control Glycemia</th>
<th>More Stringent</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, non-adherent, poor self-care capacities</td>
</tr>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

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**Table 1. Properties of Anti-hyperglycemic Agents**

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Activates AMP-kinase ↓ Hepatic glucose production</td>
<td>Extensive experience No hypoglycemia Weight neutral ↑ CVD</td>
<td>GI side effects Lactic acidosis B12 deficiency Contraindications</td>
<td>Low</td>
</tr>
<tr>
<td>SUs/ Meglitinides</td>
<td>Closes KATP channels ↑ Insulin secretion</td>
<td>Extensive experience (SUs) ↓ Microvascular risk</td>
<td>Hypoglycemia Weight gain Low durability ↑ Ischemic preconditioning</td>
<td>Low/High</td>
</tr>
<tr>
<td>TZDs</td>
<td>Activates PPAR-γ ↑ insulin sensitivity</td>
<td>No hypoglycemia Durability ↓ TGs, ↑ HDL-C ↑ CVD (pio)</td>
<td>Weight gain Edema/heart failure Bone fractures ↑ MI (rosi) ? Bladder cancer (pio)</td>
<td>High</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Inhibits DPP-4 Increases GLP-1, GIP</td>
<td>No hypoglycemia Well tolerated</td>
<td>Modest ↓ A1c ↑ Pancreatitis Urticaria</td>
<td>High</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Activates GLP-1 receptors ↑ Insulin, ↓ glucagon ↓ gastric emptying ↑ satiety</td>
<td>Weight loss No hypoglycemia ↑ B cell mass ↑ CV protection</td>
<td>GI side effects ↑ Pancreatitis Medullary cancer (mice) Injectable</td>
<td>High</td>
</tr>
<tr>
<td>Insulin</td>
<td>Activates insulin receptor ↑ peripheral glucose uptake and suppresses hepatic glucose production</td>
<td>Universally effective Unlimited efficacy ↓ Microvascular risk</td>
<td>Hypoglycemia Weight gain ↑ Mitogenicity Injectable Training requirements “Stigma” (for patients)</td>
<td>Variable</td>
</tr>
</tbody>
</table>

CVD=cardiovascular disease, DPP-4=dipeptidyl peptidase-4, GIP=glucose-dependent insulinotropic peptide, GLP-1=glucagon-like peptide-1, P1D=piglizoxone, ROSI=rosiglitazone, SU=sulfonylurea, TZD=thiazolidinedione.
Glucose Targets

Thirty years of Type 2 diabetes clinical trials were briefly summarized (Figure 1). Glycemic management has been shown to reduce microvascular disease (retinopathy, nephropathy, neuropathy), but the verdict is still out on its impact on the more prevalent macrovascular complications, such as myocardial infarction. Long-term trials suggest a benefit on cardiovascular disease, but the data are far from robust. The Position Statement emphasizes that an HbA1c target of <7% was appropriate in most patients. However, given the mainly epidemiological evidence that diabetic complications are minimized with even lower HbA1c, a near normal level (6-6.5%) may be advisable for younger patients without complications or comorbidities. Conversely, however, in the elderly or more infirm patient, more conservative targets such as 7.5-8% should be considered. The Position Statement includes a diagrammatic representation of the various elements to this sometimes complex decision-making process (Figure 2). As these elements become more challenging or more severe, less stringent efforts are indicated. The goal here would be to match the patient to his or her optimal A1c target, balancing the long-term benefits of glucose control with the potential adverse effects (and treatment ‘burden’) of medications.

Main Glucose-Lowering Recommendations

The main component of the Position Statement is seen in Figure 3. The foundation of therapy remains lifestyle change, with metformin still recommended as first-line therapy. In contrast to prior guidelines, five possible drug classes were felt to be reasonable choices as second-line, depending on the patient: sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 RAs, and basal insulin (Table 1). The figure describes the degree of expected A1c lowering efficacy, the risk of weight gain and hypoglycemia, other safety concerns, and the financial costs of each category. With treatment targets, the Position Statement emphasizes the importance of individualization or personalization of care — matching a drug’s expected benefits with its risks, in the context of that patient’s disease, lifestyle, and predicted tolerances for adverse effects. Once a two-drug combination is no longer effective, then three drugs in combination could be tried, although serious consideration at this juncture should be given to the potentially simpler and more cost effective transition to insulin. In many patients, due to declining beta cell function and insulin secretory capacity, the need for insulin injection therapy cannot be ignored. Of course, patients can be transitioned from monotherapy or two-drug combination therapy to more advanced insulin strategies when blood glucose levels fail to respond quickly, so that dangerous complications of severe hyperglycemia are avoided (dashed line arrow).

Up to 15-20% of Type 2 diabetes patients cannot tolerate or have active contraindications to metformin (e.g., renal disease). In these circumstances, clinicians should choose from one of the therapies listed as second-line drugs. In the circumstance of a greater degree of hyperglycemia — e.g., A1c >9%—consideration may be given to beginning with combination therapy (i.e., metformin plus another agent). Finally, in the setting of even more severe hyperglycemia — A1c >10-12%, especially if catabolic features are present — strong consideration must be given to insulin therapy from the outset.

When using insulin therapy, a basal formulation is typically chosen first (e.g., NPH, glargine, detemir), usually in combination with oral or other injectable agents. If greater A1c control is then needed, transition to a premixed insulin (e.g., 70-30) or the addition of one or more bolus injections of short-acting insulin analogues (e.g., lispro, aspart, glulisine) before meals would then be recommended. Figure 4 diagrams these two approaches, while describing the number of injections required, the complexity of each regimen, and its flexibility.
Special Circumstances and Considerations

Next, special clinical circumstances were reviewed. Older adults have shorter life expectancies, higher cardiovascular disease burden, reduced renal function, and are at higher risk for adverse events from polypharmacy. Accordingly, less ambitious targets are reasonable, with an emphasis on drug safety.

In the consideration of body weight, most Type 2 diabetes patients are overweight, if not obese. Here, intensive lifestyle programs are critical. Metformin and GLP-1 RAs may have specific advantages. Bariatric surgery is another option in obese individuals. In normal-weight individuals, particularly in those with features of more profound insulin deficiency, a possible diagnosis of latent autoimmune diabetes of adults (LADA) should be considered. These patients, whose diabetes results from autoimmunity (akin to Type 1 diabetes), will require insulin therapy more urgently than those with ordinary Type 2 diabetes.

There is less known about the contributions of gender, ethnicity, race, and other genetic factors to the phenotypic presentation of Type 2 diabetes and optimal pharmacological therapy. Maturity onset diabetes of youth (MODY) describes a group of diseases that present early in life with mild hyperglycemia, often responding well to sulfonylureas. In Latinos, greater insulin resistance may be manifest; in eastern Asians, beta cell dysfunction may be a more prominent manifestation of disease. How these differences might affect therapeutic choices remains debatable. Gender may certainly drive concerns about clinical practice.

Table 2. Key Points of ADA-EASD Position Statement

- 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 1-2 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 preferences, needs, and values).
- Comprehensive cardiovascular risk reduction should be a major focus of therapy.
- Patients with hepatic dysfunction are typically not included in clinical trials. Pioglitazone, while contraindicated in patients with advanced liver disease, may be particularly helpful in those with steatosis. Insulin remains the most viable option when liver disease is advanced. Extra caution is also, of course, needed in patients prone to hypoglycemia, particularly if hypoglycemia unawareness develops.

Dr. Inzucchi proceeded to summarize the key points of the Position Statement (Table 2) and to list differences compared with prior treatment guidelines. These include a less prescriptive or algorithmic approach: the emphasis on calibration of treatment targets and individualization of treatment options, with harmonization of drug therapy options after metformin; recognition of the role for initial combination therapy; endorsement of triple therapy when required; and the inclusion of insulin options beyond basal alone or ‘basal-bolus’.

In the question and answer period, several audience members questioned the ongoing inclusion of the older sulfonylureas in the guidelines, with growing evidence of their lower durability versus other classes. In response, it was noted that these agents may be the most evidence-based strategy in Type 2 diabetes. Their lower cost and lack of definitive evidence of a clear disadvantage on current clinical outcomes mandated their inclusion in the recommendations. Another audience member added that the severity of diabetes tends to progress and a patient’s status may change over time. Therefore, treatment strategies may need to be revised—individualizing to the patient’s current needs at various points of their disease.
Putting the 'D' into Pre-DM

While hypovitaminosis D level has been shown to be a risk factor for diabetes, data presented by Davidson et al. from Los Angeles, CA suggest that supplementation may not reduce this risk. The investigators randomized 72 subjects with pre-diabetes (age 51.6±7.2 years, 78% female, 83% Latino, fasting plasma glucose (FPG) 110-125 mg/dl and/or 2-hr oral glucose tolerance test (OGTT) glucose 140-199 mg/dl) to receive placebo or large weekly doses of vitamin D (dose=100-baseline vitamin D level in ng/ml x body weight [kg] x 15.7; reduced by 25% when serum level reached 80 ng/ml) (abstract 961-P). Mean vitamin D levels were similar in the 40 placebo subjects and 32 vitamin D-treated subjects at baseline (22.5±4.8 vs. 21.3±4.4 ng/ml) and increased only in the vitamin D supplementation group during the course of the study (to 60-70 ng/ml by 2 months and persisted to study end). The mean (SD) weekly D3 dose was 88,865 (±16,154) IU. There were no differences between the treatment groups based on FPG, glucose area under the curve (AUC) during an OGTT, HbA1c, and measures of insulin secretion or insulin resistance. Likewise, there was no between-group difference for new-onset diabetes (placebo 8% vs. vitamin D 9%) or reverting to normoglycemia (42% vs. 44%, respectively) at 1 year.

A Pernicious Concern?

Klen et al. from Slovenia evaluated the prevalence of vitamin B12 deficiency in 84 Type 2 diabetic patients (mean age 63 years, BMI 32.1 kg/m2) who had been treated with metformin for at least 4 years (abstract 954-P). Serum vitamin B12 levels were low (<150 pmol/l) in 15 patients (17.8%) and borderline low (150 to ≤250 pmol/l) in 22 patients (26%). Serum vitamin B12 levels were negatively associated with age (B= -2.91; SE=0.161; p=0.035) and duration of metformin treatment (B=-31.30; SE=0.16; p=0.048). Lower vitamin B12 levels were associated with a higher degree of peripheral neuropathy (p=0.002). Without a control group, it is difficult to evaluate the implications of these numbers, although other investigators have reported similar ranges. Oral B12 supplements are probably indicated in this setting.

Predicting Diabetes: HbA1c and/or FPG?

Kodama and Japanese collaborators conducted a meta-analysis of prospective studies (n=8) that examined incident diabetes relative to baseline glucose levels (abstract 1415-P). In a bivariate random-effects model, sensitivity, specificity, and corresponding 95% confidence intervals (CI) for the study-specific optimal cut-points were pooled. The combination of HbA1c and FPG improved sensitivity by more than 20% compared with HbA1c or FPG alone, but specificity was decreased (Table 3). These results suggest that use of both HbA1c and FPG cut-point values, compared to HbA1c or FPG alone, identifies more persons at high risk of developing diabetes, at the expense of possible over-detection.

Table 3. Sensitivity and Specificity (95% CI) of Fasting Plasma Glucose and/or HbA1c for Predicting Incident Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>0.69 (0.57-0.69)</td>
<td>0.82 (0.76-0.86)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.65 (0.57-0.72)</td>
<td>0.81 (0.74-0.86)</td>
</tr>
<tr>
<td>FPG + HbA1c</td>
<td>0.89 (0.83-0.95)</td>
<td>0.62 (0.56-0.68)</td>
</tr>
</tbody>
</table>

Similarly, using data from the Health, Aging and Body Composition study, Lipska and US collaborators evaluated which glycemic parameter (impaired fasting glucose [IFG], elevated HbA1c, or both) is most strongly associated with incident diabetes, specifically studying their prognostic value in older adults (aged 70-79) (abstract 1336-P). Participants were categorized as IFG (100-125 mg/dl); elevated HbA1c (5.7-6.4%); and further classified as normal (FPG <100 mg/dl and HbA1c <5.7%), IFG only, elevated HbA1c only, and combined IFG and elevated HbA1c. Participants were followed for 7 years for incident diabetes, with diagnosis based on annual self-report, use of anti-hyperglycemic agents, or any FPG ≥126 mg/dl. Of 1790 elderly patients (mean age 76.5±2.7 years, 47% men, 33% black, BMI 27.0±4.7 kg/m2), 141 (7.9%) developed diabetes. As compared with normal glycemic parameters, the presence of IFG only or elevated HbA1c only similarly increased the risk of diabetes over 7 years by more than 8-fold, whereas the risk in individuals with both abnormalities was substantially higher (~24-fold) among those with combined abnormalities, potentially identifying a group at very high risk for diabetes.

Both these studies teach us that the method by which high-risk patients are identified will influence their perceived risk of eventually developing diabetes.

Insulin Sensitizers and Incidence of Neuropathy: New Data from BARI-2D

Using data from the BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial, Pop-Busui, and North American collaborators compared the effects of the randomized glycemic control strategy—insulin-sensitizing (e.g., metformin, TZD) vs. insulin-providing (sulfonylurea, insulin)—on the incidence of diabetic peripheral neuropathy (DPN) in Type 2 diabetes patients with coronary artery disease (abstract 63-OR). The presence of DPN, defined as a clinical examination score >2 on the Michigan Neuropathy Screening Instrument (MNSI), was assessed at baseline and yearly thereafter during 4 years of follow-up. The investigators reported results for 2159 patients with valid baseline and at least one follow-up MNSI score (mean age 62±9 years, mean HbA1c 7.7±1.6%, diabetes duration 10±9 years, 70% males). Among the 1075 patients with no DPN at baseline, the 4-year cumulative incidence of DPN was lower in the insulin-sensitizing group compared to the insulin-providing group (54% vs. 63%; p=0.022). After adjusting for the in-trial HbA1c values (Cox regression models), the hazard ratio (HR) for incident DPN was 0.81 in the insulin sensitizer group (p=0.009). In subgroup analyses, greater benefit of the insulin-sensitizing strategy (compared to the insulin-providing strategy) in preventing DPN was observed in participants who were <65 years (HR=0.75, p=0.004), were male (HR=0.74, p=0.003), and had higher triglycerides (≥150 mg/dl) at baseline (HR=0.74, p=0.009). If this effect is real, the mechanism remains unclear to us—perhaps driven by inflammation, which is known to improve (at least by biochemical markers) with insulin-sensitizing drugs. What makes this study difficult to interpret is a fundamental design flaw in BARI-2D, which was the allowance of crossover therapy in both groups.
Since introduction to the market seven years ago, GLP-1 (glucagon-like peptide 1) receptor agonists (RAs) in the management of Type 2 diabetes have generally been considered third-line therapy, after failure to reach therapeutic goals with two oral agents. This role stemmed from their newer status, their injectable nature, and concerns about potential side effects. The recent ADA-EASD position statement (Diabetes Care 2012, Vol. 25, pg 1), buttressed now by emerging data from head-to-head prospective trials, suggest that these medications are now appropriate as a second-line therapy, after metformin. Large numbers of presentations this week underscored the growing role of this typeof incretin-based therapy.

GLP-1 is an endogenous peptide hormone produced by neuroendocrine cells of the distal small intestine and colon. It is often referred to as an ‘incretin.’ In response to meal ingestion, GLP-1 levels are increased. Systemically, GLP-1 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. GLP-1 RAs are approved for glucose lowering in Type 2 diabetes; available agents include exenatide (in both BID and weekly formulations) and liraglutide (QD). The frequency of their use in the US is generally modest as compared to oral agents and insulin. Several other GLP-1 RAs are in various stages of development.

Scherthnaner and European colleagues reported the results from a comparative trial between exenatide and the sulfonylurea, glimepiride, as add-on to metformin, in a Joint ADA/The Lancet Symposium on Saturday morning (Lancet, early online publication, 6-9-12). In an open-label, controlled trial (EUREXA), Type 2 diabetes patients with metformin failure were randomized to receive exenatide twice daily or glimepiride. The primary endpoint was time to therapy failure and need for alternative treatment, defined as HbA1c >9% after 3 months or HbA1c >7% at two consecutive visits after the first six months. In the intent-to-treatment population, exenatide was found to be superior to glimepiride: 41% (203/490) of exenatide patients experienced treatment failure versus 54% (264/514) in the glimepiride group (risk difference 12.4% [95% CI 6.2-18.6], HR 0.748 [0.623-0.899]; p=0.002). Additionally, a greater percentage of patients in the exenatide group achieved HbA1c values <7% (the ADA-EASD target) and <6.5% (the target of some other organizations) when compared with glimepiride: 44% vs. 31%, p<0.001 and 29% vs. 18%, p=0.0001, respectively. Secondary endpoints such as documented symptomatic, nocturnal, and non-nocturnal hypoglycemia favored exenatide, reaching statistical significance, yet, severe hypoglycemia was similar between groups. Those receiving exenatide were more likely to discontinue therapy due to adverse events (primarily gastrointestinal) during the first six months (p=0.0005), but the rate did not differ thereafter. Complete results of the extension trial will be reported in Berlin at the EASD. We might add that both drugs in this specific study fared suboptimally in this more advanced diabetic population with 4 to 5 out of every 10 patients needing additional therapies.

In a ‘late-breaking’ poster presentation, Davies and UK colleagues evaluated exenatide once-weekly (EQW) versus insulin detemir (abstract 40-LB). Patients with Type 2 diabetes inadequately controlled on metformin ± sulfonylureas were randomized to receive add-on therapy for 26 weeks with either EQW 2 mg (n=111) or insulin detemir (n=105) titrated to a fasting plasma glucose of ≤99 mg/dl. A significantly greater percentage of patients in the EQW group achieved the composite primary endpoint of HbA1c ≤7.0% and weight loss ≥1.0 kg (44.1% [95% CI 34.7, 53.9] vs. 11.4% of detemir-treated patients [6.0, 19.1]; p<0.0001). The magnitude of reduction for each component of the composite also favored EQW (each p<0.0001): weight reduction of -2.68±0.34 kg versus +0.8±0.36 kg with detemir; and decreased HbA1c of -1.3±0.08 with EQW and -0.88±0.80% with detemir.
The incidence of hypoglycemia was relatively low and similar for each drug. Gastrointestinal and injection site reactions occurred more commonly with EQW. One concern with the once weekly formulation of this GLP-1 RA is the logistics required for patient self-injection. The injection device is more complex than traditional pens, requiring several mixing steps. Also, due to the microsphere technology employed to deliver this long-acting compound, the caliber of the injection needle is larger that those used for insulin or shorter acting GLP-1 RAs.

Rosenstock and international colleagues compared albiglutide, a once-weekly GLP-1 RA in Phase 3 clinical trials, to the prandial insulin, lispro, each added to glargine and oral agents (metformin and/or thiazolidinedione [TZD]) in uncontrolled Type 2 patients (abstract 55-OR). Similar to the previous investigations, endpoints included change in HbA1c and weight after 26 weeks and 52 weeks. In this non-inferiority study, albiglutide was comparable on HbA1c lowering to lispro (administered TID with meals), when added to a backdrop of basal insulin. The GLP-1 RA, however, resulted in significant weight loss as compared to the all-insulin regimen, and this was sustained at week 52 (Table 4). Adverse drug events of nausea, vomiting, and injection site reactions occurred more frequently in the albiglutide group, whereas hypoglycemia was more common in the lispro group. Overall, the investigators concluded that albiglutide is a viable treatment option in patients inadequately controlled on basal insulin, with the added advantage of significant weight loss and less hypoglycemia when compared with lispro. We find this approach of interest and certainly simpler for our patients who are no longer controlled on basal insulin alone. We note that albiglutide is still investigational and its side effect profile may not be fully known.

Lixisenatide, a short-acting GLP-1 RA with known impact on post-prandial glucose, was also evaluated in combination with glargine and oral agents in patients inadequately controlled on one or more oral anti-hyperglycemic drugs. Rosenstock and investigators from North America and Germany randomized patients with Type 2 diabetes to receive lixisenatide 20 mcg once daily (n = 223) or placebo (n = 223) following a 12-week run-in period of glargine titrated to a fasting plasma glucose of 80-100 mg/dl (abstract 62-OR). Sulfonylurea therapy was stopped, but patients continued metformin and a TZD if currently receiving one (12%). The primary outcome measure was change from baseline HbA1c, which decreased with glargine in the run-in period (8.6 to 7.6%) and was further reduced after 24 weeks of lixisenatide (LS mean difference vs. placebo: -0.32%, p<0.0001). Additional results were reflective of the previously described investigations, including a higher percentage of patients achieving HbA1c <7.0% (56% versus 39%), significant benefit on body weight (LS mean difference -0.89 kg, p<0.0001), but an increase in nausea/vomiting in the lixisenatide group. Unlike the other trials, symptomatic hypoglycemia was actually increased in the GLP-1 treatment group.

Although accumulating evidence suggests equal or, in some patients, improved management with a GLP-1 RA compared to traditional alternatives as add-on therapy after metformin failure, the durability of response has not been well validated. MacConnell et al. (San Diego, CA) reported the results of a four-year extension of the initial DURATION-1 trial assessing EQW versus twice daily exenatide (abstract 1156-P). A total of 176 (68%) patients remained on EQW for four years; their regimens included both increases and decreases in doses of concomitant oral agents. Glycemic control and improvements in cardiometabolic parameters demonstrated a sustained improvement over the four years: HbA1c reduction (LS mean [95% CI] -1.7% [-1.9, -1.5]), 55% achieved HbA1c <7%, systolic blood pressure (-1.6 mm Hg [-4.0, 0.9]), and LDL-cholesterol (-8.0 mg/dl [-12.9, -3.2]). Major hypoglycemia was not problematic, with minor hypoglycemia primarily occurring in patients treated with concomitant sulfonylureas. The most commonly occurring adverse event in the initial trial was nausea, which decreased with ongoing therapy (85 vs. 15 events per 100-year patient exposure through week 30 and over the 4 years, respectively). We might add that such an open-label study tends to overestimate benefits in clinical trials.

The role of the GLP-1 RAs may expand because of mounting evidence of beneficial impact on HbA1c in the presence of weight loss—uncommon with all other drug strategies. As mentioned, there are currently three agents commercially available, with several others in various stages of investigation (Table 5). In his Saturday afternoon presentation, Filip Knop, MD, PhD of Denmark addressed the question, GLP-1
**Table 6. Ongoing Cardiovascular Outcome Trials With GLP-1 Based Therapies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Therapeutic干预</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXSCEL*</td>
<td>n=9,500</td>
<td>Exenatide</td>
<td>Study of Cardiovascular Event Lowering</td>
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<td></td>
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<td>Primary Outcome: Time to first confirmed CV event in the primary composite CV endpoint</td>
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<tr>
<td>LEADER†</td>
<td>n=8,754</td>
<td>Liraglutide</td>
<td>Effect and Action in Diabetes: Evaluation of CV Outcome Results</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Primary Outcome: Time from randomization to first occurrence of CV death, nonfatal MI, or nonfatal stroke</td>
</tr>
<tr>
<td>ELIXA‡</td>
<td>n=6,000</td>
<td>Lixisenatide*</td>
<td>Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary Outcome: To evaluate cardiovascular outcomes with lixisenatide compared to placebo as determined by a composite CV endpoint in patients who had experienced an ACS between 5 and 90 days prior to screening visit</td>
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<tr>
<td>REWIND¶</td>
<td>n=9,622</td>
<td>Dulaglutide*</td>
<td>Researching Cardiovascular Events With a Weekly Incretin in Diabetes (Dulaglutide)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Primary Outcome: Time from randomization to first occurrence of nonfatal MI, nonfatal stroke, or CV death</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov NCT identifiers:
*01144338; †01179048; ‡01147250; ¶01394952.

**Lessons from the TODAY Trial**

Phillip Zeitler, MD, PhD of the University of Colorado presented outcomes of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) trial to a crowded, Grand Ballroom audience. Eligibility criteria included: age of 10 to 17 years, Type 2 diabetes for <2 years, BMI ≥85th percentile for age and gender, absence of pancreatic autoantibodies, and fasting C-peptide >0.6 ng/mL. During a 2-6 month run-in period, eligible patients were weaned off non-study anti-hyperglycemic medications and were titrated to metformin 500 to 1000 mg twice daily, achieving HbA1c <8% at least once monthly for 2 months on this monotherapy.

Investigators at 15 centers then randomized 699 eligible youths (mean age 14 years, BMI 34.9 kg/m², 65% female, 84% Tanner stage 4-5, mean disease duration 7.8 months) to metformin alone (n=232), metformin combined with the TZD, rosiglitazone 4 mg twice daily (n=233), or metformin combined with intensive lifestyle intervention (n=234) (abstract CT-SY23). There was a surprisingly high prevalence of comorbidities in the study patients: 26% had a blood pressure ≥90th percentile; 13% had microalbuminuria; 80% had low HDL levels; and 10% had high triglycerides. 42% of participants were from families with an annual household income of <$25,000/year, and 26% had a highest education level of parent/guardian less than a high school degree.
The primary outcome variable was loss of glycemic control, defined as HbA1c ≥8% for 6 months or persistent metabolic decompensation (i.e., inability to wean from insulin within 3 months after its initiation or a second episode of decompensation within 3 months after discontinuation of insulin). HbA1c was measured every 2 months in the first year and quarterly thereafter.

Over a mean follow-up of 3.9 years (range 2-6.5 years), 319 patients (45.6%) reached the primary outcome with a median time to treatment failure of 11.5 months (range, <1 to 66). Mean (95% CI) failure rates were 51.7% (45.3%-58.2%); 120 of 232 patients) with metformin alone, 38.6% (32.4%-44.9%; 90 of 233 patients) with metformin plus TZD* (p=0.006 vs. metformin alone), and 46.6% (40.2%-53.0%; 109 of 234 patients) with metformin plus lifestyle intervention (Figure 5). Reasons for treatment failure and median time to failure were similar across treatment groups. BMI at baseline or on-trial were not determinants.

The “Eyes” Have It!

Improved diabetes care impacts the natural history of diabetes and its complications, including diabetic retinopathy (DR). Yet, many patients continue to develop retinal disease leading to visual loss in our practices, and diabetes remains the leading cause of blindness in the US. Understanding its pathogenesis, risk factors, and novel treatments was the topic of several presentations this week.

Pugliese and co-investigators of the RIACE (Renal Insufficiency And Cardiovascular Events) multicenter study determined the prevalence of DR, assessed by fundoscopy, and its association with risk factors and other complications, particularly chronic kidney disease (CKD), in 15,773 Italian Type 2 diabetes patients during 2007-2008 (abstract 623-P). Any retinopathy was observed in 22% (n=3,497) of patients: 12% had early DR and 10% had advanced DR (non-proliferative 4%, proliferative 4%, maculopathy 1%, blindness 0.1%). DR (both early and advanced) was independently associated with HbA1c, diabetes duration, treatment (particularly the requirement for insulin), hypertension, any previous cardiovascular disease (CVD), albuminuria, and albuminuric CKD. It was inversely associated with age at diabetes diagnosis.

Taken together, this large cohort shows that retinopathy is prevalent in more than 1 in 5 Type 2 diabetes patients, with a relatively high prevalence of advanced stages, and these correlations with surrogate indices of chronic hyperglycemia—namely, hypertension, cardiovascular events, and albuminuria. Current guidelines advise annual screening for retinopathy in Type 2 diabetes. Whether this stance is overly aggressive has been recently debated. Data regarding progression patterns based on initial screening evaluations might inform more evidence-based recommendations. Stratton et al. from the UK used longitudinal data from 14,544 patients (mean age 66.0 years, 57% male, mean diabetes duration 13.2 years) with “non-referable” (i.e., to an ophthalmologist) DR (no DR or microaneurysms) only at two consecutive annual screenings to estimate the

### Table 7. Progression to Sight-threatening Referable Retinopathy

<table>
<thead>
<tr>
<th>Screening</th>
<th>No DR</th>
<th>MA</th>
<th>MA</th>
<th>No DR</th>
<th>MA</th>
<th>MA</th>
<th>No DR</th>
<th>MA</th>
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<tbody>
<tr>
<td></td>
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<td>1 eye</td>
<td>both eyes</td>
<td>either eye</td>
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<td>DR after second screen:</td>
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<td>2%</td>
<td>3%</td>
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<tr>
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<td>15%</td>
<td>18%</td>
<td>22%</td>
<td>28%</td>
<td>41%</td>
<td>58%</td>
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DR = diabetic retinopathy, MA = microaneurysm.
time to development of sight-threatening disease (Figure 6) (abstract 612-P). Patients were grouped on the basis of presence of microaneurysms in neither, one, or both eyes at each of two annual screenings and then subsequently followed for a median of 3 years. Of 7,246 patients with no microaneurysms at both screenings, 120 progressed to sight-threatening DR (reference group) (Table 7). Of 1,778 patients with microaneurysms in neither eye at first, but then in one eye at the second screening, 80 progressed to sight-threatening DR (hazard ratio [95% CI] 2.9 [2.2–3.8] compared to the reference). Of 1,159 with microaneurysms in both eyes at both screenings, 299 progressed to sight-threatening DR (HR 18.2 [14.7–22.5]).

These results from two annual screenings enable the estimation of progression risk (Figure 6), which may inform screening frequency decisions.

On the basis of the post-hoc observation that oral fenofibrate therapy slowed progression of DR in Type 2 diabetic patients in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, Chen from Oklahoma conducted a study to determine if topical ocular administration would confer similar favorable effects in Type 1 diabetes (abstract 258-OR). First, efficient delivery to the retina was established with the optical formula. Then, the investigator demonstrated that fenofibrate eye drops* reduced retinal vascular leakage (of Evans blue dye-albumin complex) from the blood vessels into the retina in two rat models—streptozotocin-induced diabetes and oxygen-induced retinopathy. The eye drops had potent effects on retinal neovascularization and down-regulated the expression of two retinopathic factors, VEGF and ICAM-1, in the retina. Full-field electroretinogram (ERG) and histological analysis after administration showed that fenofibrate eye drops did not cause detectable functional and morphological abnormalities in ocular tissues. Accordingly, further studies, perhaps eventually in humans, appear warranted.

**Ghrelin Receptor Agonist Improves Symptoms of Diabetic Gastroparesis**

Ejskjaer et al. from Europe and the US randomized 92 patients with diabetes (65% female, mean age 49.9 ± 11.9 years, BMI 28.8 ± 5.1 kg/m²) to the Treatment Group (TGP) (n=46) and Placebo Group (n=46) (abstract 951-P). Significant improvements vs. placebo were observed in individual symptoms across all TZP-102 dose groups, with maximum improvement at the 20 mg dose. The magnitude of effects was similar in Type 1 and Type 2 diabetes patients (Figure 7).

**And No More Heartburn Either!**

In a ‘late-breaker’ poster, Hota et al. from India presented the results of a randomized, double-blind, placebo-controlled, proof-of-concept study involving the proton pump inhibitor (PPI) pantoprazole. The investigators assigned 31 Type 2 diabetes patients (diabetes duration 3.6 years) to either pantoprazole 40 mg* or placebo twice daily, added to background therapy with metformin and/or sulfonylurea for a treatment duration of 12 weeks (abstract 35-LB). The PPI significantly reduced HbA1c (7.6% at baseline to 6.8%; p<0.001 vs. baseline; p<0.05 vs. placebo). In addition, there was a significant reduction in blood glucose and increases in plasma insulin, B-cell function, GLP-1, and gastrin levels (p<0.05 for all). The impact of the PPI on glucose-insulin homeostasis was proposed to be through the feedback increases in gastrin as well as GLP-1. (We are not aware of any data, however, explaining how gastrin alone could affect glucose metabolism.) We would question whether the PPI may have altered the absorption of the sulfonylurea or metformin, enhancing their glucose-lowering effect (although, lack of gastric acid tends to, if anything, lower absorption of orally administered drugs). Larger clinical trials of diverse patient populations using different PPIs are needed to establish any therapeutic potential of PPIs in diabetes. Better mechanistic information is also needed.

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

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD
Editors, Yale University, New Haven, Connecticut
In a symposium on Monday, the trial results for Targeting INflammation using SALsalate for Type 2 Diabetes (TINSAL) were presented for the first time. This NIH/NIDDK-supported clinical trial is a proof-of-concept study that originated from the hypothesis that an anti-inflammatory agent may improve hyperglycemia in diabetes. Type 2 diabetes and its underlying insulin resistance are associated with increased systemic inflammation, manifested by raised levels of white blood cells (WBC), C-reactive protein (CRP), and fibrinogen. Inflammation is also proposed to be a contributing cause of insulin resistance (via tumor necrosis factor alpha, TNFα, and IL-6) and even pancreatic β-cell failure (via IL-1) (Figure 8).

Salicylates are the world’s oldest medication family, and have wide-spread application in treating inflammation. They exist in nature, and are critical to plants’ ability to fight “stress” (e.g., infection, extremes of temperature, drought). Mechanistically, salicylates appear to block NFκB, a potent intra-cellular signal of pro-inflammatory genes. They are present in small quantities in humans through their ingestion of certain plant-based foods. As early as the 1800’s, salicylates were used successfully to treat conditions such as rheumatic fever. As one member of the family, salsalate has the benefit of being less irritating to the stomach and does not have anti-platelet effects like its “cousin”, aspirin. In addition, salsalate has a well-established safety profile, and is generically available and extremely inexpensive.

Dr. Allison Goldfine, Joslin Diabetes Center, presented the study design and results of TINSAL. This multicenter trial involved 286 people with uncontrolled Type 2 diabetes (baseline HbA1c 7.0–9.5%) who were randomized to salsalate* 3.5 grams per day or placebo for a treatment period of 48 weeks. The primary endpoint was change in HbA1c from baseline. Inclusion criteria were age 18-75 years, Type 2 diabetes on oral therapy, and elevated HbA1c (7.0-9.5%). Exclusion criteria were use of a thiazolidinedione, insulin, or GLP-1 analogue, chronic use of NSAIDs, or glomerular filtration rate <60 ml/min. Medical management of patients was by their primary care physicians, not the study team, and changes to baseline medications were avoided if possible over the first 24 weeks of the trial. The characteristics of the final participants were mean age 56 ±10 years, 55% male, 53% Caucasian, diabetes duration 5 years, BMI 33.3±6.7 kg/m², and HbA1c 7.7±0.7%. Most participants were on metformin (88%) and/or a secretogogue (82%), with 41%, 49%, and 6% of the participants on one, two, or three anti-hyperglycemic medications, respectively. Aspirin was used by 41% of participants, and could be continued throughout the trial; 60% of participants were on a statin at baseline.

After 48 weeks, patients treated with salsalate had a 0.24% reduction in HbA1c relative to those on placebo (p<0.001), which is a very modest clinical outcome. Of note, however, the majority of those on salsalate had an initial ≥0.5% reduction in HbA1c, but this effect may have been attenuated by salsalate-treated patients who had hypoglycemia events early in the trial requiring a reduced dose of their baseline glycemic medications. Overall, 62% of patients receiving salsalate had a lowering of their glycemic medications. In contrast, 87% of patients on placebo required an increase in medication dosing. These changes to concomitant medications may have minimized the apparent HbA1c-lowering effect of salsalate.

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**Figure 8. Mechanisms for Inflammation-Induced Diabetes**

- **Obesity**
- **Insulin resistance**
- **β-cell failure**
- **↑ NFκB activated gene transcription**
- **↑ Inflammatory mediators**
  - TNFα, IL-1, IL-6
Not surprisingly, the salsalate-treated group experienced a lowering of WBC (p<0.001), neutrophils (p=0.003), and lymphocytes (p<0.001) from baseline, although these all remained within the normal range. While no change in CRP was found, adiponectin increased and uric acid decreased by 11% from baseline. Surprisingly, insulin levels increased by 2.8 µU/ml (p=0.003) from baseline, which may be a result of decreased insulin clearance by the liver, although this was not measured in the study. Also, the salsalate group gained weight (mean 1 kg, p<0.001).

A more concerning effect was an increase in lipids in the salsalate-treated group (total cholesterol +6.6 mg/dl, p<0.001; LDL +8.2 mg/dl, p<0.001). HDL was unchanged, and triglycerides were slightly reduced (p<0.02). An increase in microalbuminuria (mean change 1.8 µg albumin/mg creatinine) was found in the salsalate-treated group by 12 weeks into the trial but improved in most patients by study end. For those with ≥30µg albumin/mg creatinine, monitoring was continued after study end. Very few of the placebo-treated patients had any alteration in microalbuminuria after stopping placebo, whereas the salsalate-treated patients experienced a decrease in microalbuminuria, indicating that salsalate was likely responsible during the trial. Tinnitus also occurred in 11.0% of salsalate-treated patients versus 4.8% of placebo-treated patients.

Although this study gives some support to the theory that inflammation may be a therapeutic target in dysglycemic states, we do not believe that salsalate* specifically is a remedy for our patients with Type 2 diabetes. We also speculate that some of the glucose-lowering effects of the drug may have been due to increased insulin exposure (? related to hepatic clearance) and may have nothing at all to do with its anti-inflammatory effect.

While glycemic control remains the hallmark of diabetes management, overly stringent methods may result in hypoglycemia. Given that it is an independent risk factor for mortality, hypoglycemia remains a concern for all clinicians caring for diabetic patients. This year’s ADA Scientific Sessions began with a symposium on this complication of diabetes care and its relationship to cardiovascular disease.

Dr. Gabriella Gruden from Turin, Italy discussed the likely role of hypoglycemia in the “Dead in Bed Syndrome,” a tragic occurrence typically in young patients with Type 1 diabetes, which some have attributed to possible nocturnal hypoglycemia precipitating an acute cardiac arrhythmia. Hypoglycemia, both provoked and spontaneous, has been shown to induce QTc interval prolongation, an ominous manifestation of abnormalities in myocardial repolarization, which can result in ventricular tachycardia. A prolonged QTc on baseline ECG is known to be an independent marker of increased mortality in Type 1 patients. Gruden reviewed the findings from the EURODIAB IDDM Complications Study, involving 3,248 patients with Type 1 diabetes from 31 centers throughout 16 European countries (Diabetes Care 2012;35:125). Herein, logistic regression analysis demonstrated that the frequency of severe hypoglycemia (defined as an event requiring assistance from another individual) was associated with baseline QTc prolongation, as well as increased diabetes duration, lower HbA1c, and chronic renal disease. While cardiac autonomic dysfunction can be associated with prolonged QTc, the link between hypoglycemia and QTc remained significant after adjusting for both cardiovascular disease (CVD) (OR 1.27 [95% CI 1.02-1.58]) and markers of autonomic neuropathy (1.27 [1.02-1.58]). Additionally, controlling for nephropathy (1.27, [1.03-1.58]), diabetic retinopathy (1.38 [1.08-1.78]), and distal symmetric polyneuropathy (1.27 [1.01-1.58]) did not alter the association.

One caveat however was raised: The potassium-lowering effect of insulin might also act synergistically with baseline conduction system abnormalities to increase the risk of arrhythmia. This may therefore play a role in the increased mortality—an effect that may be difficult to isolate from that of low blood glucose alone, since both would be related to some extent to insulin dose.

Although a positive correlation was found between hypoglycemia and QTc, the EURODIAB investigators have not been able to demonstrate a link to actual long-term cardiovascular outcomes. In another of Gruden’s studies examining 2,181 patients involved in this study (Diabetes Care, 2012, doi: 10.2337/dc11-1531), the frequency of self-reported hypoglycemia was determined using questionnaires. Fatal and nonfatal CVD were then assessed after a median of 7.3 years of follow-up. Severe hypoglycemia at baseline was not associated with an increased incidence of cardiovascular events, based on logistic regression analysis (adjusted OR [95% CI]: 1-2 episodes, 0.87 [0.55-1.37], ≥3 episodes 1.09 [0.68-1.75]).

These results are consistent with those of the DCCT (Diabetes Control and Complications Trial) and UKPDS (UK Prospective Diabetes Study), which showed that tighter glycemic control, while clearly increasing the risk for severe hypoglycemia, had no negative effect on cardiovascular outcomes. In fact, in the long-term follow-up studies of these cohorts, fewer cardiovascular events were observed in the group originally randomized to more intensive therapy. This decreased vascular complication rate likely resulted from improvement in glycemic control. Conceivably, it may have mitigated any deleterious effect of hypoglycemia on the heart.

Hypoglycemia and its impact in Type 2 diabetes in another larger prospective study, ACCORD, was the topic of a lecture by Dr. David Brillon from New York. He reported on a post hoc epidemiological analysis on the effects of baseline characteristics, anti-hyperglycemic therapy, and HbA1c on the risk of developing on-trial severe hypoglycemia in 10,209 participants. While the incidence of hypoglycemia was predictably higher in the intensive treatment group (3% vs. 1% in the standard treatment group), further analysis revealed various subsets to be at substantially higher risk than others. For example, women (p=0.03), African-Americans (p<0.0001), those with less than a high school education (p<0.05), the elderly (p<0.0001), and those on insulin at baseline (p<0.0001) were at significantly greater risk of hypoglycemia even after multivariable analyses. Interestingly, and somewhat counterintuitively, for every 1% unit decline in HbA1c at follow-up, there was a 28% (95% CI, 19-37%) and a 14% (4-23%) reduction in hypoglycemic events in both treatment arms, respectively. As previously reported (Riddle MC, Diabetes Care 2010;33:983), ACCORD patients with poor glycemic control who failed to respond promptly to treatment were at the highest mortality risk (Figure 9), regardless of treatment assignment. Accordingly, those study participants on intensive therapy who achieved glycemic targets did not experience either the most hypoglycemia or the most mortality.
A retrospective epidemiological study by Bonds and colleagues looking at the association between symptomatic, severe hypoglycemia and mortality in 10,194 patients from ACCORD was next discussed (Bonds DE, BMJ 2010; Jan 8,340:b4909). The investigators found increased mortality (2.8%) in intensively managed patients who had one or more severe hypoglycemic episodes compared to those with no episodes (1.2%) (adjusted HR 1.41; 95% CI, 1.03-1.93). Interestingly, this trend was also seen in the standard control group: 3.7% vs. 1.0%, respectively (adjusted HR 2.3; 95% CI, 1.46-3.6). So, symptomatic severe hypoglycemia was associated with increased risk of death in both treatment arms. There were no obvious temporal relationships between hypoglycemia and death, and only one study patient appeared to have died from a hypoglycemic event. These findings lend credence to the theory that hypoglycemia is not typically a proximate cause of mortality. Instead, it serves as a marker of a more compromised patient who happens to be at higher mortality risk.

The final segment of the symposium was presented by Dr. Simon Heller from the UK, who reviewed the potential pathophysiological links between hypoglycemia and cardiovascular mortality. These include (in addition to possible precipitation of arrhythmias) decreased thrombolysis, induction of low-grade inflammation, and increased sympathomimetic stimulation. Vagal tone has also been shown to increase during spontaneous nocturnal hypoglycemia. Moreover, repeated episodes of hypoglycemia are well known to promote hypoglycemia unawareness by blunting counter-regulatory responses at the level of the central nervous system.

Hypoglycemia undoubtedly is associated with increased risks for morbidity and mortality. The exact nature of this connection remains debatable. Regardless, efforts to avoid hypoglycemia remain an important aspect of safe diabetes care.

The thiazolidinediones (TZDs) had a fair amount of “bad press” in the past few years. Rosiglitazone is available only on a very limited basis due to concerns of increased risk of myocardial infarction. Pioglitazone has been associated with bone loss and, more recently, bladder cancer. These concerns are added to this classes’ well-known tendency for weight gain and edema formation, and, in certain patients, increased risk of heart failure. Yet, the TZDs are still recognized as effective and durable agents that improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production. Pioglitazone is almost unique in demonstrating a modest cardioprotective effect* in both a randomized clinical trial (PROactive Lancet 2005;366:1279) and a high-quality meta-analysis (Lincoff AM, JAMA 2007;298:1180). TZDs have recently been included as reasonable second-line drugs after metformin in the new ADA-EASD guidelines (see Diabetes 2012, Edition 1, page 1).

In a ‘late-breaking’ poster session (abstract 66-LB), Currie and UK colleagues presented a retrospective review of outcomes associated with second-line glucose-lowering therapies after metformin failure in patients with Type 2 diabetes (Figure 10). The primary endpoint of all-cause mortality, major adverse cardiovascular events (MACE; defined as MI and stroke), cancer, and a combined endpoint of the three were assessed utilizing data from the UK General Practice Research Database.
over a 10-year period. Hazard ratios were calculated for each endpoint as well as the composite. Metformin in combination with sulfonylurea was the most commonly utilized regimen. Sulfonylurea therapy was identified as the least desirable regimen with respect to patient outcomes. The combination of metformin and pioglitazone was significantly superior to other regimens for all-cause mortality and for the combined endpoint.

In a related study, Perez and US coworkers completed a meta-analysis of 36 randomized controlled trials involving pioglitazone to evaluate MACE and serious congestive heart failure (abstract 468-P). In this analysis, MACE was defined as the composite of cardiovascular death and nonfatal MI or stroke. Over 20,000 patients were evaluated from comparative studies of pioglitazone (n=12,506) versus placebo or active control (n=10,212), with treatment duration ranging from 4 to 42 months. Hazard ratios (HR) and confidence intervals were calculated based on the time from first dose of drug to first event. Patients receiving pioglitazone demonstrated a statistically significant risk reduction in MACE versus comparator (HR 0.82 [95% CI, 0.71–0.95]). Notably, this HR is entirely consistent with the 16% relative risk reduction in MACE observed in the randomized PROactive trial. The increased heart failure risk for pioglitazone confirmed known data (HR 1.41 [95% CI, 1.15–1.74]). Heart failure mortality, however, was not increased.

Investigators from the BARI 2D trial (NEJM 2009;360:2503) hypothesized that patients assigned to the insulin-sensitizing (IS) group (i.e., metformin and/or rosiglitazone) versus those in the insulin-providing (IP) group (sulfonylurea and/or insulin) might have a different risk of developing peripheral arterial disease (PAD). The incidence of PAD in BARI 2D participants who did not have that diagnosis at study entry (as measured by ankle brachial index [ABI]) and had at least one follow-up measure (abstract 332-P) was evaluated. A total of 1389 BARI 2D enrollees had normal ABI (0.9 < ABI > 1.3) at study entry. After an average of 4.6 years of follow-up, 21.1% (n=293) were diagnosed with incident PAD (i.e., ABI <0.9). Among this group, the incidence of PAD was significantly lower among patients assigned to receive IS therapy vs. IP drugs (17.6% vs. 24.6%, p=0.001). When the data were further stratified by baseline insulin use, there was also a statistically significant difference favoring IS therapy based on lower incidence of PAD: 21.7% IS vs. 33.5% IP, p=0.013 if insulin was being used and 16.2% IS vs. 21.6% IP, p=0.026 if insulin was not being used at baseline. Additionally, those assigned to the sensitizer arm of the trial experienced fewer amputations (p<0.001) and lower extremity revascularizations (p=0.069). From these data, the investigators concluded that insulin-sensitizing drugs may confer an advantage over insulin-providing medications in the prevention of PAD.

On June 15, 2011, the Food and Drug Administration published an FDA Safety Alert suggesting that pioglitazone may be associated with an increased risk of bladder cancer and required the manufacturer to include this information in the package labeling. Studies are ongoing to further inform on this potential relationship. Erdmann et al. from Germany and the US provided a six-year update from the PROactive study, a double-blind placebo-controlled trial that assessed pioglitazone for secondary prevention of macrovascular events (abstract 928-P). During the original trial, there was no difference in the cumulative incidence of all malignancies (3.7% pioglitazone vs. 3.8% placebo) over a 34.5-month follow-up duration. Yet, bladder cancers were more numerous (n=14) with pioglitazone versus placebo (n=5). Following completion of PROactive, 74% patients (n=3599) entered a 10-year observational study, which includes reporting of any new malignancy. Table 8 provides data from a 6-year interim analysis, showing that the incidence of bladder cancer is similar between patients originally assigned to pioglitazone versus placebo in the original double-blind study, both in the 6-year observational period and in the combined randomized study/observational periods (up to 9.7 years total, mean 8.7 years). A complete 10-year analysis is planned.

At present the connection between pioglitazone and bladder cancer remains tenuous, with observational data from various studies pointing in different directions. We clearly need more information on this important topic.

### Table 8. Any Malignancy or Bladder Cancer During PROactive Study and Six-Year Observational Follow-up

<table>
<thead>
<tr>
<th>Treatment period and endpoint</th>
<th>Original treatment assignment during double-blind period</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational period only</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any malignancy</td>
<td>164 (9.0%)</td>
<td>156 (8.8%)</td>
<td>1.03</td>
</tr>
<tr>
<td>Bladder malignancy</td>
<td>10 (0.5%)</td>
<td>17 (1.0%)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Double-blind period +</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>observational period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any malignancy</td>
<td>257 (9.9%)</td>
<td>247 (9.4%)</td>
<td>1.05</td>
</tr>
<tr>
<td>Bladder malignancy</td>
<td>23 (0.9%)</td>
<td>22 (0.8%)</td>
<td>1.06</td>
</tr>
</tbody>
</table>

**Self-monitoring of blood glucose** (SMBG, i.e., ‘fingersticks’) is a mainstay in the management of Type 1 and Type 2 diabetes mellitus. SMBG provides objective, real-time feedback on the effect of lifestyle and drug therapy on glucose levels. For people on insulin therapy, the requirement for SMBG is absolute—to monitor hyperglycemia and prevent hypoglycemia. But for people with Type 2 diabetes on oral therapy or lifestyle interventions alone, it is unclear whether the benefits outweigh the costs. After more than 20 years, 25 randomized control trials (RCTs), and 10 meta-analyses, the role of SMBG remains controversial. It is a billion dollar industry and represents a significant expense to healthcare systems already burdened with the costs of multiple chronic illnesses in an aging population. Should we be more discriminating in advising SMBG be performed? A *Pros and Cons* debate was initiated by Lutz Heinemann, PhD from Neuss, Germany, who argued that SMBG is essential in those with Type 2 diabetes mellitus.
diabetes. RCTs and meta-analyses show that monitoring is associated with HbA1c reductions in the 0.2% to 0.4% range, but these studies are flawed due to poor randomization and generally already low baseline HbA1c. Many studies also do not include the requisite self-management training, which likely leads to a systematic underestimation of the impact of SMBG. One study found an HbA1c reduction of 0.5% with applied structured response protocols for altering therapy when blood glucose excursions were recorded (Franciosi et al. Diabetic Med 2011;28:789).

Indeed, fingerstick monitoring offers the opportunity for patient reflection and active self-management—becoming a series of small, “teachable moments” instead of merely a mindless chore. Now that glucose monitors can be connected to computers and even to smart phones, modern technology offers the potential for glucose information to be forwarded to devices with automated feedback messages to assist further in diabetic control. He advocated for a long-term study of 2, 5, or even 10 years duration to evaluate the efficacy of SMBG within a structured self-care program.

The counter argument was provided by Jeffrey Stephens, PhD from the UK, who argued that fingerstick monitoring does not decrease the HbA1c to a clinically meaningful degree in Type 2 diabetes patients on oral therapy. RCTs suggest that the use of fingersticks fails to reach an HbA1c reduction of 0.5%, generally regarded as a threshold for clinical significance. One exception are those with newly diagnosed disease, who demonstrated a larger HbA1c decrease (-0.5% [95% CI -0.9 to -0.1]) with SMBG (Malanda UL et al., Cochrane Database Syst Rev. 2012 Jan 18;1:CD005060). Dr. Stephens agreed that improvements in clinical outcomes come from the effective use of blood glucose information for making clinical decisions, not merely the collection and recording of isolated values. SMBG is appropriate for patients at risk for hypoglycemia, or during short-term intervals (e.g., change in therapy, intercurrent illness). But the onus is on clinicians to assess the patient’s ability to self-manage and educate them on the day-to-day dietary and treatment changes to achieve short-term goals. Otherwise, SMBG provides data that may be unused—or, even worse, misunderstood. In addition, self-monitoring is an activity that is time-consuming, intrusive, uncomfortable, and expensive.

We advise fingerstick glucose monitoring in our Type 2 diabetes patients on insulin and in those who experience hypoglycemia on any therapy. In those using oral agents or non-insulin injectables, we also advise monitoring at and soon after diagnosis, during treatment changes, and during acute illness. However, in stable patients under good control, particularly in those not taking any drug that is associated with hypoglycemia, we encourage less frequent monitoring over time, for control surveillance in between HbA1c measurements.

### Does Diet Matter?

Dr. Beth Mayer-Davis, University of North Carolina, co-author of a recently published systematic review of the literature on “Macronutrients, Food Groups, and Eating Patterns in the Management of Diabetes” (Wheeler ML, Diabetes Care 2012;35:434), summarized their findings, which will be the foundation for an update to the current (2008) ADA Nutrition Position Statement. Studies included in the review were published between January 2001 and October 2010; evaluated patients with established diabetes; were conducted in outpatient settings; contained ≥10 participants in each arm; and had one of the following designs: clinical trials (controlled, randomized controlled), prospective observational studies, cross-sectional observational studies, or case-control studies. Dr. Mayer-Davis mentioned that isolating the effects of dietary macronutrient composition on glycemic control and cardiovascular risk is difficult due to confounding factors, especially by weight loss, and the use of and changes in medications. Likewise, altering the proportion of one macronutrient affects the proportions of other macronutrients, limiting assessment of true exposure. Blinding of patients and investigators is extremely difficult. And, definition of “standard” terms (e.g., low-fat, low-carbohydrate, low-glycemic index diet) are lacking, thereby compromising comparison of results across studies.

In investigations evaluating reduction in total carbohydrate intake, markers of glycemic control and insulin sensitivity improved in some studies, and serum lipoproteins improved in fewer studies (Table 9). With regard to type of carbohydrate, there was little difference between low-glycemic index and high-glycemic index diets in glycemic control and/or cardiovascular risk factors. Small improvements in glycemia with low-glycemic index diets were likely confounded by higher fiber intake. While low-fat intake may improve total cholesterol and LDL-cholesterol, HDL-cholesterol may also be lowered. When controlling for total fat amount, the type of fatty acid (saturated vs. monounsaturated) did not appear to affect glycemic control. There were also no consistent benefits of omega-3 fatty acid supplementation on glycemia or lipids, although triglycerides reduction was seen in some studies. In the absence of chronic kidney disease, higher-protein composition (30% of calories) had mixed effects on HbA1c but appeared to improve one or more cardiovascular risk measures. There is currently no evidence to recommend one protein source over another. And, the Mediterranean diet (e.g., legumes, fruit, vegetables, whole grains, olive oil) did not demonstrate an overall advantage over other diets on glycemic control. The effects of the Mediterranean diet on cardiovascular risk factors were mixed.

Dr. Mayer-Davis concluded her presentation by encouraging attendees to utilize the “lukewarm” data as an impetus for future research. A better understanding of inter-individual variation in response to diet as well as the biochemical mechanistic underpinnings of nutrition-related changes in glycemia and cardiovascular risk is needed.

### Table 9. Results from Studies of Macronutrients

<table>
<thead>
<tr>
<th>Type of Diet</th>
<th>No. of Studies</th>
<th>HbA1c</th>
<th>TGs</th>
<th>HDL-C</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very-low carbohydrate</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Low carbohydrate</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Low glycemic index</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Low fat</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* The product is not labeled for the use under discussion or the product is still investigational.
The Grand Ballroom was almost full an hour before a major symposium on Monday, with attendees eagerly awaiting the results of the much anticipated trial, ORIGIN (Outcome Reduction with Initial Glargine Intervention). This landmark study involved 12,537 patients from 573 centers in 40 countries, after being conceptualized 10 years ago. The main aim of the study was to determine whether basal insulin-mediated normoglycemia or the use of omega-3 fatty acids could reduce cardiovascular morbidity and/or mortality in people at high risk for vascular disease—with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or early Type 2 diabetes. The primary endpoint in the glargine arm was cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (a second co-primary endpoint expanded this to include revascularization and heart failure [HF]); in the omega-3 fatty acid arm, the primary endpoint was cardiovascular death. Several secondary endpoints included a variety of other cardiovascular disease composites. The eligibility criteria are presented in Table 10. The participants were randomized to receive either glargine, titrated to achieve a fasting BG of ≤95 mg/dl or standard care (lifestyle modification and antihyperglycemic agents per routine local conventions). In the glargine group, the median insulin dose was 0.3-0.4 units/kg/day and the median glucose was reduced 94 mg/dl at study end. In contrast, in the standard care group, the median glucose was 123 mg/dl at this time. In a 2x2 factorial design, each participant was also randomized to receive either 1g of omega-3 fatty acids daily or placebo.

After a median follow up of 6.2 years (IQR 5.8-6.6), results for the effect of glargine are seen in Table 11 and Figure 11, while those for omega-3 fatty acids are in Table 12.

So, in patients with mild dysglycemia at high cardiovascular risk, the use of glargine titrated to attain normoglycemia or omega-3 fatty acids over a period of 6 years did not reduce cardiovascular outcomes. For the glyceemia part of the trial, these data clearly demonstrate an overall neutral effect from the normalization of blood glucose with basal insulin therapy. Further subgroup analyses

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**Table 10. Eligibility Criteria for ORIGIN Trial**

**Inclusion Criteria**
- Age ≥50 years
- Have either IGT*, IFG†, or early T2DM‡, or taking one oral antidiabetic drug at a stable dose ≥10 weeks
- At risk for cardiovascular risk (history of myocardial infarction ≥5 days; history of stroke ≥5 days; history of coronary, carotid or peripheral arterial revascularization; angina with documented ischemic changes; microalbuminuria; left ventricular hypertrophy; ≥50% stenosis on angiography of a coronary, carotid or lower extremity artery, ankle brachial index <0.9
- Able to use self-glucose-monitoring device and self-inject insulin
- Not pregnant

**Exclusion criteria**
- Type 1 diabetes or known (+)anti-GAD Ab
- Requiring insulin
- HbA1c ≥150% upper limit of normal
- Coronary artery bypass grafting ≤4 years
- Serum creatinine >2.0 mg/dl
- Active liver disease or elevation of ALT or AST ≥2.5x above upper limit of normal
- Chronic or recurrent treatment with corticosteroids or niacin
- Heart failure of NYHA functional class III or IV
- History of or awaiting a heart transplant
- Expected survival of <3 years for non-cardiovascular causes

*IGT – postprandial plasma glucose (PPG) 140-199 mg/dl, with fasting plasma glucose (FPG) <126 mg/dl
†IFG – FPG 110-125 mg/dl, with 2-hr OGTT glucose of <200 mg/dl
‡Early Type 2 diabetes—FPG ≥126 mg/dl or PPG ≥200 mg/dl or previous diagnosis of diabetes, and on no pharmacological treatment ≥10 weeks prior to screening and HbA1c <150% upper limit of normal.
The effect of incretin enhancers on long gastric emptying or on appetite suppression are not high enough to have any significant effect on this area over the past several years.

Table 11. Hazard Ratios for the Effect of Glargine on Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, CV death*</td>
<td>1.02</td>
<td>0.94-1.11</td>
<td>0.63</td>
</tr>
<tr>
<td>MI, stroke, CV death, revascularization, heart failure*</td>
<td>1.04</td>
<td>0.97-1.11</td>
<td>0.27</td>
</tr>
<tr>
<td>Microvascular outcomes</td>
<td>0.97</td>
<td>0.90-1.05</td>
<td>0.43</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.98</td>
<td>0.90-1.08</td>
<td>0.70</td>
</tr>
<tr>
<td>Myocardial infarctions (fatal and non-fatal)</td>
<td>1.02</td>
<td>0.88-1.19</td>
<td>0.75</td>
</tr>
<tr>
<td>Stroke (fatal and non-fatal)</td>
<td>1.03</td>
<td>0.89-1.21</td>
<td>0.69</td>
</tr>
<tr>
<td>CV death</td>
<td>1.00</td>
<td>0.89-1.13</td>
<td>0.98</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>0.90</td>
<td>0.77-1.05</td>
<td>0.16</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1.06</td>
<td>0.96-1.16</td>
<td>0.24</td>
</tr>
<tr>
<td>Angina</td>
<td>0.95</td>
<td>0.85-1.05</td>
<td>0.29</td>
</tr>
<tr>
<td>Limb or digit amputation</td>
<td>0.89</td>
<td>0.60-1.31</td>
<td>0.55</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>1.00</td>
<td>0.94-1.07</td>
<td>0.90</td>
</tr>
<tr>
<td>Non-CV hospitalization</td>
<td>0.99</td>
<td>0.94-1.05</td>
<td>0.85</td>
</tr>
<tr>
<td>Any cancer</td>
<td>1.00</td>
<td>0.88-1.13</td>
<td>0.97</td>
</tr>
<tr>
<td>Death from cancer</td>
<td>0.94</td>
<td>0.77-1.15</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Table 12. Hazard Ratios for the Effect of Omega-3 Fatty Acids on Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death*</td>
<td>0.98</td>
<td>0.87-1.10</td>
<td>0.72</td>
</tr>
<tr>
<td>MI, stroke, CV death</td>
<td>1.01</td>
<td>0.93-1.10</td>
<td>0.81</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.98</td>
<td>0.89-1.07</td>
<td>0.63</td>
</tr>
<tr>
<td>Fatal arrhythmias</td>
<td>1.10</td>
<td>0.93-1.30</td>
<td>0.26</td>
</tr>
<tr>
<td>Myocardial infarction (fatal and non-fatal)</td>
<td>1.09</td>
<td>0.93-1.27</td>
<td>0.28</td>
</tr>
<tr>
<td>Stroke (fatal and non-fatal)</td>
<td>0.92</td>
<td>0.79-1.08</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>1.02</td>
<td>0.88-1.19</td>
<td>0.76</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.96</td>
<td>0.87-1.05</td>
<td>0.39</td>
</tr>
<tr>
<td>Angina</td>
<td>1.00</td>
<td>0.90-1.10</td>
<td>0.94</td>
</tr>
<tr>
<td>Limb/digit amputation for ischemia</td>
<td>1.09</td>
<td>0.74-1.62</td>
<td>0.67</td>
</tr>
<tr>
<td>Hospitalization for CV cause</td>
<td>0.98</td>
<td>0.92-1.04</td>
<td>0.50</td>
</tr>
</tbody>
</table>

* Primary outcomes. CV=cardiovascular.

Incretin Enhancers

The incretin enhancers, glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP), thereby increasing their activity profile through incretins (Figure 12). This, in turn, results in an increase in glucagon-like peptide 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 on appetite suppression. The effects of these ‘incretin enhancers’ on long-term clinical outcomes are entirely unknown, however.

In a joint ADA/The Lancet Symposium, Dr. Pablo Aschner from Columbia, South America, presented the results of a multicenter, randomized open-label trial comparing insulin glargine versus sitagliptin in insulin-naive patients with Type 2 diabetes uncontrolled on metformin (EASIE) (The Lancet, early online publication, 6-9-12). Dr. Aschner reminded the audience that, to date, there are little data comparing these two treatment strategies head-to-head after metformin failure. A total of 515 patients were randomized to receive sitagliptin 100 mg OD (n=265) or insulin glargine (n=250) for 24 weeks, the latter titrated to a fasting plasma glucose of 71-100 mg/dl (dose=0.5 units/kg/day at study end). The primary endpoint was the change in HbA1c from baseline. HbA1c decreased to a greater extent in the insulin glargine group at 12 and 24 weeks (adjusted mean difference in HbA1c at week 24, -0.59% (95% CI, -0.77 to -0.42; p<0.0001). A larger percentage of patients achieved HbA1c values <7.0% (68% vs. 42%; p<0.0001) and <6.5% (40% vs. 17%, p<0.0001) with glargine versus sitagliptin. Rates of symptomatic hypoglycemia favored sitagliptin over glargine (0.50±0.09 vs. 4.21±0.54 events per patient-year; p<0.001).
There was slight weight loss with sitagliptin and slight weight gain with glargine (adjusted mean difference = 1.5 kg, p < 0.0001). From these data, Dr. Aschner concluded that basal insulin was a more efficacious option over a DPP-4 inhibitor after metformin monotherapy.

In a comparison between sitagliptin and the sulfonylurea, glipizide, and American coworkers evaluated Type 2 diabetes patients with moderate to severe renal failure (abstract 1009-P). Patients were randomized to sitagliptin, dose adjusted for renal impairment (50 mg and 25 mg daily for moderate and severe impairment, respectively) or to glipizide 2.5 mg daily titrated to a maximum of 20 mg daily based on level of glycemic control. The primary outcome measured was the proportion of patients achieving the predetermind composite endpoint of glycemic control (HbA1c reduction of >0.5%), without weight gain or hypoglycemia, from baseline to week 54. A greater percentage of patients in the sitagliptin group (35.7% of 140 patients) versus the glipizide group (14.2% of 148 patients) achieved the composite endpoint (between-group treatment difference, 22.1% [95% CI, 12.4-31.9]).

Galwitz and colleagues (US and Germany) evaluated the two-year composite outcome in Type 2 diabetes patients on metformin, who were randomized to either linagliptin (another DPP-4 inhibitor) 5 mg/day or glimepiride 1-4 mg/day (abstract 1044-P). Final analysis was completed on a per-protocol population who did not require ‘rescue’ medication for uncontrolled hyperglycemia after two years. Both groups achieved a mean HbA1c reduction of -0.6% at 2 years and an equal proportion of patients achieved HbA1c <7% (76%). However, a higher proportion of patients in the linagliptin group (54%) group achieved the composite endpoint of target HbA1c, no weight gain, and no hypoglycemia compared to glimepiride (23%) (OR 3.9 in favor of linagliptin, 95% CI 2.6-5.7; p < 0.0001).

As the role of the DPP-4 inhibitors becomes further defined, a remaining question is whether there are meaningful differences between the entities within the drug class. This issue was addressed by Adrian Vella, MD, Mayo Clinic, in his presentation at the Incretin-Based Therapies Symposium entitled, DPP-4 Inhibitors—Are they all the same? Dr. Vella began his presentation by comparing chemical structures of the DPP-4 inhibitors. He commented that structurally, the drugs appear quite different, but each shares the same mechanism of action and has a similar magnitude of enzyme inhibition (~80%). In terms of off-target effects, although there may be some slight differences in selectivity for DPP-4 and inhibition of other serine peptidases, the clinical significance between each is not yet known and likely to be small. There are some variations, however, in their pharmacokinetic profiles. For example, saxagliptin is predominantly excreted in the feces (~85%) and does not require dosage adjustment for renal compromise, whereas sitagliptin and saxagliptin are dose-adjusted for certain degrees of renal impairment. Each DPP-4 inhibitor is well absorbed orally, given once daily, and requires infrequent monitoring. Adverse drug reaction profiles are similar, and, in general, the DPP-4 inhibitors are quite well tolerated. Therapeutically, each drug decreases HbA1c ~0.7%, with little hypoglycemia and no weight gain. Thus, in summary, other than some pharmacokinetic differences that may alter dosing, if one evaluates other parameters such as mechanism, non-glucose effects, adverse drug events, and therapeutic efficacy, Dr. Vella concluded that “Yes”, they are all the same.

**The Monday morning symposium, New Lessons in Hypertension and Diabetes—An Update on Clinical Trials and Clinical Guidelines** addressed four general areas: the role of endothelial dysfunction in hypertension, lessons learned from recent outcomes trials, selection of drug therapy, and a critical appraisal of current guidelines. Francis Kim, MD, University of Washington reviewed the role of endothelial dysfunction in diabetes and hypertension. He reminded the audience that, by surface area, the endothelium is the largest organ in the body. Nitric oxide, only expressed in endothelial cells, has tremendous vasculoprotective properties: vaso-relaxation and vasodilation, anti-inflammatory activity, inhibition of platelet aggregation, and suppression of smooth muscle. There is a relationship between cardiovascular disease risk factors (i.e., dyslipidemia, hypertension, diabetes, cigarette smoking, etc.) and decreased nitric oxide production. Although much more complex than stated in this synopsis, Dr. Kim presented elegant data supporting the interplay between glucose and free fatty acid production leading to inflammation, decreased nitric oxide production and subsequent insulin resistance and endothelial dysfunction. He recognized that it is still not determined if insulin resistance is a cause, a consequence, or a common antecedent to endothelial dysfunction and hypertension. Although exceedingly complex with multiple cellular mechanisms involved, given that endothelial dysfunction is likely an underlying factor for many cardiovascular risk factors, future drug therapy that targets vascular function via a nitric oxide pathway may be important in decreasing both insulin resistance and hypertension (Figure 13).

**The second speaker, Jackson Wright, MD, PhD, Case Western Reserve, provided an overview of lessons learned from outcomes studies. He began with his conclusion to the question, “What is the optimal blood pressure (BP) lowering drug regimen?” His answer was**
The debate over how to report HbA1c is divided by the Atlantic ocean, potentially ending efforts toward global standardization of HbA1c measurement and reporting. David Nathan, MD from Harvard University, US and Sally Marshall, MD from Newcastle upon Tyne, United Kingdom went head to head in an entertaining debate over whether HbA1c should be reported in % DCCT or in international system (SI) units of mmol/mol.

David Sacks, MD, Chair of the National Glycohemoglobin Standardization Program (NGSP) Steering committee, led off the presentations by reminding us that there are currently over 100 methods to measure HbA1c. So within the US and throughout the world, commercial laboratories use different methods on their own machines to detect the quantity of HbA1c in a given blood sample. But recent “standardization” of HbA1c measurements has been enabled by the calibration of each machine to one reference technique for measuring HbA1c, as designed by the International Federation of Clinical Chemistry (IFCC). Each lab then uses a master equation to convert its measurements to read the results in % HbA1c of total hemoglobin or in millimole HbA1c per mole of total hemoglobin (SI units used in the IFCC reference technique).

Dr. Nathan argued that clinicians and researchers are accustomed to interpreting % HbA1c, and aligning therapeutic goals with the data provided by the landmark DCCT and other trials over the last 30 years. He emphasized that changing reporting now only promotes confusion without any discernable benefit since the actual techniques for measuring HbA1c have not changed. In her counter-argument, Dr. Marshall indicated that the IFCC reference standard is the “anchor” keeping the various measurement techniques appearing similar, hence the results should be reported in mmol/mol. Over the past year, England made the switch—now reporting HbA1c in mmol/mol vs. %—without chaos.

On this disagreement, we would agree fully with Dr. Nathan—introducing a new system seems unwarranted and apt to confuse more than clarify!
In an oral abstract presentation, Dr. Umpierrez from Atlanta presented a multicenter trial that sought to determine the best discharge glucose control program for patients with Type 2 diabetes who were recently hospitalized (abstract 10-OR). Their discharge algorithm, based on recent HbA1c, is seen in the Table 13.

There were 224 patients in the study (mean age 58±12 years, diabetes duration 9±8 years). After discharge they were followed every 4 weeks with the glucose-lowering regimen adjusted to achieve a HbA1c <7%. In total, 8 (4%) were sent home on diet alone, 81 (36%) on their admission oral agent regimen alone, 20 (9%) on glargine alone, 61 (27%) on orals + glargine, and 54 (24%) on glargine + glulisine. Mean HbA1c at 6 and 12 weeks was 7.9% and 7.3%, respectively, ranging from 6.6% (oral agents only) to 8.0% (glargine-glulisine at week 12). Hypoglycemia (<70 mg/dl) occurred in 29% of all patients, with the highest rate in the glargine-glulisine group (44%). Severe hypoglycemia (<40 mg/dl), however, was uncommon, occurring in 3% of patients, also mainly in the glargine-glulisine group (6%). The investigators concluded that their proposed algorithm was safe and effective for the management of patients at discharge. While we find the hypoglycemia rates in this study too high, we like the adaptive discharge planning design, employing information garnered from the baseline HbA1c. Perhaps a more conservative dosing schedule might result in less hypoglycemia.

Table 13. Discharge Algorithm for Type 2 Diabetes Patients

<table>
<thead>
<tr>
<th>Admission HbA1c</th>
<th>Discharge Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7%</td>
<td>Resume prior outpatient regimen</td>
</tr>
<tr>
<td>7-9%</td>
<td>Glargine QD at 50-80% of hospital dose + outpatient oral regimen</td>
</tr>
<tr>
<td>&gt;9%</td>
<td>Glargine QD at 80-100% of hospital dose + outpatient oral regimen OR Glargine QD at 80-100% of hospital dose + mealtime glulisine TID</td>
</tr>
</tbody>
</table>

Several investigational anti-hyperglycemic compounds were highlighted in presentations this week, a sample summarized here. Fouqueray and associates from the US and Europe conducted a 12-week phase 2 study of imeglimin,* the first in a new tetrahydrotriazine-containing class of oral anti-hyperglycemic agents (‘glimins’) as add-on therapy in patients with Type 2 diabetes inadequately controlled on metformin monotherapy (abstract 1004-P). The mechanism of action of the glimins is not known, but may involve activation of AMPK and suppression of hepatic glucose production. There are some data to suggest improved β-cell function as well. This multicenter, double-blind study randomized 156 patients to imeglimin (1500 mg BID) or placebo, each added to a stable dose of metformin (~1900 mg per day). Imeglimin treatment led to small, but statistically significant, reductions from baseline in HbA1c (-0.65% vs. -0.21% with placebo; p<0.001), fasting plasma glucose (-16 vs. +6 mg/dl, p<0.001), and pro-insulin/insulin ratio, a marker of β-cell function (-4.79 vs. 13.42, p=0.007) at week 12. In an subgroup analysis by baseline HbA1c, imeglimin reduced HbA1c from baseline to week 12 by 0.41%, 0.68%, and 0.78% in the subgroups having baseline values of <8.0%, 8.0 to 9.0%, and >9.0%, respectively. There was no difference between treatment groups for adverse events.

In another 12-week double-blind phase 2 study, Kazda et al. from the US, France, and Singapore randomized 87 patients with Type 2 diabetes (mean age 52.3 years, 54% female, diabetes duration 4.2 years, BMI 32.4 kg/m², HbA1c 7.7%) who were naïve to antidiabetic medications or taking stable metformin dose (59%) to the selective glucagon receptor antagonist, LY2409201* 10 mg, 30 mg, or 60 mg or to placebo once daily for 12 weeks (abstract 981-P). At 12 weeks, HbA1c was decreased (p<0.05) in all active dose groups: LS mean changes from baseline of -0.83%, -0.65%, and -0.66% for the 10 mg, 30 mg, and 60 mg groups, respectively, versus 0.11% with placebo. No significant changes in lipids, weight, or blood pressure were observed. Total, direct, and indirect bilirubin were unchanged vs. placebo, but dose-dependent increases in transaminases were observed.

SGLT-2 inhibitors increase glucosuria by inhibiting a sodium-glucose transporter in the renal nephron. Wilding et al. from the UK, Belgium, and US reported the results of double-blind, phase 3 trial in which 462 patients with Type 2 diabetes inadequately controlled on metformin and sulfonylurea were randomized to canagliflozin* 100 mg, 300 mg, or placebo for 26 weeks (abstract 1022-P). The primary endpoint of HbA1c was significantly decreased (p<0.001) in the canagliflozin 300 mg arm (8.1% to 7.0%), and the 100 mg arm (8.1 to 7.2%) versus placebo (8.1% to 7.9%). Both the 100 and 300 mg doses significantly decreased weight, improved FPG, and had a higher percentage of patients achieving an HbA1 <7.0% versus placebo (p<0.001). Rates of adverse events and adverse event-induced discontinuation were comparable in all three groups. However patients in the canagliflozin arms experienced higher rates of genital mycotic infections when compared with placebo (women: 18.7% versus 3.8%; men: 4.9% versus 1.3%). Rates of urinary tract infections were similar in all groups.

A new and still investigational formulation, insulin degludec* (abstracts 348-OR, 349-OR, 387-P), has an ultra-long flat action profile (40+ hours). Several studies have shown reduced rates of nocturnal and overall hypoglycemia as compared to glargine. A recent study observed four times less within-subject variability with degludec compared to glargine. Because of its ultra-long duration of action, degludec may also offer greater flexibility in terms of variations in administration times, if required.

Which of these agents are eventually approved for clinical use is unclear. The SGLT-2 inhibitors and degludec are probably closest to market.

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

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

Editors, Yale University,
New Haven, Connecticut
Diabetes 2012 Test
Volume 25

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

1. Which of the following drug classes is not recommended in the “2012 ADA/EASD Position Statement on Management of Type 2 Diabetes” as second-line therapy to metformin, or first-line for the up to 20% of patients who cannot tolerate metformin?
   a. sulfonylureas
   b. basal insulin
   c. alpha-glucosidase inhibitor
   d. thiazolidinediones (TZD)

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

3. “Lower is not necessarily better” for glycemia control in Type 2 diabetes; a near-normal HbA1c level (6-6.5%) may be advisable for younger patients without complications or comorbidities, whereas more conservative targets (7.5-8.0%) should be considered for the elderly and more infirm patients.
   a. true
   b. false

4. Aggressive management of hyperglycemia to lower, more stringent HbA1c may not be suited for which of the following patient factors?
   a. > 20 year history of Type 2 diabetes
   b. long life expectancy
   c. adherent patient with excellent self-care capacity
   d. patient with no vascular complications

5. Select the false statement from the following about the use of insulin sensitizers (metformin, TZDs) in patients with Type 2 diabetes.
   a. Patients treated with insulin sensitizers are at low risk of hypoglycemia.
   b. Insulin sensitizers improve (biochemical markers of) inflammation.
   c. According to results from the BARI-2D trial, the risk of new-onset peripheral neuropathy is decreased by 20% during treatment with insulin sensitizers vs. insulin-providing agents (e.g., insulin or sulfonylurea).
   d. The BARI-2D trial showed an increased risk of new-onset peripheral arterial disease during treatment with insulin sensitizers vs. insulin-providing agents.

6. During chronic treatment with metformin, serum vitamin B12 levels are increased to borderline-high levels in ~40% of patients.
   a. true
   b. false

7. In elderly patients, the risk of new-onset Type 2 diabetes developing over the next 7 years is 4-fold higher among those with impaired fasting glucose (IFG; 100-125 mg/dl) and elevated HbA1c (5.7-6.4%) versus either abnormality alone.
   a. true
   b. false

8. In Type 2 diabetes patients who have absence of retinopathy and microaneurysms in both eyes at two consecutive annual screenings, the risk of progression to retinopathy is quite low (<10%) over the next 10 years.
   a. true
   b. false

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 or her glycemic target.
   a. thiazolidinedione
   b. insulin
   c. glucagon-like peptide 1 (GLP-1) receptor agonist

9. The patient is also extremely obese
10. The patient also has steatosis
11. The patient has HbA1c of 12.3%

12. In the TINSAL study, salalate was used as a glucose-lowering agent. The theory behind this study involves which of the following pathophysiological targets in Type 2 diabetes?
   a. inflammation
   b. obesity
   c. abnormal incretin levels
   d. urinary glucose excretion

13. In the ORIGIN trial, glargine insulin therapy over a period of 6 years in patients with early Type 2 diabetes or prediabetes increased the risk of malignancy.
   a. true
   b. false

14. In the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study, approximately half of the children and adolescents with Type 2 diabetes did not achieve sustained glycemic control with metformin monotherapy.
   a. true
   b. false

15. Which of the following is not a potential pathological link between hypoglycemia and cardiovascular mortality?
   a. precipitation of arrhythmias
   b. decreased thrombolysis
   c. decreased sympathomimetic stimulation
   d. induction of low-grade inflammation

16. There is little difference between low-glycemic index and high-glycemic index diets on glycemic control.
   a. true
   b. false

17. While hypovitaminosis D level has been shown to be a risk factor for diabetes, data presented at the 2012 ADA Scientific Sessions suggest that vitamin D supplementation may actually not reduce this risk.
   a. true
   b. false

18. Select the false statement from the following about results (over a 6-year period) from the ORIGIN (Outcome Reduction with Initial Glargine Intervention) study of patients with mild dysglycemia at high cardiovascular risk.
   a. The use of glargine titrated to attain normoglycemia did not reduce cardiovascular outcomes.
   b. The use of omega-3 fatty acids reduced cardiovascular outcomes.
   c. There was nearly a 30 mg/dl difference in the mean fasting glucose between the glargine and standard-care groups.
   d. In the pre-diabetic cohort, glargine (versus standard care) reduced the risk of progression to Type 2 diabetes by 28%.

19. Each of the following can be expected during treatment with sodium-glucose transporter-2 (SGLT-2) inhibitors except______.
   a. decreased HbA1c
   b. glucosuria
   c. genital fungal infections
   d. increased weight

20. Each of the following might be expected during treatment with GLP-1 receptor agonists except______?
   a. glucose-dependent increase in insulin secretion
   b. weight loss
   c. hypoglycemia
   d. GI side effects
Diabetes 2012 Evaluation
Volume 25

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.
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: July 2012 to December 31, 2012.

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 25

1. (a) (b) (c) (d) 11. (a) (b) (c)
2. (a) (b) (c) (d) 12. (a) (b) (c) (d)
3. (a) (b) 13. (a) (b)
4. (a) (b) (c) (d) 14. (a) (b)
5. (a) (b) (c) (d) 15. (a) (b) (c) (d)
6. (a) (b) 16. (a) (b)
7. (a) (b) 17. (a) (b)
8. (a) (b) 18. (a) (b) (c) (d)
9. (a) (b) (c) 19. (a) (b) (c) (d)
10. (a) (b) (c) 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 25

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: ________________

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