Volume 31

Highlights from the
75th Annual Scientific
Sessions of the American
Diabetes Association

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Dear Colleague:

Time restraints prevented many of you from attending the 75th Annual Scientific Sessions of the American Diabetes Association (ADA) which was held a few weeks ago in Boston, MA. Therefore, we developed Diabetes 2015 so that important information presented at the Conference could be shared with you on a timely basis.

Diabetes 2015, a newsletter CME program, is being offered to you by Yale School of Medicine with the support of educational grants from Eli Lilly and Company, Merck & Co., Inc., sanofi-aventis U.S. 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 2015 newsletters and a post-test. After successfully completing the test online you will qualify for a maximum of 5.0 AMA PRA Category 1 Credits™ to be issued by Yale School of Medicine. Term of approval: June 2015 to December 31, 2015.

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

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with 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, inflammation, and atherosclerosis in patients with Type 2 diabetes.
- Underscore the importance of lifestyle change, exercise, and dietary interventions in the management of diabetes.
- Compare the mechanisms of actions of a growing array of oral and injectable pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper evidence-based 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 healthcare systems.

Given the recent explosion of information on diabetes, as well as its relationship to cardiovascular diseases, we began publishing this newsletter series 15 years ago. We hope the information presented in these newsletters will prove useful to you in the management of your patients.

Sincerely,

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

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Educational Needs

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

Learning Objectives

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

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
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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 healthcare systems.

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 sent by e-mail to the office of participating physicians. Shortly after the ADA conference concludes, participants will receive a Diabetes 2015 booklet via e-mail in PDF form containing all of the newsletters, a program highlights summary from the program co-editors, a course evaluation form, and a post-test. The Diabetes 2015 booklet PDF and post-test will also be available on-line at www.cme.yale.edu. The post-test must be completed on-line (not by US mail or fax).

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 provide continuing medical education for physicians.

Designation

The Yale School of Medicine designates this enduring material for a maximum of 10 AMA PRA Category 1 Credit(s)™ (5.0 credits per test). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Medical Association has determined that physicians not licensed in the US who participate in the CME activity are eligible for AMA PRA Category 1 Credits™.
# Table of Contents

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

**Issue One**

Management of Hyperglycemia in Type 2 Diabetes ..................................................................... 3
Medical Nutrition Therapy: A Fundamental Component of Diabetes Management .......................... 6
Trending Diabetes Epidemiology and Care ....................................................................................... 8

**Issue Two**

Non-Insulin Adjunct Therapy in Type 1 Diabetes ......................................................................... 9
Top Shelf Insulin ............................................................................................................................. 11
Advances and Challenges in Diabetic Kidney Disease ................................................................. 12
Mother and Child .......................................................................................................................... 13

**Issue Three**

SGLT-2 Inhibitor Update .............................................................................................................. 14
mHealth and Diabetes Management .............................................................................................. 16
Closed-Loop System and Bionic Pancreas ..................................................................................... 17
The Eyes Have It! .......................................................................................................................... 18
So Many Posters, So Little Time.................................................................................................... 19

**Issue Four**

A Tale of Two Trials ...................................................................................................................... 20
Advances in Insulin Therapy ........................................................................................................ 22
GLP-1 Agonists: Novel Uses and Formulations .......................................................................... 23
Hypoglycemia: Effects and Predictors .......................................................................................... 24
Feet Facts ..................................................................................................................................... 25
So Many Posters, So Little Time.................................................................................................... 26

Diabetes 2015 Test ......................................................................................................................... 27
Diabetes 2015 Evaluation .............................................................................................................. 28
In this issue of the Diabetes 2015 monograph, we summarize important new diabetes information that was presented at the 75th Annual Scientific Sessions of the American Diabetes Association (ADA) in Boston, MA.

On the opening day “Meet-the-Expert” sessions this week, Professor David Matthews of Oxford and Dr. Silvio Inzucchi from Yale discussed the most recent update of the ADA-EASD Position Statement on the Management of Hyperglycemia in Type 2 Diabetes (Diabetes Care 2015;38:140-9; Diabetologia 2015;58:429-42). This set of recommendations serves as the official position on pharmacological therapy for this disease from the two leading professional societies in diabetes care, the ADA and the European Association for the Study of Diabetes (EASD). Dr. Matthews reviewed the various patient and disease characteristics that may guide clinicians in determining the optimal, safest HbA1c to target at the individual patient level—risk of hypoglycemia and other adverse drug effects, disease duration, life expectancy, comorbidities, established vascular complications, patient attitude/expected treatment efforts, and patient resources/support systems. For example, younger individuals without established diabetic complications or comorbidities should probably be targeted at a near-normal HbA1c. This will send them down a healthy path for their lives to prevent long-term complications and disability (so-called ‘metabolic memory’). In contradistinction, those of advanced age with multiple comorbidities are likely to be best managed in a more conservative fashion, with vigorous attempts to avoid hypoglycemia and caution regarding other adverse effects of our glucose-lowering medications. In the next section of the session, Dr. Inzucchi reviewed the main treatment recommendations of the Position Statement, again underscoring that glucose-lowering strategies themselves require individualization. Lifestyle change (diet, weight optimization, and increased physical activity) and diabetes education should always be the foundation of therapy. If blood glucose is not controlled with these interventions alone, then metformin is the best first choice for drug monotherapy. Beyond metformin, if additional glucose-lowering therapy is needed, the addition of one of six treatment options—sulfonylureas, thiazolidinediones (TZDs), DPP-4 inhibitors, GLP-1 receptor agonists, basal insulin, and sodium glucose co-transporter (SGLT)-2 inhibitors—could be considered based on their relative efficacy, the risk of hypoglycemia, effects on body weight gain, other key side effects, and relative cost. After dual combination therapy, if additional glucose lowering is required, a triple combination is suggested, with the choice of drugs obviously becoming more limited as one works through the options. Ultimately, however, some patients who fail to respond to these conventional therapies will require advancing to combination injectable therapy. The Position Statement also presents insulin therapy options in Type 2 diabetes.

During another opening-day session, adjunct non-insulin therapy for Type 1 diabetes was discussed, an important topic in light of the ~70% of Type 1 patients who do not achieve a target HbA1c of <7.5% and the fact severe hyperglycemia and diabetic ketoacidosis (DKA) remain too common in this population. The first speaker, Dr. Kristen Nadeau, Denver, CO noted that both youth and adults with Type I have reduced insulin sensitivity when matched with non-diabetic controls of similar weight, lipid profile, and activity level. Also, insulin resistance, which has been documented to occur at the levels of muscle, liver, and adipose tissue, conceivably could contribute to at least macro- if not microvascular complications. She reviewed data showing that cardiovascular disease (CVD) outcomes in Type 1 patients may be partially related to either insulin resistance and/or one of its sequelae, namely increased exogenous insulin exposure. She stated that insulin resistance is a concern in patients with Type 1 diabetes and should be treated, with mounting data to support such interventions. Nitesh Kuhadiya, MD, PhD of SUNY at Buffalo then discussed targeting hyperglucagonemia in Type 1 diabetes. Of note, no excess adverse pancreatie events with the GLP-1 receptor agonist and no excess heart failure hospitalizations were observed. A non-significant, numerically higher number of pancreatitis cases with sitagliptin is noteworthy. We should remain vigilant about this potential rare complication of DPP-4 inhibitor therapy.

On the final full day of this year’s Scientific Sessions, the results of two anxiously awaited major CVD outcomes clinical trials—ELIXA (the GLP-1 agonist, lixisenatide, vs. placebo) and TEOS (the DPP-4 inhibitor, sitagliptin, vs. placebo)—were revealed. Taken together, results of these trials indicate that incretin-based therapy appears to either increase or decrease major adverse cardiovascular (MACE) events in high-risk patients. It would be unlikely to find anything else, given these trials enrolled high-risk patients to increase event rates and shorten the length of study with the aim of complying with FDA guidance to study the CV safety of new diabetes drugs. Larger, more long-term studies involving patients perhaps with no overt CV at baseline are needed to determine whether these drugs, when compared with standard therapy, might actually provide additional cardiovascular protection. Of note, no excess adverse pancreatic events with the GLP-1 receptor agonist and no excess heart failure hospitalizations with sitagliptin were observed. A non-significant, numerically higher number of pancreatitis cases with sitagliptin is noteworthy. We should remain vigilant about this potential rare complication of DPP-4 inhibitor therapy.

Presentations made at the ADA 2015 Scientific Sessions added to the evidence base for GLP-1 receptor agonists in Type 2 (and as previously noted, Type 1) diabetes and obesity treatment. Rosenstock and US colleagues reported the results of a phase 3 trial involving ITCA 650*, an osmotic mini-pump system, placed subdermally, designed to deliver continuous subcutaneous release of exenatide (abstract 278-OR). After the initial placement, the device provides drug at a precise predetermined rate for up to 12 months. If approved, this innovative delivery device could be a choice for patients who have difficulties with adherence and routine subcutaneous injections. Several studies involved the use of GLP-1 RAs with basal insulins to prevent the need to progress to basal-bolus insulin therapy, for example the combination of the long-acting basal insulin, degludec, formulated with liraglutide (IDegLira*) (abstract 166-OR) and a basal insulin/GLP-1 combination (glargine/lixisenatide* or “LixiLan”) (abstract 169-OR), both achieving greater reductions in HbA1c with no increase in hypoglycemia relative to patients managed with insulin glargine alone.

Innovations in insulin therapy continue to be studied, for example basal insulins, peglispro*, which has a two to three day half-life and preferential hepatic action due to its large molecular size (abstract 93-OR), and PE0139*, a recombinant human monomeric insulin molecule with a pharmacokinetic profile that supports once-daily (abstract 100-OR). Given the increasing number of diabetes patients who require large doses of basal insulin to overcome insulin resistance, a number of concentrated formulations are in development (e.g., glargine U-300* [abstract 1030-P]). And, atelisoparin (ORM-8001*) is making another entrance as an investigational pre-prandial adjunct to subcutaneous insulin for Type 1 diabetes (abstract 1058-P).

More details on these and other topics are found in this volume of Diabetes 2015.

* The product is not labeled for the use under discussion or the product is still investigational.
Management of Hyperglycemia in Type 2 Diabetes

In one of the opening “Meet-the-Expert” sessions this week, Professor David Matthews of Oxford and Dr. Silvio Inzucchi from Yale discussed the most recent update of the ADA-EASD Position Statement on the Management of Hyperglycemia in Type 2 Diabetes. This set of recommendations serves as the official position on pharmacological therapy for this disease from the two leading professional societies in diabetes care, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Dr. Matthews led off the discussion, providing a historical overview. While several guidelines and algorithms have emerged over the past decade, neither the ADA nor the EASD had ever endorsed a specific approach to managing glucose in patients with Type 2 diabetes. In 2011, because of the rapidly growing complexity in the pharmacological armamentarium for the disease, both groups felt that the time had come to develop such a manuscript. Five members from each organization were identified to serve as a writing group, chaired by the session’s speakers. The Position Statement was originally published in 2012 (see Diabetes 2012 Vol. 25, page 4), with a recent update published this year (Diabetes Care 2015;38(1):140-9, Diabetologia 2015;58(3):429-42). Its main tenets are the individualization of both treatment targets as well as treatment strategies, each incorporated into a patient-centered approach to care. 

Individualization of Treatment Targets

Traditionally, the ADA had endorsed a general HbA1c target of <7%, based primarily on

Figure 1. Modulation of the Intensiveness of Glucose Lowering Therapy in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Patient/Disease Features</th>
<th>Approach to the Management of Hyperglycemia</th>
<th>More Stringent</th>
<th>HbA1c 7%</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia, other drug adverse effects</td>
<td>Low</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few/mild</td>
<td>Severe</td>
<td></td>
</tr>
<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>
<td></td>
<td></td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Care 2015;38:140-9; Diabetologia 2015;58:429-42.
outcomes data from large randomized clinical trials, specifically the UKPDS, whose primary data were released in 1998. This concluded that achieving an HbA1c in this range translated into glycemic control, but it soon became clear that this approach has little benefit in older individuals with overt or risk factors for cardiovascular disease (CVD), and came with some risk, especially hypoglycemia. In the ACCORD trial, for example, increased mortality was actually found in those patients managed more intensively. It soon became obvious that a one-size-fits-all approach to treatment was unwise, and that the benefits of glucose control were somewhat discrepant as they relate to microvascular vs. macrovascular complications.

To this end, Dr. Matthews reviewed the various patient and disease characteristics that may guide clinicians in determining the optimal, safest HbA1c to target at the individual patient level (Figure 1). For example, younger individuals without established diabetic complications or comorbidities should probably be targeted at a near-normal HbA1c. This will send them down a healthy path for their lives to prevent long-term complications and disability (so-called ‘metabolic memory’). In contradistinction, those of advanced age with multiple comorbidities are likely to be best managed in a more conservative fashion, with vigorous attempts to avoid hypoglycemia and caution regarding other adverse effects of our glucose-lowering medications. In Figure 1, features towards the right-hand side favor the need to approach this type of patient more judiciously, whereas those toward the left encourage the clinician to be more stringent in his or her management strategies. The main difference to the original 2012 statement is the acknowledgement that two specific domains—patient attitude/expected treatment efforts and patient resources/support systems—could change or be modified over time. This is an important concept—we as providers and health care systems are obligated to at least attempt to

Figure 2. General Recommendations for Antihyperglycemic Therapy in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy</th>
<th>Triple therapy</th>
<th>Combination injectable therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin intolerance or contraindication</td>
<td>HbA1c ≥ 9%</td>
<td>Uncontrolled hyperglycemia (catabolic features, BG ≥300-350 mg/dL, HbA1c ≥10-12%)</td>
<td>Combination injectable therapy</td>
</tr>
<tr>
<td>Healthy Eating, Weight Control, Increased Physical Activity &amp; Diabetes Education</td>
<td>Metformin</td>
<td>Metformin +</td>
<td>Metformin +</td>
</tr>
<tr>
<td>Efficacy</td>
<td>high</td>
<td>moderate risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>low</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight</td>
<td>moderate</td>
<td>high</td>
<td>intermediate</td>
</tr>
<tr>
<td>Side effects</td>
<td>hypoglycemia</td>
<td>edema, HF, Fx's</td>
<td>rare</td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference - choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D</td>
<td>DPP-4-Inh</td>
<td>GLP-1 RA</td>
<td>SGLT2-i</td>
<td>GLP-1 RA</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>DPP-4-I</td>
<td>SGLT2-I</td>
<td>GLP-1 RA</td>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
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</tr>
<tr>
<td>SU</td>
<td>T2D</td>
<td>DPP-4-I</td>
<td>Insulin</td>
<td></td>
<td></td>
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<tr>
<td>or</td>
<td>or</td>
<td>or</td>
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</tr>
<tr>
<td>SU</td>
<td>T2D</td>
<td>SGLT2-I</td>
<td></td>
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<td>or</td>
<td>or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D</td>
<td>DPP-4-I</td>
<td>SGLT2-i</td>
<td>GLP-1 RA</td>
<td>GLP-1 RA</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>DPP-4-I</td>
<td>SGLT2-I</td>
<td>GLP-1 RA</td>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>T2D</td>
<td>DPP-4-I</td>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>T2D</td>
<td>SGLT2-I</td>
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<tr>
<td>SU</td>
<td>Insulin</td>
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<td>or</td>
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</tbody>
</table>

Fx = fracture, HF = heart failure, I = inhibitor, RA = receptor agonist, SGLT = sodium-dependent glucose-linked transporter, SU = sulfonylurea, T2D = thiazolidinedione.

*Diabetes Care* 2015;38:140-9; *Diabetologia* 2015;58:429-42.
address non-constructive patient behaviors and social predicaments, in an effort to maximize the quality of care for each individual. Clearly, this can be a challenge in many situations.

In the next section of the session, Dr. Inzucchi reviewed the main treatment recommendations of the Position Statement (Figure 2), again underscoring that glucose-lowering strategies themselves require individualization. Lifestyle changes (diet, weight optimization, and increased physical activity) are paramount. This and diabetes education should always be the foundation of therapy. If blood glucose is not controlled with these interventions alone, then metformin is considered the best first choice for drug therapy. Beyond metformin, if additional glucose-lowering therapy is needed, the addition of one of six treatment options could be considered. In the original Position Statement, five options were endorsed—sulfonylureas, thiazolidinediones (TZDs), DPP-4 inhibitors, GLP-1 receptor agonists, and basal insulin. In the 2015 update, the SGLT2 inhibitors were added to the dual therapy options based on demonstrated efficacy and tolerability over three years of availability in Europe and the US.

Each category of drugs obviously has its own set of risks and benefits. Figure 2 describes various key features of each class that should be used by patients and clinicians in choosing the best drug for that individual. These include relative efficacy, the risk of hypoglycemia, effects on body weight gain, other key side effects, and relative cost.

After dual combination therapy, if additional glucose lowering is required, a triple combination is suggested, with the choice of drugs obviously becoming more limited as one works through the options (Figure 2). Ultimately, however, some patients who fail to respond to these conventional therapies will require advancing to combination injectable therapy. In the past, this meant basal insulin plus meal-time rapid acting insulin, consisting of three to four injections per day. More recently, the equal efficacy in many patients of basal insulin plus a GLP-1 receptor agonist has been demonstrated. Accordingly, the update emphasizes this option in patients progressing to this point.

For those patients with contraindications to metformin, one of the dual therapy option drugs could be considered instead. Initial combination therapy with two drugs could be considered in patients with HbA1c levels in excess of 9%. Finally, when hyperglycemia is extreme, especially if catabolic features are present, immediate therapy with combination injectable therapy should be used, with a preference, at least initially in most circumstances, for combination insulin therapy. The Statement also presents insulin therapy options in Type 2 diabetes (Figure 3). These include the classical basal-bolus approach (as above, three to four injections per day), with consideration for the simpler basal-plus strategy (i.e., one injection of basal and a single injection of rapid acting insulin before the largest meal) or the often more convenient pre-mixed insulin, dosed twice daily. The figure reviews starting doses, cautious dose titration, and recommendations if hypoglycemia occurs.

How to choose a drug in a specific patient is not an entirely intuitive exercise. Dr. Inzucchi proposed that clinicians consider the six ‘P’s’ of medication selection. These include pathophysiological considerations, such as how insulin resistant or deficient a patient might be and whether hyperglycemia is predominantly fasting or postprandial (or both). Drug potency is of obvious importance since certain agents are more efficacious than others. Precautions are key factors and may largely guide therapy in many patients, especially those with prevailing contraindications, the elderly, or those with specific intolerances. In certain circumstances, certain ‘pluses’ or side benefits of individual drugs could be considered (e.g., weight loss, effect on lipids or blood pressure, etc.). Other practicalities should be recognized, such as dosing frequency or the need for glucose monitoring. Finally, price has become an exceedingly important concern, particularly in those with limited healthcare access or restrictive insurance coverage for pharmaceuticals.

To close the session, Dr. Matthews next reviewed certain common clinical conditions that would necessarily limit the choices of therapy. For example, in an individual in whom a major intent of care is to avoid hypoglycemia, dual therapy options obviously exclude sulfonylureas and insulin, and are restricted to a TZD, DPP4-inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist. In a patient in whom it would be preferable to avoid weight gain, sulfonylureas, insulin, and TZDs should not be used, with therapy after metformin restricted to a DPP4-inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist. Finally, in an individual where cost is a critical factor, therapy beyond metformin is limited to a generic TZD,
sulfonylurea, and/or human insulin. In the question and answer period, the importance of lifestyle change and the need to de-emphasize pharmacotherapy as the sole manner to achieve glycemic control were discussed. The speakers acknowledged this important point. The need to avoid ‘gluco-centricity’ was also mentioned—focus on blood pressure and lipid control is likely to be even more important to prevent macrovascular complications. Other points made by audience members included the dangers of older sulfonylureas such as glyburide with respect to hypoglycemia; the possibility that some patients with very high blood glucose levels could be treated with immediate combination oral therapy and avoid insulin; and, the difficulty in practically assessing the various pathophysiological contributions to an individual patient’s diabetes.

The foundation of diabetes therapy is nutrition—a point made by several speakers this week at the Scientific Sessions. On an opening “Meet the Experts” session conducted by Linda Delahanty, MS, RD of the Massachusetts General Hospital, the importance of medical nutrition therapy (MNT) for diabetes and pre-diabetes was discussed along with ADA recommendations. Although genetics is a contributor to the risk of developing diabetes, it has been shown that lifestyle modification is more powerful than the genes we possess. Nutrition and physical activity are clearly the most important and the most modifiable approaches to preventing the onset of diabetes as well as helping control the disease once it is established. In Type 1 diabetes, consistency of macronutrient intake and meal planning take priority over weight loss (if not obese), and to some degree, physical activity. Conversely, in Type 2 diabetes, weight loss and physical activity are key, in conjunction with pharmacotherapy when required.

A healthy diet is a priority when formulating a treatment plan for any patient with either type of diabetes. It is important for each patient to understand his or her individual nutritional needs; there is no standard “diabetic diet” that works for all. Ideally, consultation with a registered dietitian (RD) will help arrive at a macronutrient distribution personalized to a patient’s weight and metabolic profile. The corresponding Dietary Reference Intakes (DRIs) from the Institute of Medicine, endorsed for otherwise healthy patients with diabetes, range widely between 45-65% of total daily calories from carbohydrates, 20-35% from fat, and 10-35% from protein.

Two major components of MNT in diabetes are setting goals and developing interventions. Goals can differ from person to person, but three important ones include (1) improving blood glucose control, (2) optimizing lipoprotein profiles, and (3) assisting in blood pressure control. In addition, for most patients with Type 2 diabetes, weight reduction through decreased calorie intake is required. To achieve these goals, interventions may include reduced energy and fat consumption, consistent carbohydrate intake (or “carb-counting”), healthy food choices (fruits and vegetables, complex carbohydrates such as whole grains and lean meats), exchange lists, and/or simplified meal plans. See Figure 4 for the current ADA ‘Plate Method’ of approximating the composition of a meal. They are complemented by regular physical activity and other behavioral strategies.

A registered dietitian takes into consideration each patient’s personal and cultural preferences that influence dietary habits, as well as literacy when it comes to making food purchases and meal choices. Unfortunately, many barriers exist to adopting healthful dietary patterns, including access to healthy foods and patients’ willingness to modify their own behaviors. Fortunately, modern MNT is no longer a rigidly prescribed set of rules and does not endorse abstention from certain food types. Instead, it focuses on moderation and balance. The goal is for the patient to easily understand food choices and to make meal planning practical and simple, with a focus on the overall nutritional plan rather than individual macronutrients, micronutrients, or single food types. Such an approach can make it much simpler for the patient to modify his or her dietary habits.

Carbohydrates

Carbohydrates are a vital part of any diet—the major source of energy—and should not be restricted to <130 grams/day. Any less can increase the risk of hypoglycemia and concomitantly reduces excellent sources of vitamins, minerals, and dietary fiber. Some have proposed that even restricting sucrose is not necessary because it is the total amount of carbohydrates eaten at one meal that has the greatest impact upon postprandial glucose levels. The actual type or form of starch is less important. However, the focus of the diet should remain on complex carbohydrates, vegetables, particularly green leafy vegetables, fruits, and whole grains.

It is, however, important for the patient with diabetes to monitor his or her carbohydrate intake throughout the day to help achieve glycemic control, especially in those who use insulin. Methods include carb-counting, food exchanges, or, simply, experience. The key is that starch consumption in diabetes should be as consistent as possible from day-to-day. In those on fixed insulin doses, the intake should ideally remain consistent from meal-to-meal, though this is less important when the insulin dose is self-titrated by the patient, based on his or her anticipated carbohydrate intake. In summary, aiming for a consistent carbohydrate intake at each meal can help prevent large fluctuations in blood glucose and lead to better HbA1C levels.

The glycemic index is a controversial topic. It should generally not be used in place of other forms of carb-counting. The index, however, may be useful when it comes to comparing two different foods that have similar properties to determine which may have a greater immediate effect on blood glucose post-ingestion. In some individuals, focusing on food items with lower glycemic index may help to stabilize post-prandial glycemia. Generally speaking, these foods consist of complex carbohydrates that are digested more slowly and can help maintain greater stability in blood glucose. Simple or refined carbohydrates do the opposite. Despite this general sense in the nutrition community, actual evidence for a substantive impact of the types of carbohydrates on actual long-term measures of blood glucose control, such as HbA1c, has proven elusive. Moreover, it should be kept in mind that...
Fats

Patients with diabetes are at much higher risk for CVD, a risk that could potentially be modified through dietary fat restriction. In those without dyslipidemia, the recommended fat intake is similar to that for the general public, 20-35% of total calories. However, the type of fat consumed has become the focus of most guidelines. Specifically, the American Heart Association (AHA) recommends limiting saturated fat to being 5-6% of the diet (or about 120 calories per day based on a 2,000 calorie diet). Trans fat should be restricted even more - to less than 1% of calories a day (just 20 calories per day based on a 2,000 calorie diet). The ADA recommends that in those individuals who choose to drink, alcoholic beverages be consumed in moderation in patients with diabetes.

Protein

Protein does not have a direct influence on glycemic control as carbohydrates do. The current ADA recommendation for protein intake in patients with diabetes without chronic kidney disease is the same as for the general public. The recommended daily intake of protein is 0.8 grams/kg of body weight (most Americans consume slightly over 1 gram/kg/day) (Diabetes Care 2015 38:S20). This intake is sufficient and appropriate for most individuals with normal renal function as well as those with early kidney disease. A lower protein diet (0.6 gram/kg/day) is advocated by the National Kidney Foundation in those individuals with advancing chronic kidney disease (CKD), when the eGFR is <25 ml/min (CKD Stage 4-5). Such restriction may lead to slower progression of albuminuria and less decline in glomerular filtration rates. Additionally, studies involving higher protein diets (>20% of calories) have suggested a deleterious effect on renal function in patients with diabetic kidney disease, so these should be avoided. Of course, it is important to remember that with low protein intake, adequate calories and nutrients must still be obtained without compromising blood glucose levels or the quality of food consumed. Despite having relatively small effects on blood glucose levels, foods high in protein such as lean meats, low fat dairy, nuts, and beans can also help the diabetic patient remain full and satisfied throughout the day.

Exercise as a Complement to Diet

The ADA has also published exercise advice (Table 1). The benefits of exercise in diabetes are numerous, including weight reduction, better blood glucose control, reduced cardiovascular risk factors, and an overall improvement in the sense of well-being. Exercise just over 18 weeks has been shown to decrease HbA1c on average by 0.66% (Boulé et al, JAMA 2001;286(10):1218-27) — similar to glycemic reductions achieved with many recently developed oral agents! Additionally, exercise slows the loss of mobility in those who are obese and prevents disability in aging individuals.

Alcohol

The ADA recommends that, in those individuals who choose to drink, alcoholic beverages be limited to no more than 2 servings per day in men and 1 in women. Alcohol can directly decrease hepatic glucoseogenesis, which is particularly a problem when food intake is limited. Accordingly, care must be taken especially by those on insulin or insulin secretagogues to always consume alcohol with food and to monitor glucose levels closely after drinking.

Table 1. ADA Exercise Recommendations for Persons with Diabetes

- Children with diabetes or prediabetes should be encouraged to engage in at least 60 minutes of physical activity each day.
- Adults with diabetes should be advised to perform at least 150 minutes/week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise.
- All individuals, including those with diabetes, should be encouraged to reduce sedentary time, particularly by breaking up extended amounts of time (90 minutes) spent sitting.
- In the absence of contraindications, adults with Type 2 diabetes should be encouraged to perform resistance training at least twice per week.

Sodium

As with other dietary constituents, optimal sodium intake should be determined on an individualized basis. In general, the goal is <2,300 mg/day of sodium per day—the same as in the general population. For those with coexisting hypertension, further reductions should be considered. The AHA advises a sodium target of 1500 mg/day in this setting. A decrease in blood pressure has been shown to correlate with low-sodium diets in some studies. Sodium recommendations should take into account palatability, availability, extra cost of low-sodium products, and the potential challenges in maintaining a low-sodium yet nutritionally adequate diet. As with other dietary constituents, moderation is probably the best approach.
Pre-diabetes in US Adolescents and Young Adults

Imperatore et al. from the Centers for Disease Control and Prevention (CDC) estimated the prevalence of pre-diabetes among US adolescents (aged 12-18 years) and young adults (aged 19-34 years) by sex, race/ethnicity, and BMI status (abstract 1382-P). The study included 4,028 non-pregnant participants aged 12-34 years without diabetes mellitus from the 2005-2012 National Health and Nutrition Examination survey (NHANES) in whom fasting and 2-hour post-load plasma glucose and HbA1c were measured. Their logistic regression models adjusted for age, sex, obesity, and race/ethnicity. The prevalence of prediabetes, defined by impaired fasting glucose (IFG, fasting plasma glucose 100-125 mg/dL), impaired glucose tolerance (IGT, 2-hour plasma glucose 140-199 mg/dL), or increased HbA1c (5.7-6.4%), was approximately 1 in 5 adolescents (17.8%, 95% CI: 15.5%-20.4%) and 1 in 4 young adults (23.6%, 95% CI: 21.4%-26.0%). The largest proportion of prediabetes was due to IFG (prevalence 11.7% and 15.6%, respectively, among adolescents and young adults). In multivariable analysis, pre-diabetes prevalence was higher among males (26.3% vs. 17.0% of females; prevalence ratio [PR]: 1.6 [95% CI 1.4-1.9]), obese people (33.9% vs. 16.1% of normal weight individuals; PR 2.0 [1.7-2.4]), and among minorities (24.9% of non-Hispanic blacks, 25.2% of Hispanics, vs. 19.2% of non-Hispanic whites; PR 1.3 [1.1-1.6] for both non-Hispanic blacks and Hispanics). Longitudinal studies will inform the natural history of prediabetes categories in youth and young adults.

Disability due to Diabetes Mellitus Among Older US Adults

Bardenheier et al. from the CDC, Emory University, and Merck and Co. estimated the incidence of disability and mortality by self-reported diabetes status among 11,141 adults aged ≥50 years in the Health and Retirement Study (baseline years 1998 and 2004, follow-up until 2010 (abstract 1472-P). The researchers reported that diabetes significantly reduces quality of life by exposing adults to disability at earlier ages and reducing disability-free years remaining compared to those without diabetes. From age 50, diabetes patients had approximately 8-8 years earlier onset of disability, 2-4 fewer total years of remaining life, and 6-7 fewer disability-free total years of life. Thus, increases in diabetes incidence and life expectancy have led to an increased number of years spent with diabetes, with a concomitant reduction in disability-free years, with the impact on disability even greater than that on longevity. These are important data and underscore the broad impact of diabetes outside of the usual quantification of macro- and microvascular complications.

Racial Disparities in Insulin Use and Diabetes Control

Selvin et al. from Johns Hopkins and the International Diabetes Center, Minneapolis, MN conducted a cross-sectional study of 4,310 diabetes patients in NHANES to examine trends in glycemic control by insulin and oral antihyperglycemic agent use (abstract 1652-P). Over the 20+ year study period (from 1988-1994 to 1999-2010), the duration of diabetes for those on any insulin increased (13 to 17 years, p<0.0001) compared to that for persons on oral medication (7 to 8 years, p=0.04). In the most recent period (2005 to 2010), Mexican Americans were significantly less likely than whites to receive insulin therapy, after adjustment for potential confounding factors (duration of diabetes, age, gender, BMI, education). Many patients treated with insulin did not meet glucose control target. In addition, HbA1c was higher in Mexican Americans and blacks than in whites. These results suggest improvements are needed in education about or access to insulin formulations in certain ethnic groups, so that they may be able to take advantage of newer, safer insulins and newer, simpler delivery devices. Our systems of care in diabetes need to focus on these critical issues, with particular attention to racial and socioeconomic disparities that remain in glucose control and type(s) of treatment.

Trends in Hospitalization and Health Care Costs for Type 2 Diabetes

Using the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) from 2000 to 2011, Belokovskaya et al. from New York, NY, Philadelphia, PA, and Jersey City, NJ examined trends in the number of hospitalizations and health care costs related to Type 2 diabetes (abstract 1659-P). 14,766,564 admissions of patients ≥18 years of age were analyzed. Overall, hospitalizations of Type 2 diabetes patients increased by 87.2% from 2000 to 2011 and mean cost of these hospitalizations grew from $9,975 to $12,149 respectively (23.4%, p<0.001). The resulting expenditures by the US healthcare system increased by 116.8% from $45 billion to $93 billion. These staggering figures reflect not only increasing prevalence, but also skyrocketing costs.

Intensive Glycemic Treatment Among Elderly Adults with Diabetes

Casagrande et al. from the NIDDK and NIH used cross-sectional data from NHANES to determine the extent to which older adults with diabetes are intensively treated to lower HbA1c levels and whether this practice has changed between 1999 and 2012 (abstract 1678-P). Participants were adults age ≥20 years who self-reported a physician diagnosis of diabetes (n=1,333, NHANES 1999-2004; n=1,128, NHANES 2005-2008; n=1,313, NHANES 2009-2012). They found few differences over time in the prevalence of any antihyperglycemic agent use, regardless of age. Findings from these national data on antihyperglycemic medication use and HbA1c levels do not align with current guidelines that set lifelong as an important factor in setting glycemic targets. Among those with HbA1c < 7.0%, 52.0% of adults age ≥65 and 20.6% of those age 20-49 were taking insulin and/or sulfonylureas. In addition, among adults taking insulin and/or sulfonylureas, mean HbA1c was lower (7.3%) for adults age ≥65 compared to those age 20-49 (8.3%, p<0.001). The investigators concluded that clinicians should carefully consider the risks/benefits of tight glycemic control and intensive medication use in older patients. We might add, however, that the fact that an older individual is treated aggressively does not imply improper care. Current guidelines suggest that age and life expectancy be used as merely one consideration in setting HbA1c goals. In our opinion, if an older individual with diabetes is achieving stringent glycemic control safely and without hypoglycemia, there is no reason to back off on therapy, unless the clinical status changes or if new safety risks emerge. A hidden message of this study could be that younger individuals are, if anything, being undertreated.

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At the first day of the 75th ADA Scientific Sessions an entire symposium was dedicated to “adjunct” therapies for Type 1 diabetes. Each of the presenters acknowledged that despite significant advances in insulin formulations and delivery systems, only 30% of Type 1 patients actually achieve a conservative target HbA1c of <7.5%. Moreover, severe hypoglycemia and diabetic ketoacidosis (DKA) remain too common in this population.

Dr. Kristen Nadeau, Denver, Colorado opened the symposium describing the role of insulin sensitizers in Type 1 diabetes. Very simply, she stated: (1) insulin resistance is frequently present and therefore a concern in patients with Type 1 diabetes; (2) it should be treated; and, (3) there are mounting data to support such interventions. Both youth and adults with Type 1 have reduced insulin sensitivity when matched with non-diabetic controls of similar weight, lipid profile, and activity level. Also, insulin resistance, which has been documented to occur at the levels of muscle, liver, and adipose tissue, conceivably could contribute to at least macro- if not microvascular complications. The mechanisms here are not fully elucidated, but may involve a secondary response to prolonged peripheral exposure to hyperinsulinemia, chronic hyperglycemia, relative lack of delivery of insulin to the portal circulation, or, potentially, impaired glucagon regulation. A current issue in the assessment of insulin resistance is the lack of a practical tool to measure it in the setting of Type 1 diabetes, in which, by definition, there is no endogenous insulin production, obviating the ability to measure insulin levels as a marker. Clinical prediction equations have been developed (e.g., eIS-CACTI from the Coronary Artery Calcification in Type 1 Diabetes Study), revealing that insulin resistance correlates with cardiovascular (CV) risk factors, mortality, and renal health in Type 1 diabetes. Given these data, development of therapies that improve insulin sensitivity for administration with current standards of care (i.e., insulin, diet, and exercise) may be worthwhile. Previous studies have demonstrated that metformin may improve glycemic control (reduced Hba1c and insulin doses) in Type 1 diabetes,* however, the effect appears to be short-lived: it is lessened at six months and absent by one year. Nevertheless, Nadeau shared results of her recent study evaluating the impact of metformin on CVD risk factors in 140 overweight and obese adolescents with Type 1 diabetes (abstract OR-9). After 26 weeks, metformin therapy was associated with a significant decrease from baseline versus placebo in BMI (p<0.001), body fat composition (p=0.04), and total fat mass (p=0.005). She added that longer-term studies are required to determine whether this might have any impact on other CVD risk factors and identified two such trials that are underway. One is EMERALD (Effects of Metformin on Cardiovascular Function in Adolescents with Type 1 Diabetes), and the second is REMOVAL (Reducing with Metformin Vascular Adverse Lesions in Type 1 diabetes). The other known insulin sensitizers are the TZDs. Nadeau shared data from studies involving pioglitazone and rosiglitazone in adolescent Type 1 patients. * Data were not as promising as only small changes in HbA1c were observed with pioglitazone and neither TZD had a beneficial impact on BMI or other CVD risk factors (Bhat R, et al. Diabetes Res Clin Practice, 2007; Stone ML, et al. Ped Diabetes, 2008). Dr. Nadeau concluded that CVD outcomes in Type 1 patients may be partially related to either insulin resistance and/or one of its sequelae, namely increased exogenous insulin exposure. Data, although modest, with metformin warrant further study.

Nitesh Kuhadiya, MD, PhD of SUNY at Buffalo followed with his presentation, Targeting Hyperglucagonemia in Type 1 Diabetes. He acknowledged the concern for insulin resistance and agreed that plausible mechanisms include peripheral administration of insulin that bypasses the normal portal circulation and the liver as well as counter-regulatory hormones that promote...
hyperglycemia. Despite reasonable HbA1c values, many patients with Type 1 diabetes have considerable glycemic excursions with excessive post-prandial glucose fluctuations as well as nocturnal hypoglycemia. Given that glucagon is increased in the postprandial period in patients with Type 1 diabetes and not corrected by exogenous insulin, he proposed that its suppression may be a rational pharmacologic target.

Pramlintide, a synthetic analog of the peptide amylin, suppresses glucagon, slows gastric emptying, and decreases caloric intake. Clinical effects include modest HbA1c lowering, decreased insulin requirements, and modest weight loss. Similarly, the GLP-1 receptor agonists may also be beneficial in this disease, given their similar impact on gastric emptying and hyperglucagonemia. The speaker shared results from a recent prospective study of liraglutide versus placebo in Type 1 diabetes (abstract P-1141). In addition to the anticipated decrease in HbA1c values and reduced insulin doses, therapy with liraglutide 1.8 mg daily for 12 weeks resulted in decreases in glucose variability, carbohydrate intake, gastric emptying, weight, post-prandial glucagon levels, as well as certain inflammatory markers (e.g., C-reactive protein, free fatty acid, and endotoxin). He reiterated that these agents, which are now approved for use only in Type 2 diabetes (or obesity) may help Type 1 patients largely due to this modulation of glucagon exposure after meals and decreased rate of delivery of carbohydrates to the small bowel. Additionally, insulin sensitivity and, as a result, peripheral glucose disposal may be ameliorated by their impact on inflammation.

Finally, Dr. Kuhadiya shared data relative to the DPP-4 inhibitor, sitagliptin, in Type 1 patients (Garg SK, et al. Endocrine Practice 2013). Despite increased GLP-1 levels, sitagliptin had no impact on post-prandial glucagon, although other studies have suggested modest benefits. To summarize, glucagon is a culprit in uncontrolled diabetes and targeting hyperglucagonemia may emerge as an important approach to care. Pramlintide has demonstrated benefits, but requires multiple daily injections and the side effect of nausea limits its utility. The GLP-1 receptor agonists are promising, with liraglutide and exenatide being the most studied.

The third presenter, Dr. Julio Rosenstock, Dallas, TX, closed the symposium with a review of the potential uses of SGLT-2 inhibitors in Type 1 diabetes. He made it very clear to the audience that SGLT-2 inhibitors, which reduce glucose levels in Type 2 diabetes through the induction of glucosuria, are currently not approved by the FDA for use in Type 1 diabetes. (We would reiterate this important point for the aforementioned metformin, TZDs, and GLP-1 receptor agonists.) He also shared that despite advances in insulin therapy, most Type 1 patients are unable to maintain any semblance of normoglycemia with traditional strategies. He then reviewed the pharmacology of SGLT-2 inhibitors and gave the rationale for their use in this disease: (1) their mechanism of action is independent of insulin deficiency, degree of beta-cell dysfunction, or insulin resistance; (2) they have been demonstrated to indirectly enhance insulin sensitivity; and (3) they improve any degree of residual beta-cell function. However, they have also been shown to increase hepatic glucose production as a compensatory mechanism. He then mentioned that there are likely no clinically relevant differences between the currently available SGLT-2 inhibitors, canagliflozin, dapagliflozin, and empagliflozin, each being similar with respect to glycemic outcomes in Type 2 patients in a variety of mixed regimens.

Combination studies with insulin reveal an additional lowering in HbA1c of about 0.6-0.7% when SGLT-2 inhibitors are added to baseline insulin therapy in Type 2 diabetes patients. Patients treated in this manner, not unexpectedly, experience an increase in genital mycotic infections but no apparent difference in UTe rates, no significant impact on hypoglycemia, and no major adverse events associated with the osmotic diuresis that is induced. A recent 2-week pilot study utilizing dapagliflozin in Type 1 diabetes patients (Henry RR, et al Diabetes Care 2015) found that dose-related reductions in glycemic variability occurred as well as decreased insulin requirements (decreased predominantly in mealtime doses, without change in basal). Data from an eight-week open-label trial involving empagliflozin found similar results (Perkins BA, et al Diabetes Care 2014). Patients experience improvements in glycemic variability and decreased insulin doses, modest changes in HbA1c, and increased urinary glucose excretion rates, similar to that seen in Type 2 patients. Dual SGLT-1/SGLT-2 inhibitors are investigational agents that block both transporters in the kidney and the former in the gut. This leads to not only an increase urinary glucose but also a decrease in the absorption of sugars. Preliminary data in Type 1 diabetes appear promising with these compounds. There are currently multiple randomized controlled trials on-going evaluating both SGLT-2 and dual SGLT inhibitors in Type 1 diabetes."

Lastly, Dr. Rosenstock reminded the audience of an emerging new concern with these agents, “euglycemic DKA”, which was the subject of a recent FDA Safety Alert (5/15/15). To date, there have been about 20 cases reported and, despite the lack of an FDA-labeled indication, the majority of cases have been in Type 1 patients during off-label use. The most common precipitating factor is a recent decrease in insulin dose following SGLT-2 administration. Rosenstock shared his working hypothesis why this likely occurs (Figure 5) and strongly emphasized the need to recognize the potential for the risk and educate patients. Specifically, if a patient is not feeling well, despite a normal blood glucose, urine ketones should be checked. Accordingly, great caution is advised in the development of these drugs for use in Type 1 diabetes.

Although these emerging concepts are interesting, we remind our readers that insulin, diet, and healthy lifestyle remain the mainstay of Type 1 diabetes treatment.
Cost is fast becoming one of the biggest considerations in choosing a medication regimen for patients. This is particularly true in diabetes since insulin prices have been steadily increasing, especially over the past decade.

Ir! Hirsch, MD, from Washington, began his talk titled “Changing Costs of Insulin Therapy in the US” during the symposium Costs of Medications for Diabetes by tracing the cost of insulin since its discovery in 1921. Interestingly, Drs. Fred Banting and Charles Best sold the patent for insulin for just $1.00. In the 1960s, purified extract of pig and cow pancreas were marketed at less than $1.00/vial, increasing to $1.50-3.00 in the 1970s. It was with the introduction of synthetic human insulin (Humulin®) in 1982 that the first dramatic increase in price was noted. In 1996, the second analog insulin (lispro) was released and was marketed at $24.00/vial. Five years later, aspart insulin was introduced. At that time, aspart and lispro were sold at $35.00/vial, while Humulin® R was $20.00/vial.

In 2005 an estimated $7.3 billion was spent globally for insulin due to increasing prevalence of diabetes, increasing cost of medication, and increasing use of insulin analogs. Over the past five years, 30 branded drugs have been identified to have doubled in price. Half of the top six drugs are insulins. Humulin U-500 increased by 325%, while Levemir and Lantus increased by 169% and 168%, respectively. Considering a 20.9% cumulative inflation rate over the past decade, the dramatic price increases of insulin are striking (Table 2).

Table 2. Percent Increase in Insulin Price from 2005 to 2015

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Percent Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro</td>
<td>264%</td>
</tr>
<tr>
<td>Aspart</td>
<td>389%</td>
</tr>
<tr>
<td>Glargine</td>
<td>348%</td>
</tr>
<tr>
<td>NPH</td>
<td>364%</td>
</tr>
<tr>
<td>U-500</td>
<td>508%</td>
</tr>
</tbody>
</table>

Dr. Hirsch also noted a great discrepancy between drug prices in the US compared to other parts of the world. For example, North America accounts for 7% of the prevalence of diabetes in the world, while it is responsible for 52% of the total cost of sales for insulin. On the other hand, China accounts for 25% of diabetes prevalence and only 4% of the total cost for insulin. He also compared the price of Lantus® and Humalog® among different countries (Table 3).

Table 3. Cost of One Vial of Lantus® and Humalog® in Various Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost of Lantus®</th>
<th>Cost of Humalog®</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>$386</td>
<td>$405</td>
</tr>
<tr>
<td>Spain</td>
<td>$81</td>
<td>$53</td>
</tr>
<tr>
<td>Argentina</td>
<td>$286</td>
<td>$148</td>
</tr>
<tr>
<td>Germany</td>
<td>$102</td>
<td>$78</td>
</tr>
</tbody>
</table>

The New England Comparative Effectiveness Public Advisory Council, a program of the Institute for Clinical and Economic Review, estimates that 80% of Type 2 diabetes patients requiring insulin use a basal insulin analogue. Switching half of these patients to NPH would result in savings of $100 million. Dr. Hirsch added that NPH is highly under-utilized and encouraged more teaching regarding its use to primary care providers, students, residents, and fellows.

Hirsch pointed out that, although the costs of developing synthetic insulin were paid years ago, their prices continue to increase. With the mission of nearly all insulin manufacturers being to help patients and cure diabetes as stated in their websites, it would be ideal that a portion of their profits be allocated toward improving global access to insulin as well as further research and development. The Access to Medicine Index ranked pharmaceutical companies with respect to their efforts to improve access to medicine in developing countries. Three insulin manufacturers—Novo Nordisk, Sanofi, and Eli Lilly—were actually in the top 20.

Biosimilar Insulins

Biosimilar insulins were discussed by the final speaker, Lutz Heinemann, PhD, from Germany. Biosimilar agents are approved copies of already marketed biological medications that have lost patent protection—similar to generic formulations of ordinary medications. The FDA, however, places a much higher bar in the regulatory approval process for these agents than conventional generics, which merely need to demonstrate equal pharmacokinetic properties to branded products. Abasaglar® by Eli Lilly is the first biosimilar insulin (a version of insulin glargine, now sold solely as Lantus®) and has already received market approval in Europe.

Along with increased availability of biosimilar agents that are offered at a lower cost comes the need for global regulatory standards. Unfortunately, while there are several prevailing guidelines regarding biosimilar agents, none are specific to insulin.

Compared to the cost of generic drugs, which are typically discounted by 40-50%, and in some instances up to 80%, biosimilar medications have traditionally been only 25 to 40%, at times even only 15%, less expensive than the original branded product. The pricing structure for abasaglar has not yet been released.

The savings offered by biosimilar insulin must, however, be taken in the proper context. Dr. Heinemann outlined several possible challenges with this new approach. Agents from different manufacturers with subtle differences in bioavailability and/or pharmacodynamic properties may be viewed as interchangeable by insurers, and substitutions may occur at the pharmacy level without the prescriber’s knowledge. So, insurance companies may compel switching between various biosimilars once available—similar to what frequently occurs these days with test strips. A larger variety in available biosimilar insulins may also be accompanied by greater variability in delivery devices. This may result in the need for more time and effort on the part of practices to teach patients. It could also lead to some degree of patient confusion. Lastly, high investments in regulatory approval and possible narrower profit margins pose the question about willingness of manufacturers to invest in research for development of new drugs and new technology.

While “bioinsulin™” may increase the affordability of insulin for diabetic patients, it may add complexity to our practices. For now, the quest to provide the best affordable care for our patients with diabetes continues.

We conclude by noting that it is difficult to evaluate cost of medications without considering the total cost of care. In some circumstances, the expense of drugs can be more than offset, if they demonstrate increased efficacy and/or safety. In this context, future research must delineate the value-added of newer formulations of insulins as well as other medications for diabetes.
In the Joint ADA/American Society of Nephrology (ASN) Symposium *A New Day for Diabetic Kidney Disease*, Mohammed K. Ali, from Emory University in Atlanta discussed the successes and challenges in treating chronic kidney disease (CKD). The prevalence of CKD in the US is 13.6%, with the great majority being Stage III, i.e., with a glomerular filtration rate (GFR) of 30-59 mL/min. Not surprisingly, diabetes and hypertension are the leading causes of CKD, accounting for 44% and 28% of cases, respectively. On the global scale, this changes a bit, with diabetes being the most common etiology in first world countries and ‘unknown’ causes in the third world. Ali proceeded to enumerate common factors among hypertension, diabetes, and CKD that may be potential targets for both pharmacologic and non-pharmacologic treatment in an effort to prevent long-term complications of these chronic diseases (Figure 6).

The speaker discussed recent successes in the field of CKD. Over the past decade, increased attention has been given to kidney disease as not just a subject of research, but also a topic in the mainstream media. There is now also increased federal surveillance efforts and establishment of standards in management of the disease (Table 4). Furthermore, there has been improvement in testing and risk factor control as shown by numerous studies in patients with diabetes, resulting in better HbA1c levels, blood pressure, LDL-cholesterol, and smoking cessation rates. An increasing trend in the use of ACEi and ARBs for renal protection has also been observed. However, while the frequency of urine testing as part of screening for CKD is increasing, this trend was unfortunately only seen in diabetic patients, highlighting the lower likelihood of screening and early diagnosis in the non-diabetic population. The biggest hallmark of success over the past several years has been that the progression of renal complications from diabetes, which ultimately lead to end-stage renal disease (ESRD), has declined.

Over the past several years, improvements in mortality and other key outcomes have also been documented. For example, diabetic patients with ESRD who are undergoing dialysis or who had transplants now have survival rates approaching those in patients with normal kidney function. Furthermore, there has been a decline in all-cause hospitalizations, especially for infection and cardiovascular diseases. Likewise, re-hospitalization rates have been reduced.

Ali then discussed challenges facing the field of CKD. While there is increasing awareness of the role of diabetes in the development of renal dysfunction, the role of prediabetes has not been emphasized. Given that 86 million people in the US have prediabetes, many of whom will progress to diabetes, this is a large group potentially at risk for developing future CKD. Also, despite increasing awareness of CKD nationally, there still is an apparent lack of attention for it on a global level. The absolute burden, especially in third world countries, remains on the rise. Back in the US, unfortunately, as with many other diseases, a disparity in the response to treatment and risk for kidney failure has been demonstrated among ethnic groups. For example, while African Americans comprise 13% of the US population, they account for 32% of dialysis patients due to kidney failure. This translates to an over three-fold higher kidney failure rate compared to that of Caucasians. Possible etiologies for this imbalance include less access to care and a higher prevalence of and more poorly controlled hypertension. Some investigators have also measured a greater degree of endothelial dysfunction in African Americans.

Markers of CKD were then reviewed. Spot urine albumin/creatinine ratio, 24-hour urine albumin excretion, and estimated (e)GFR each has its limitations, but all three markers independently predict progression of CKD as well as mortality. The speaker highlighted that doubling of creatinine is equivalent to a 50% loss of kidney function, which, impressively, then translates to a 99% risk of ESRD in the next 10 years. However, GFR is often estimated rather than measured, which thus raises the question of accuracy. Equations calculating GFR are tailored more for advanced CKD and may yield varying results due to differences in reference ranges across

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Yearly measurement of creatinine, urinary albumin excretion, potassium</td>
</tr>
<tr>
<td>45–60</td>
<td>Referral to a nephrologist if the possibility for nondiabetic kidney disease exists (duration of Type 1 diabetes &lt;10 years, heavy proteinuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in GFR, or active urinary sediment)</td>
</tr>
<tr>
<td></td>
<td>Consider the need for dose adjustment of medications</td>
</tr>
<tr>
<td></td>
<td>Monitor eGFR every 6 months</td>
</tr>
<tr>
<td></td>
<td>Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone at least yearly</td>
</tr>
<tr>
<td></td>
<td>Assure vitamin D sufficiency</td>
</tr>
<tr>
<td></td>
<td>Consider bone density testing</td>
</tr>
<tr>
<td></td>
<td>Referral for dietary counseling</td>
</tr>
<tr>
<td>30–44</td>
<td>Monitor eGFR every 3 months</td>
</tr>
<tr>
<td></td>
<td>Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, weight every 3–6 months</td>
</tr>
<tr>
<td></td>
<td>Consider the need for dose adjustment of medications</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Referral to a nephrologist</td>
</tr>
</tbody>
</table>

Table 4. Management of CKD in Diabetes

measurement methods. Moreover, calculated GFRs may not be accurate across all ethnic groups.

Measurement of urinary albumin has its pitfalls as well. For example a decline in GFR may occur in up to 50% of patients with diabetes, even in the absence of albuminuria. There is also lack of precision in measurement due to intra- and inter-individual variation and non-standardized collection methods. Obviously, the use of a combination of GFR (Table 5) and urine albumin as indicators of CKD, as advocated by the National Kidney Foundation (NKF)’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, would increase accuracy. He also briefly mentioned cystatin C, a low molecular weight protein freely filtered in the kidney, which is much less influenced by age, gender, and size. It has a potential for predicting GFR with greater accuracy and has gained popularity in nephrology circles. Studies to determine its optimal mainstream use are currently underway.

All ended his portion of the symposium by calling for increased advocacy and attention for CKD, especially in the context of the disease.

### Mother and Child

In a well-attended symposium, John Kitzmiller, MD, MS from Santa Clara Valley Health Centers discussed the controversies over diagnostic criteria for gestational diabetes mellitus (GDM). The goal of diagnosing GDM is to effectively prevent fetal complications as a result of maternal hyperglycemia. These include large-for-gestational-age (LGA), shoulder dystocia, and neonatal hypoglycemia. Ever since John O’Sullivan published the first evidence-based criteria in 1964, subsequent criteria such as those of Carpenter and Coustan in 1982 and most recently the International Association of Diabetes and Pregnancy Study Group (IADPSG) in 2010 have tightened the glycemic thresholds for diagnosis to further reduce fetal sequelae (Table 6). The IADPSG criteria are based on evidence from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which found a continuum in the relationship between elevated maternal blood glucose and adverse pregnancy outcomes. Hence, determining a specific glucose threshold became more or less arbitrary. The IADPSG criteria were controversial in selection of glucose exposure associated with a 75% increased odds (1.75 OR) of having LGA babies, among other complications. The IADPSG criteria were also based on the routine 2-hour 75-gm glucose challenge used for diagnosis of diabetes in other settings, and abandoned both the need for a 3-hour glucose measurement as well as the initial screen with the 1-hour glucose challenge test (GCT). That is, the IADPSG protocol involves just one step.

Since release of the IADPSG criteria, which became adopted by the ADA but rejected by the American College of Obstetrics and Gynecology, several prospective studies have demonstrated that the new and lower thresholds significantly increased the prevalence of GDM by up to three-fold in many communities, as compared to the prevailing traditional criteria. However, treating to the stricter criteria also reduced the incidence of LGA by up to 20%. Initial analyses also indicate a potential for cost savings using the new criteria, although more studies need to be done.

In a related abstract, Anny Xiang, PhD and colleagues found that the small increase in maternal obesity during pregnancy, even when corrected for age and the impact of metabolic programming that involves more than glucose levels. Dr. Denice Feig and colleagues found that women who delivered three to four deliveries had a higher risk of developing diabetes compared to nulliparous women, adjusted HR 1.34 (95% CI 1.26-1.43) and 1.75 (1.55-1.98), respectively. Their study population of 283,023 women over a nine-year period in Ontario, Canada enabled analysis by ethnic group too, and the influence of parity was greatest in women of Chinese ethnicity. It remains to be determined whether this relationship is due to increased weight gain and retention of weight, or deterioration in beta cell function.

Studies such as these expand our knowledge of the delicate interplay between maternal diabetes, fetal health, and long-term outcomes for both mother and child.

### Table 5. Stages of CKD

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

*Kidney damage is defined as abnormalities on pathological, urine, blood, or imaging tests.

### Table 6. Comparison of Criteria for Diagnosing Gestational Diabetes

**Carpenter & Coustan, 1982**

<table>
<thead>
<tr>
<th>Criteria based on:</th>
<th>100g GTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose, mg/dL</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>1-Hour Glucose, mg/dL</td>
<td>&gt; 180</td>
</tr>
<tr>
<td>2-Hour Glucose, mg/dL</td>
<td>&gt; 155</td>
</tr>
<tr>
<td>3-Hour Glucose, mg/dL</td>
<td>&gt; 140</td>
</tr>
</tbody>
</table>

**IADPSG, 2010**

<table>
<thead>
<tr>
<th>Criteria based on:</th>
<th>75 g GTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose, mg/dL</td>
<td>≥ 92</td>
</tr>
<tr>
<td>1-Hour Glucose, mg/dL</td>
<td>≥ 180</td>
</tr>
<tr>
<td>2-Hour Glucose, mg/dL</td>
<td>≥ 153</td>
</tr>
<tr>
<td>3-Hour Glucose, mg/dL</td>
<td>Not necessary</td>
</tr>
</tbody>
</table>

†Diabetes Care 2010; 33(3):676-82.

* The product is not labeled for the use under discussion or the product is still investigational.
The FDA approved the first sodium glucose co-transporter (SGLT)-2 inhibitor just two years ago for the management of Type 2 diabetes, with an additional year of experience in Europe. There are now three molecular entities in this class, multiple combination products, and a growing body of research defining their optimal use. Additionally, dual SGLT-1 and SGLT-2 inhibitors are under investigation as well for their potential use in Type 1 diabetes. A significant number of the presentations at the 75th Scientific Sessions was devoted to this evolving drug class.

These oral agents promote urinary excretion of glucose via inhibition of SGLT-2 in the proximal renal nephron (Figure 7), resulting in a reduction of glucose reabsorption and a lowering of the renal threshold for glucose excretion. SGLT-1 is additionally expressed in the gastrointestinal (GI) tract and allows for glucose absorption. Because of the history of phlorizin (an older non-selective dual inhibitor of each transporter) and its intense GI side effects, clinical utility of inhibiting SGLT-1 alone has not been aggressively pursued. However, partial inhibition of SGLT-1 has limited GI toxicity and, when used in combination with SGLT-2 inhibition, may provide further actions beyond those observed with sole inhibition of either transporter alone.

John Buse, MD, PhD, Chapel Hill, NC presented data on behalf of co-investigators from a phase 2 trial with the dual SGLT-1 and SGLT-2 inhibitor, sotagliflozin,* in a Saturday morning session devoted to novel clinical interventions in diabetes management. Patients with Type 1 diabetes (n=33; HbA1c 7-9%) were randomized to receive sotagliflozin 400 mg daily or placebo for 29 days. The primary endpoint was change in mealtime insulin dosing from baseline. Secondary endpoints included glycemic control and metabolic parameters. Bolus insulin dosing significantly decreased (-32% vs. -6.4%, p=0.007) in the sotagliflozin group versus placebo from baseline to day 29. Secondary endpoints that were statistically significant and favoring sotagliflozin (versus placebo) include: HbA1c (-0.55% vs. -0.06%, p=0.002),

* DKA appears to occur when initiation of the drug leads to a significant drop in the insulin dose, although effects on glucagon dynamics may also play a facilitatory role (refer to “Non-Insulin Adjunct Therapy in Type 1 Diabetes”, Issue 2, page 9).

Figure 7. Normal Glucose Handling by the Kidney

<table>
<thead>
<tr>
<th>Collecting Duct</th>
<th>SGLT1</th>
<th>SGLT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>~90%</td>
<td>~10%</td>
</tr>
<tr>
<td>No Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 segment of proximal tubule</td>
<td>SGLT1 expression</td>
<td>SGLT2 expression</td>
</tr>
<tr>
<td>Distal S2/S3 segment of proximal tubule</td>
<td>Glucose reabsorption</td>
<td>-10% reabsorption</td>
</tr>
<tr>
<td>-90% reabsorption</td>
<td>Glucose</td>
<td>No Glucose</td>
</tr>
</tbody>
</table>
An entire symposium dedicated to the SGLT-2 inhibitors addressed several facets of these medications: (1) intra-class comparison; (2) impact on sodium balance and blood pressure; (3) optimal patient selection; and (4) non-glycemic effects.

Dr. Robert Henry, San Diego, California reviewed “Similarities and Differences Between SGLT-2 Blockers”. There are three commercially available drugs in the US—canagliflozin, dapagliflozin, and empagliflozin. Canagliflozin, at doses of 300 mg or greater, also has affinity for SGLT-1. Whether this translates into meaningful clinical benefits, by inhibiting GI glucose absorption relative to the others, remains to be determined. There are currently no head-to-head trials comparing the three medications in the management of Type 2 diabetes. Henry proceeded with identifying commonalities of the three with respect to outcomes: HbA1c lowering ranging from 0.5-1.0% and consistent weight loss (on average, about 3% of total body weight, with 1/3 of weight loss from lean mass and 2/3 fat mass) that appears reasonably durable (based on a two-year dapagliflozin trial). Each consistently lowers systolic blood pressure ranging from 4-6 mm Hg. Each is associated with decreases in eGFR initially and, over time, rates then stabilize and return to normal upon drug discontinuation, suggesting that this effect relates to volume contraction. Adverse events are also relatively consistent between the three, with urogenital infections a concern. Other considerations include glycemic efficacy in the setting of renal impairment, unknown effects on cardiovascular outcomes, the possibility of fracture risk due to urinary calcium losses, and osteopenia.

Given the osmotic diuresis observed with SGLT-2 inhibitors, George Bakris, MD of Chicago, Illinois presented “Effects of Sodium Balance and Hypertension”. He reviewed the pathophysiology of hypertension along with the known pharmacologic actions and data associated with the SGLT-2 inhibitors. Natriuretic effects occur only acutely with minimal effects chronically. The natriuretic effects are equivalent to ~ 4 mg of hydrochlorothiazide. Osmotic diuresis does not explain sustained blood pressure lowering. One explanation is the concept that these drugs may work through tubuloglomerular feedback—a mechanism of the kidney to preserve blood volume by increasing afferent glomerular arteriole tone when extra sodium is delivered to the distal convoluted tubule and macula densa (as occurs when SGLT-2 is inhibited proximally). Dr. Bakris closed his presentation with the acknowledgment that the precise mechanism of action of blood pressure lowering is not fully elucidated, despite speculation.

Another intriguing aspect of these drugs is their potential ability to affect the progression of diabetic nephropathy. In a poster presentation, researchers Heerspink et al. from the Netherlands and Sweden characterized the impact of dapagliflozin on albuminuria (assessed via albumin:creatinine ratio [ACR]) and eGFR in a pooled data analysis from two placebo controlled trials in Type 2 diabetes patients with micro- or macro-albuminuria and hypertension stabilized on ACEi or ARB therapy (abstract 1176-P). Dapagliflozin 5 mg and 10 mg doses each substantially reduced ACR in comparison with placebo even after adjusting for changes in HbA1c, systolic blood pressure, and eGFR (adjusted % change from baseline: dapagliflozin 10 mg [-45.8, 95% CI: -53.1,-37.3], dapagliflozin 5 mg [-47.4, 95% CI: -57.3,-35.3], and placebo [-18.9, 95% CI: -29.5, -6.7]). Dapagliflozin was also associated with a decrease in eGFR in comparison with placebo, however, this was readily reversed within one week after the last dose. No serious renal-related adverse events were reported and a minority of patients (<2.5%) in the dapagliflozin and placebo groups had increases in serum creatinine ≥1.5 x baseline or potassium ≥6 mEq/L. From this initial analysis, the investigators determined that dapagliflozin decreases ACR in patients with Type 2 diabetes and hypertension maintained on renin-angiotensin system blockade without stimulating an increase in renal adverse events. Whether this will have any impact on long-term renal outcomes is unknown, however.

The aforementioned concept of tubuloglomerular feedback was also addressed by Dr. Matthew Weir, Baltimore, Maryland during an oral presentation (abstract 107-OR) in which he described an initial rapid decrease in GFR on the order of 5-10% in study participants assigned to canagliflozin therapy (100, 300 mg/day), but with subsequent stabilization. In the comparator group, however, which was administered glimepiride, a slow but progressive decline in renal function was measured, such that by the end of two years loss of GFR was greater in the sulfonylurea patients. Statistical comparisons, however, were not provided.

In a related study, Cherney and international colleagues evaluated the influence of renal function on blood pressure and HbA1c lowering by another SGLT-2 inhibitor, empagliflozin, using pooled data from five placebo-controlled trials (n=2286 Type 2 diabetes patients) (abstract 1177-P). Changes from baseline in systolic blood pressure and HbA1c were assessed as a function of renal status. HbA1c values decreased with declining eGFR whereas decreases in systolic blood pressures were maintained even in patients with lower eGFR. This suggests that blood pressure modulation may involve mechanisms beyond urinary glucose excretion such as diuretic effects, weight loss, reduced arterial stiffness, or direct vascular effects.

Dr. Vincent Woo, Winnipeg, Manitoba, addressed the question “Which Patients Might Benefit Most?” He declared that no one individual patient population has been identified as that which might benefit more from SGLT-2 inhibition. He reviewed the positioning of the SGLT-2s in current consensus guidelines, agreeing that metformin remains the first drug of choice with patient factors determining sequential add-on therapy. However, Woo made the case for early intensive lowering with the SGLT-2s given their HbA1c lowering efficacy, potential for weight loss,” reasonable side effect profiles, and potential for long-term benefits (e.g., blood pressure lowering). He also identified the following patterns in outcomes identified in clinical trials: (1) HbA1c lowering is not impacted by baseline BMI; (2) weight loss is not dependent on baseline HbA1c; (3) those with higher HbA1c values experience more significant blood pressure lowering; and (4) patients with higher baseline BMI do not experience the magnitude of blood pressure lowering that those with lower BMI do. Subgroups that may experience a greater glycemic benefit based on pooled data analysis include: those with higher baseline HbA1c (consistent with other glucose-lowering drugs) and higher eGFR and, to lesser extent, those younger in age and with a higher BMI. Possible indications for these drugs, pending confirmatory clinical trial data, include: pre-diabetes, Type 1 diabetes, obesity (in combination with either GLP-1 receptor agonists or phentermine), and prevention/treatment of diabetic nephropathy.” Woo concluded that another benefit of the SGLT-2 inhibitors is their utility throughout the continuum of Type 2 diabetes, irrespective of insulin secretory capacity.

Triple therapy involving dapagliflozin, saxagliptin, and metformin was evaluated in two “mirror image” trials. In the first conducted by Mattheai and international co-investigators, saxagliptin was assessed as add-on therapy to dapagliflozin and metformin in Type 2 patients (abstract 104-OR). In the second, Mattheai et al. evaluated dapagliflozin as add-on to saxagliptin-metformin (abstract 105-OR). Both trials demonstrated statistical improvements in glycemic control when the third oral agent was added to the regimen, with low rates of hypoglycemia. Interestingly, however, when dapagliflozin was the third agent added, a greater effect on HbA1c relative to placebo was seen (Table 7). In fact, previous trials have shown a relatively disappointing decrease in HbA1c (on the order of 0.3-0.4%) when a DPP-4 inhibitor is added to an SGLT-2-inhibitor. Clearly the combined benefit of using these drugs together,

**Diabetes 2015**

*75th Annual Scientific Sessions of the American Diabetes Association* ■ Boston, MA ■ Volume 31 ■ June 8, 2015
which do have complementary mechanisms of action, is driven primarily by the glucosuric agent. Treatment arms with dapagliflozin were also associated with higher rates of genital infections and UTIs. Of course, comparisons between trials cannot easily be made given entirely different patients with varying baseline characteristics.

Finally, risks and potential benefits of the SGLT-2 inhibitors were explored by Richard Gilbert, MD, PhD, Toronto, Ontario in his presentation “Nonglycemic Effects of SGLT-2 Inhibition—Long Term Risks vs. Potential Benefits”. As described earlier, the SGLT-2 inhibitors generally decrease eGFR initially, but over time eGFR returns to baseline. The potential for long-term renal protection reminiscent of captopril is currently under investigation in multiple clinical trials.” As mentioned it is hypothesized that tubulo-glomerular feedback may ultimately decrease intraglomerular pressure to offer protection against renal injury.

Another interesting area of investigation is SGLT-2 inhibitor-induced reduction in plasma urate levels as a therapeutic initiative in the management of chronic kidney disease.” Preliminary data suggest that allopurinol-mediated decreases in uric acid may slow progression of CKD. Thus, this may be a potential niche for SGLT-2 inhibitors.

As with all classes of antihyperglycemic drugs, long-term cardiovascular benefits or risks are of interest. Preliminary data suggest changes in plasma volume with dapagliflozin may decrease preload, benefitting patients with heart failure.” Along this line of thinking, Kosiborod and colleagues (US and Sweden) conducted a pooled data analysis of five clinical placebo-controlled clinical trials (abstract 1211-P). The researchers hypothesized that SGLT-2 inhibitors may be uniquely suited as antihyperglycemic drugs for the growing number of patients with heart failure and diabetes given the osmotic diuresis they induce and their weight loss and blood pressure lowering effects. Clinically meaningful placebo-adjusted decreases in HbA1c (-0.55%, 95% CI: -0.80, -0.30), weight (-2.67 kg, 95% CI: -3.88, -1.47), and systolic blood pressure (-21 mm Hg, 95% CI: -5.68, 1.57) were observed in the dapagliflozin-treated patients over the course of one year. There were no changes in heart rate in either group, and rates of orthostatic hypotension, syncope, and hypoglycemia were similar. Given these positive pilot observations in this patient population, the investigators suggested that prospective studies in heart failure patients with Type 2 diabetes are warranted. Speculating, if this drug class was found to have a benefit on heart failure outcomes, this could allow clinicians to better tailor or personalize therapy for Type 2 diabetes (see Issue 1, page 3, “Management of Hyperglycemia in Type 2 Diabetes”). Gilbert shared that in a small (n=16), unpublished clinical trial, hospitalization for heart failure was reduced by 40% (HR 0.6) in the setting of empagliflozin. The EMPA-REG OUTCOME trial results detailing cardiovascular outcomes with empagliflozin will be presented at the 2015 EASD meeting in Stockholm, Sweden. The SGLT-2 inhibitors are a unique class of antihyperglycemic compounds, the precise pharmacology of which is not fully understood. At this early stage, their effect on risk markers for both cardiovascular and renal diseases are provocative. Possible side effects include genitourinary infections, polyuria, orthostasis, and small increases in LDL-cholesterol. As with any new pharmacological class, caution is advised for judicious use until full data sets of mid- and long-term outcomes are available.

### Table 7. Two Clinical Trials Evaluating Triple Therapy in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Endpoint at 24 Weeks</th>
<th>Saxagliptin as Add-On to Dapagliflozin and Metformin (abstract 104-OR)</th>
<th>Dapagliflozin as Add-On to Saxagliptin and Metformin (abstract 105-OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saxagliptin + Dapagliflozin + Metformin (n=153)</td>
<td>Dapagliflozin + Saxagliptin + Metformin (n=160)</td>
</tr>
<tr>
<td></td>
<td>Placebo + Dapagliflozin + Metformin (n=162)</td>
<td>Placebo + Saxagliptin + Metformin (n=160)</td>
</tr>
<tr>
<td>Baseline HbA1c, %, Mean (SD)</td>
<td>8.1 (7.0)</td>
<td>8.24 (0.97)</td>
</tr>
<tr>
<td></td>
<td>-0.35 (-0.52, -0.18), p &lt; 0.0001</td>
<td>-0.72 (-0.91, -0.53), p &lt; 0.0001</td>
</tr>
<tr>
<td>FPG, mg/dL, mean difference (95% CI) versus placebo</td>
<td>-4 (-11.0, 3.6), p = 0.32</td>
<td>-28 (-35.4, -19.6), p &lt; 0.0001</td>
</tr>
<tr>
<td>2-hr PPG, mg/dL, mean difference (95% CI) versus placebo</td>
<td>-6 (-14.9, 3.1), p = 0.20</td>
<td>-36 (-46.3, -24.7), p &lt; 0.0001</td>
</tr>
<tr>
<td>Body weight, kg, mean difference (95% CI) versus placebo</td>
<td>Not reported</td>
<td>-1.5 (-2.12, -0.89), p &lt; 0.0001</td>
</tr>
<tr>
<td>(%) Patients with HbA1C &lt; 7%, mean difference % (95% CI) versus placebo</td>
<td>12 (3.4, 2.10), p = 0.0068</td>
<td>26 (16.7, 34.4), p &lt; 0.0001</td>
</tr>
</tbody>
</table>

### mHealth and Diabetes Management

Dr. Robert Istepanian, of Imperial College, London, UK, spoke at a plenary session today about “Mobile Applications (Apps) for Diabetes Management—Challenges and Efficacy Issues”. Istepanian is a pioneer in the field, having coined the term “mHealth”, which he defined as “emerging mobile communications and network technologies for healthcare”.

The speaker characterized mHealth as a “lucrative market”, a $1.3 billion industry today and projected to be $20 billion by 2018. In 2014, 19% of US adults downloaded and used at least one mobile health app. With regard to diabetes, there are currently ~1,100 apps (e.g., supporting blood glucose monitoring, diet and carbohydrate management, insulin/medication administration, education), with the largest growth in the areas of continuous glucose monitoring (CGM) and support for patients using an insulin pump. According to healthline.com, in 2014, the most popular diabetes apps for the iPhone were: Fooducate, Glooko, Diabetic Connect, Glucose Buddy, Diabetes App, dbees.com, Diabetes Pilot, and WaveSense Diabetes Manager.

According to Istepanian, clinical evidence to confirm the value of mHealth on outcomes of diabetes patients is ambiguous and debatable. In a Cochrane review of 16 studies of self-management interventions for Type 2 diabetes, including internet-based interventions that could be used from home and mobile phone-based interventions, small benefits on glycemic control were observed (pooled effect on HbA1c: -0.2%, 2637 participants; 11 trials) (Cochrane Database Syst Rev. 2013 Mar 28;3:CD008776). He stressed the need for randomized, controlled trials to validate the benefit(s) of such apps. In the absence of such data, the speaker advised the cautious use of apps for diabetes care, noting that security/privacy features among others require further consideration and refinements.
Stuart Weinzimer, MD from Yale began the Joint ADA/JDRF Symposium on “closed-loop” technology in youth by illustrating an actual closed loop system, which is an integration of a subcutaneous CGM that reads interstitial glucose (which, in steady state, usually correlates well with blood glucose), an insulin pump, and a controller device that communicates to the insulin pump the dose of bolus and basal insulin to be administered based on data gathered by the CGM (Figure 8). Developing such a system is quite challenging, but even more so for the pediatric population. Insulin sensitivity varies greatly among pediatric patients, with the younger children being very insulin sensitive, while adolescents are more insulin resistant. Activity levels in children are also quite variable, and insulin sensitivity during and after exercise may vary. Furthermore, children often have unpredictable schedules when it comes to physical activity. Likewise, meals, as well as meal patterns, can also be highly unpredictable. The pediatric population, as a result of such variability, is generally more susceptible to hypoglycemia and may be at higher risk to its adverse neurological consequences. The relatively small surface area of younger children also poses a challenge in developing devices.

With advances toward making a fully closed-loop system comes increased automation and system complexity. Early data revealed good glycemic control overnight. However, wide excursions during meal time occurred because automated insulin was too late to blunt postprandial spikes, demonstrating the need for manual anticipatory prandial dosing of insulin. Next came the development of a system that automatically suspends insulin delivery upon reaching a threshold low interstitial glucose level. This was followed by more complex modifications such as a “predictive suspend” function, then a hybrid closed-loop during either the day or night, and finally a full, integrated, closed-loop.

The predictive glucose suspend feature suspends insulin delivery before hypoglycemia ensues based on the trend of previously detected interstitial glucose readings. This was initially tested in children and was found to decrease episodes of overnight hypoglycemia. An overnight closed-loop hybrid in the home setting demonstrated a significant reduction in variance and hypoglycemia in two studies involving 65 subjects (overnight) and 15 subjects (4 nights). An overnight closed-loop camp study was also conducted, involving 20 subjects over five to six nights, and demonstrated a significant reduction in hypoglycemia and increased time in the target glucose range. Similar findings were noted in the longest study using overnight closed-loop in 16 adolescents monitored over three weeks. The development of a full day/night hybrid closed-loop followed. Initial studies in 10 subjects over six days and nights demonstrated glyemic control equivalent to routine patient-driven use of the latest Medtronic pump (530G) with its threshold suspend feature turned on. Subsequent studies to date have shown a reduction in glycemic variability and increased time in target range.

It is worth mentioning that studies in adults are also underway. Overnight closed-loop control in adults aiming for tight glycemic control every morning in an effort to ‘reset’ the patient to normoglycemia prior to waking up led to an improvement in overnight and daytime glycemic control, as well as avoidance of hypoglycemia in a multicenter study by Brown and colleagues (224-OR).

Advances in the “bionic pancreas” was then discussed by Dr. Edward Damiano from Boston University in Massachusetts. In contrast to previously discussed systems that utilize conventional pumps administering only insulin, the bionic pancreas is bihormonal and infuses both insulin and glucagon. The bionic pancreas utilizes a Dexcom G4® transmitter and G4AP receiver, an Apple iPhone®, and two Tandem T-slim® pumps, one containing insulin and the other containing glucagon. The only variable provided is the body weight of the patient. The system subsequently adapts to the weight and delivers the optimal insulin or glucagon dose based on reported glucose levels. The use of the bionic pancreas demonstrated a reduction in mean glucose and increased time in target range, using similar total daily insulin doses (TDD) in the 2013 Bionic Pancreas Summer Camp study of teens, 2014 Bionic Pancreas Summer Camp Study of preteens (abstract 222-OR), and a home study in adult subjects (Table 8).

Damiano emphasized that the above studies in both adults and adolescents demonstrate that timing and distribution of insulin delivery is as important as the actual dose given. Similar total daily doses of insulin were used in the bionic pancreas group and control group in all the studies. However, there was a remarkable difference in mean glucose and time in target range. The decreased glycemic variability in the bionic pancreas is likely due to refinement in the timing of insulin administration.

The results of initial trials regarding variations of a closed-loop system as well as the bionic pancreas are all certainly very promising. While they demonstrate effectiveness across the board, they are currently all short-term and involve small study populations. Larger-scale and longer duration studies are still needed to demonstrate safety and effectiveness in order to obtain regulatory approval and increase availability for mainstream use in our diabetic patients. Nonetheless, we have been impressed by the enormous progress in this area over the past five years.

### Table 8. Comparison Between Bionic Pancreas and Insulin Pump Therapy

<table>
<thead>
<tr>
<th>2013 Bionic Pancreas</th>
<th>2014 Bionic Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summer Camp</td>
<td>Summer Camp</td>
</tr>
<tr>
<td>n = 32 teens, 5 days</td>
<td>n = 19 preteens, 5 days/5 nights</td>
</tr>
<tr>
<td>n = 38 adults, 11 days</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Bionic Pancreas</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CGM (mg/dL)</td>
<td>142±12</td>
<td>158±27</td>
</tr>
<tr>
<td>Projected HbA1c</td>
<td>6.8%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Time &lt;60mg/dL</td>
<td>1.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Time &gt;180mg/dL</td>
<td>21%</td>
<td>31%</td>
</tr>
<tr>
<td>TDD (units/kg/day)</td>
<td>0.82</td>
<td>0.79</td>
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<table>
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<tbody>
<tr>
<td>Mean CGM (mg/dL)</td>
<td>138±11</td>
<td>168±30</td>
</tr>
<tr>
<td>Projected HbA1c</td>
<td>6.4%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Time &lt;60mg/dL</td>
<td>1.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Time &gt;180mg/dL</td>
<td>17%</td>
<td>36%</td>
</tr>
<tr>
<td>TDD (units/kg/day)</td>
<td>0.68</td>
<td>0.68</td>
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<table>
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<tr>
<th></th>
<th>Bionic Pancreas</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Mean CGM (mg/dL)</td>
<td>141±10</td>
<td>162±29</td>
</tr>
<tr>
<td>Projected HbA1c</td>
<td>6.5</td>
<td>7.3%</td>
</tr>
<tr>
<td>Time &lt;60mg/dL</td>
<td>0.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Time &gt;180mg/dL</td>
<td>20%</td>
<td>34%</td>
</tr>
<tr>
<td>TDD (units/kg/day)</td>
<td>0.66</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Figure 8. Closed Loop System**

- Controller device
- Adjusts basal/rate and bolus dose
- CGM levels
- Insulin pump
Among the microvascular complications of diabetes, a third of diabetes patients in the US develop some degree of retinopathy (Zhang X et al., JAMA. 2010;304[6]:649–56), with macular edema affecting approximately 4%, or 750,000 diabetic persons in the US aged 40 years or older (Varma R, et al. JAMA Ophthalmol 2014;132[11]:1334–40). Elevated HbA1c (OR, 1.47; 95% CI: 1.26–1.71 for each 1%; p<0.001) and longer duration of diabetes (OR, 8.51; 95% CI: 3.70–19.54 for ≥10 vs. <10 years; p<0.001) are associated with macular edema prevalence. Other risk factors include elevated lipids and blood pressure. Thus, the control of diabetes-associated metabolic abnormalities (i.e., hyperglycemia, hypertension, and hyperlipidemia) is important in preserving visual function.

The natural progression of diabetic macular edema (DME) leads to significant vision loss within 2 years in half of individuals (Chen E, et al. Current Medical Research and Opinion 2010;26[7]:1587–97). Also, DME is the leading cause of blindness in people with diabetes.

Dr. Lloyd Paul Aiello, MD, PhD of the Joslin Clinic, Harvard Medical School, discussed “Out with the Old, in with the New—Emerging Therapies for Diabetic Macular Edema” in a plenary session at the ADA annual meeting dedicated to The Eyes are the Windows of the Soul. He noted that a paradigm shift in the treatment of DME—from laser photocoagulation and vitrectomy to intravitreal injection—began in the mid-1990s with the appreciation that vascular endothelial growth factor (VEGF) production plays a major role in angiogenesis and abnormal vascular permeability in diabetic retinal disease (Aeillo LP et al., NEJM 1994; 331:1480–7). Forging the path to advances in treatment, the National Institutes of Health (NIH)-sponsored Diabetic Retinopathy Clinical Research Network (DRCRN; 109 participating sites and over 320 physician investigators throughout the US) was established in 2002, and has initiated more than 20 multicenter studies. The results of the most recently completed were presented this week (Sun et al., abstract 290-OR; summarized below).

Three intravitreally-administered VEGF inhibitors have been shown to reduce retinal edema and improve visual outcomes in eyes with central-involved DME. Two VEGF inhibitors—ranibizumab (in 2012) and aflibercept (in 2014)—are approved by the FDA for DME and earlier this year for diabetic retinopathy in patients with DME. The third agent, bevacizumab,* is used off-label for DME in repackaged aliquots containing 1/500th of the systemic dose used in approved cancer therapy. While anti-VEGF therapy is usually administered on a chronic basis, fewer injections may be needed over time to maintain a ‘dry’ retina. In the open-label extensions to the RIDE and RISE trials of ranibizumab, approximately one in every four patients did not require injections beyond 3 years of therapy, and the average patient required only 4 injections per year.

The three agents were compared to one another in a landmark DRCRN-sponsored double-blind, multicenter (n=89) trial conducted in the US (abstract 290-OR, NEJM 2015;372[13]:1193-203). A total of 660 adults with decreased visual acuity from DME (confirmed by optical coherence tomography [OCT]) and no history of anti-VEGF treatment in the most recent 12 months were randomized to a standardized treatment protocol of intravitreal aflibercept 2.0 mg (n=224), bevacizumab 1.25 mg (n=218), or ranibizumab 0.3 mg (n=218) injection into one affected eye. Study eyes were followed every 4 weeks with visual acuity and retinal central subfield thickness measured on OCT. The primary outcome was change in visual acuity at 1 year. Irrespective of baseline visual acuity, from baseline to 1 year, the mean visual-acuity letter score (range, 0 to 100, higher score indicating better visual acuity with a score of 85 equivalent to 20/20 vision) improved by 13.3 letters with aflibercept, by 9.7 letters with bevacizumab, and by 11.2 letters with ranibizumab (overall p<0.001 for aflibercept vs. bevacizumab and p=0.03 for aflibercept vs. ranibizumab). The between-group differences depended on baseline vision (p<0.001 for interaction with visual acuity as a continuous variable). When the initial visual-acuity loss was mild (i.e., 78 to 69, 20/32 to 20/40; 51% of participants), there was no statistically significant difference between treatment groups (mean improvement 7.5 to 8.3 letters). However, when initial visual acuity was worse, (initial letter score <69), aflibercept therapy led to better visual outcomes: the mean improvement was 18.9 letters with aflibercept, 11.8 letters with bevacizumab, and 14.2 letters with ranibizumab (p<0.001 for aflibercept vs. bevacizumab, p=0.003 for aflibercept vs. ranibizumab, and p=0.21 for ranibizumab vs. bevacizumab). Improvement was observed by four weeks in all three treatment groups (Figure 9).

The study groups were similar in the rates of serious adverse events (p=0.40), hospitalization (p=0.51), death (p=0.72), or major cardiovascular events (p=0.56).

In concluding his presentation, Aiello noted other potential non-VEGF mediators of DME, with kallikrein identified in proteomic studies. Emerging evidence suggests that inhibitors of kallikrein and other non-VEGF mediators may provide additional therapeutic opportunities to reduce retinal vascular permeability and improve vision in patients with diabetic retinopathy.

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*Note: solid lines indicate baseline visual acuity of 20/50 or worse, and dashed lines indicate baseline visual acuity of 20/32 to 20/40. Outlying values were truncated to 3 SD from the mean. The number of eyes assessed at each 4-week interval ranged from 195 to 224 in the aflibercept group, 188 to 218 in the bevacizumab group, and 188 to 218 in the ranibizumab group.

A New Risk Factor for Diabetes?

Kaiser Permanente Northern California (KPNC) is a large integrated delivery system with more than 3 million members. Cunningham and coworkers from Atlanta, GA and Oakland, CA used KPNC data from 2005-11 to estimate the average annual incidence of diabetes among members ages 18-79 and also just among those members with a co-residing partner diagnosed with diabetes within the previous year (abstract 72-OR). Incident diabetes among KPNC members overall was similar to that reported by the CDC for US adults (Figure 10). Spouses of persons with recently diagnosed diabetes however, developed diabetes themselves at twice the KPNC population rate for all ages combined (1.71% vs. 0.83%), with the rate of incident diabetes higher in each age group (18-44 years: 1.08% vs. 0.34%; 45-64 years: 1.74% vs. 1.17%; 65-79 years: 2.18% vs. 1.50%). Women with newly diagnosed spouses had 90% higher risk than women in the overall KPNC population (1.35% vs. 0.71%); men with newly diagnosed spouses had 133% higher risk than men in the overall KPNC population (2.22% vs. 0.96%). These findings suggest that spouses of persons with diabetes should be considered a high-risk group and targeted for diabetes screening and prevention. The nature of this association is interesting to consider. It likely reflects similar lifestyles or, perhaps, greater awareness of diabetes and a greater tendency to be screened. It does not appear that the investigators controlled the data for frequency of laboratory testing, and this may have partially answered this question.

Figure 10. 1-Year Incidence of Diabetes Among US Adults, KPNC Members, and Spouses of KPNC Members Diagnosed with Diabetes

A Novel Glucose Monitoring Device

Monitoring blood glucose via fingersticks is a challenge for many patients, and hope for a truly non-invasive method has ebbed and flowed for decades. Theise et al. of Cliffside Park, NJ reported results of a rapid-response, colorimetric, single-use test for non-invasively measuring glucose in saliva (Glucose Pop Test™, GPT™) (abstract 936-P). They studied 2 devices: GPT-1 (detecting down to 0.7 mg/dL salivary glucose) and a further optimized GPT-2 (detecting down to 0.25 mg/dL). Results of both tests can be read semi-quantitatively (by visual color chart comparison) or quantitatively (digital reader). GPT requires that a saliva sample be tested more than 15 minutes after food ingestion followed by a water mouth rinse. GPT evaluations for screening of diabetes mellitus (n=123) and from a glucose challenge study (n=154) indicated that saliva glucose is consistently ~1% of blood glucose, independent of dental hygiene.

GPT-1: Accuracy and precision were 100% and 96%, respectively, vs. reference saliva glucose method (BioAssay System Enzymench Glucose Test) but only 44.4% and 92.9%, respectively, vs. blood glucose test using paired plasma samples. Comparison of novice vs. expert color-chart reads showed ≥93% agreement. Clarke error grid analysis indicated 95.9% in zones A and B (“clinically accurate” and “benign effect on therapy”, respectively).

GPT-2: Accuracy and precision were both 100% vs. reference saliva glucose method (r=1.0, regression analysis) and 90.0% and 93.2%, respectively, vs. plasma sampling (r=0.822 regression analysis) Clarke error grid analysis indicated 100% in zones A and B.

The investigators concluded that the sensitivity and specificity of GPT suggests a role for saliva testing of glucose in population screening for diabetes mellitus and possibly for pre-diabetes, as well as self-monitoring of blood glucose among diabetic patients, replacing needle sticks. We are generally impressed by the accuracy of the second system, particularly since this is even higher than most fingerstick meters. However, larger studies are needed across a range of glucose and patient populations. We also wonder how much longer the process takes relative to the extremely quick and efficient fingerstick devices many of our patients are using.

Long-Term Glycemic Remission Following Insulin-Pump Treatment of Type 2 Diabetes Patients

In a retrospective study, Dr. Choi and Korean colleagues evaluated 18 Type 2 diabetes patients (8 males; median age at diagnosis, 51 [32-57] years; median duration of Type 2 diabetes, 0.9 [0.0–23.0] years) who had achieved remission (i.e., maintained normal fasting and postprandial glucose levels for 6 months after discontinuation of all anti-diabetic medications) after being treated with insulin by pump (abstract 1056-P). Blood glucose was measured at fasting and 120 minutes after ingestion of a mixed meal (500 kcal) at baseline and 6-month intervals during the treatment and follow-up periods. The patients attended routine check-up visits from March to June, 2014. Two patients had been newly diagnosed and 16 patients had taken oral antihyperglycemic medications before insulin pump therapy. Mean baseline HbA1c level was 7.4±2.1%, and median total daily insulin dose at the initiation of insulin pump therapy was 55 (22-344) IU. The median time to remission was 23 (5-108) months, and the median duration of remission was 25 (7-108) months. During follow-up of 4.5 (1.7–10.0) years, 4 patients had Type 2 diabetes relapse and restarted insulin pump therapy (median remission duration, 16 [7-36] months). Among the 14 patients with sustained remission, the most current HbA1c level was significantly lower than the initial level (6.1±0.4 vs. 7.7±2.1%, p=0.009), their most current BMI was lower (24.4±3.7 vs. 25.2±3.4 kg/m2, p=0.033), and their disposition index, a measure of the relationship between insulin secretion and insulin resistance, had improved from 0.14±0.09 (initial) to 0.35±0.15 (maximum) (p=0.002). Taken together, insulin pump therapy in this very small cohort appeared to improve B-cell function (presumably due to abolition of glucose toxicity) and led to long-term glycemic remission among patients with a history of diabetes of up to 23 years. These data are similar to prior prospective studies from China that suggest that early intensive glycemic control with insulin pumps can lead to long-term diabetes remission. However, the retrospective nature of the Korean study makes any conclusions highly tentative.

* 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
On the final full day of this year’s Scientific Sessions, the results of two anxiously awaited major clinical trials—ELIXA and TECOS—were revealed.

Leading off the afternoon’s back-to-back symposia was the presentation from the ELIXA investigators. The study sought to assess the CV safety and potential effectiveness in reducing CV endpoints of the GLP-1 agonist, lixisenatide, in 6068 patients (from 49 countries) with Type 2 diabetes and recent acute coronary syndrome (ACS). Patients with diabetes and ACS are a particularly vulnerable group, at increased risk for recurrent ischemic events and death. Accordingly, it is a reasonable population to test glucose-lowering drugs for CV safety. Exclusion criteria included age <30 years, prior incretin-based therapy, HbA1c <5.5% or >11%, significantly elevated pancreatic enzymes or history of pancreatitis, eGFR under 30 mL/min, planned revascularization within 90 days, or percutaneous coronary intervention within the previous 15 days. Patients were recruited within 180 days of their ACS event and randomized to 10 mg uptitrated to 20 mg of lixisenatide versus placebo. The remainder of the antihyperglycemic regimen was left up to the patient’s personal physician. The primary endpoint was the composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina. Secondary endpoints included portions of the primary, as well as a variety of metabolic and renal markers, and all-cause mortality.

Overall, the follow-up was 2.1 years. Only about 1% of patients were lost to follow-up and about one-quarter discontinued study medication, very typical in these long-term diabetes trials. Baseline characteristics of the study population are seen in Table 9.

Dr. Matthew Riddle from Oregon Health Sciences Center presented the metabolic data. Patients randomized to lixisenatide had a 0.27% lower HbA1c than placebo by the end of the trial, a reflection of the mandate to investigators to target standard-of-care in all patients. So, ideally, there would have been no difference between the two groups, although invariably such studies generally find a 0.3-0.4% better result in active therapy patients. There was also a 0.7 kg difference in weight, a 0.8 mm Hg difference in blood pressure, less progression of albuminuria (24% vs. 34% increase from baseline), each in favor of lixisenatide, and similar amount of hypoglycemia. Overall, adverse events were similar in number between the groups, but, of course, three- to four-fold more nausea and vomiting among lixisenatide patients. Of special interest were pancreatic adverse events; there were equal and small numbers of patients with pancreatitis and pancreatic malignancies.

Dr. Marc Pfeffer from Harvard University proceeded to present the CV endpoints data. For the primary endpoint, the hazard ratio (HR) was 1.02 (95% CI: 0.89-1.17), with about 13-14% of patients experiencing an event. There were also no differences between the groups in any of the CV secondary endpoints. Dr. Pfeffer concluded that ELIXA had ruled out any short-term increase in risk from this form of therapy over 2 years in patients with Type 2 diabetes and recent ACS. Upon analysis of various pre-specified subgroups (such as baseline therapies, nature of CVD at.
baseline, severity of diabetes), there remained no imbalance between the randomized groups.

The independent discussant at the conclusion of the investigators’ presentations was Dr. Silvio Inzucchi from Yale, who complimented the collaborating cardiologists and endocrinologists on a well-conducted study with robust results. He quickly reviewed some 40 years of diabetes clinical trials, reminding the audience that the effect of glucose on microvascular complications is undisputed, whereas the effect on CV outcomes remains controversial. It is difficult to demonstrate a benefit in the context of relatively short clinical trials. This may reflect the multiplicity of risk factors for CVD, whereas the major influences on microvascular disease remain glucose, blood pressure, and genetics (Figure 11). When trial participants are followed for up to a decade or more post-trial, however, a modest benefit of previous, more intensive glucose control emerges. The effect on CVD endpoints from specific drugs is equally controversial, with metformin and perhaps pioglitazone probably having a beneficial impact (outside of heart failure with the latter), but other drugs demonstrating, essentially, neutrality (Table 10).

He then reviewed the history of FDA guidance to industry mandating the demonstration of CV safety with all new diabetes drugs. The response has been to recruit high-risk patients to increase the event rates and shorten the trials. However, while acknowledging that the demonstration of safety was important, Dr. Inzucchi wondered if clinicians might not be more interested in long-term effectiveness data—i.e., whether these drugs when compared with standard therapy might actually provide additional CV protection. Given the relatively modest influence of glucose on CV outcomes, such a trial would likely take many more years than are being studied in the large CV outcomes trials in Type 2 diabetes patients now underway.

The next presentation was from the TECOS investigators, the mega-trial of sitagliptin (n=14,671) and CV outcomes (Green JB et al., NEJM epub 6/8/15). This trial was of somewhat less interest at this week’s sessions because two prior studies involving this drug class (SAVOR with saxagliptin [Scirica BM et al. NEJM 2013;369(14):1317-26] and EXAMINE with alogliptin [White WB, et al. NEJM 2013;369(14):1327-35]) have already been published, confirming neutrality on major adverse CV events (MACE). However, saxagliptin was associated with a 27% increased relative risk for heart failure hospitalization, the explanation for which has remained elusive since this class of drugs has never been associated with any substantive effects on either ventricular function or renal sodium handling.

Similar to ELIXA, TECOS was set up to test non-inferiority of active therapy with sitagliptin over placebo, and then, in a hierarchical design, to test superiority. This was a different and more stable population of patients than ELIXA. Instead of ACS, the inclusion criteria were established Type 2 diabetes on either oral agents or insulin (with or without metformin) and one of the following: prior history of MI, stroke, coronary revascularization, coronary or carotid disease by angiography or ultrasound, respectively, or documented peripheral arterial disease. Patients with significant prior hypoglycemia, eGFR <30 mL/min, use of an incretin-based drug, cirrhosis, and planned revascularization procedure were excluded. The primary endpoint was identical to that of ELIXA, basically an expanded MACE to include unstable angina hospitalization.

As with ELIXA, patients randomized to active therapy experienced a 0.29% difference in HbA1c compared with placebo patients, who were also treated to the standard-of-care. Patients on active therapy had somewhat less need for additional glucose-lowering drugs, including insulin, as one would expect based on the trial design.

For the primary endpoint data, which were presented by Dr. Rury Holman of Oxford University, the HR was 0.98 (95% CI: 0.88-1.09; p-value for non-inferiority, <0.001), with about 11-12% of patients in each group experiencing an event. There were also no differences between the groups in any of the secondary CV endpoints, including heart failure hospitalization. The latter was of some interest, given the SAVOR trial results. Clearly, sitagliptin does not increase the risk of heart failure. There also was no interaction for any of the subgroups, with the sole exception of a trend towards better outcomes with sitagliptin in obese patients.

Adverse events overall were similar between the groups. Pancreatitis occurred in a small number of patients, and there were nearly twice as many cases in the sitagliptin group (OR 1.93 p=0.065), but no imbalance for pancreatic cancer or other malignancies.

A conclusion from these trials is that incretin-based therapy appears to neither increase nor decrease MACE events in high-risk patients. It would be unlikely to find anything else, given the manner in which these trials are designed. Larger, more long-term studies involving patients perhaps with no overt CVD at baseline are needed. Who
Efficacy and safety trials were presented for several new insulin formulations at this meeting, including ultralong basal, concentrated, and oral insulins.

Dissecting insulin’s action at various responsive organs has been an active area of research. In the liver, insulin suppresses glucose production to control overnight and pre-prandial blood glucose. In skeletal muscle, the hormone activates glucose transport and disposal with a major effect on postprandial glucose. Developing insulin formulations with preferential activity at a particular tissue may assist in developing an individualized treatment program for patients. Perhaps more importantly, one of the failures of subcutaneously injected insulin and insulin analogs currently available is their inability to approach the normal high portal levels obtained when insulin is secreted endogenously by the endocrine pancreas. As a result, peripheral hyperinsulinism occurs, and some have proposed that this not only increases the risk of hypoglycemia but also might promote CVD. Developing hepatic-specific insulins may thus serve to address these deficiencies in our current treatment paradigms for insulin-requiring patients.

Dr. Melanie Davies from the United Kingdom presented randomized, controlled trial (RCT) data comparing basal insulin peglispro to glargine in patients with Type 2 diabetes, mean HbA1c 8.5% on ≥2 oral agents, followed to 52 and 78 weeks (abstract 93-OR). Peglispro has a half-life of two to three days, with preferential hepatic action due to its relatively large size. The investigators found that mean HbA1c reduction was similar by 78 weeks (7.1 vs. 7.0%) but that more people on peglispro achieved HbA1c ≤7.0% (51.0 vs. 42.1%). While the incidence of total and severe hypoglycemia was similar, the use of peglispro reduced the risk of nocturnal hypoglycemia (RR 0.73; 0.59, 0.91, p=0.005). By 78 weeks, overall insulin dosing and increases in body weight were similar between peglispro- and glargine-treated diabetics. Of note, triglycerides (172 vs. 154 mg/dL) and ALT (33 vs. 27 IU/L) were higher in peglispro-treated diabetics, which may be a result of its preferential hepatic activity.

For another new basal insulin, PE0139, Strange et al. from the US presented the findings of an initial safety study in people with Type 2 diabetes, who were already on daily glargine (abstract 100-OR). PE0139 is a recombinant human monomeric insulin molecule that acts like a depot with slow uptake, enabling once-weekly dosing. After an initial wash-out period, patients received either placebo (n=13) or one of four PE0139 doses, 0.05-1.35 mg/kg (n=6, each), and followed for 28 days. PE0139 demonstrated dose-related increases in serum concentrations, with mean decreases in fasting plasma glucose in the range of -2 to -34 mg/dL (p=0.06) compared to placebo. Free fatty acid levels were also lowered by a total mean of -0.35 mEq/L (p<0.05) compared to placebo, as measured 7 days after dosing. No dose-limiting toxicities were reported. Mild injection site erythema was reported for 2 PE0139 recipients and 1 placebo recipient. Although this was a small study with a short duration, the PE0139 pharmacokinetic profile supports a peakless, basal insulin with convenient once-weekly dosing. Of course, the risk of hypoglycemia will need to be carefully considered in larger trials.

Rizel and colleagues presented a meta-analysis of three phase 3 studies comparing insulin glargine 300 U/mL (Gla-300*) and glargine 100 U/mL (Gla-100) in patients with uncontrolled Type 2 diabetes (abstract 1030-P). The three-fold concentrated formulation may be more convenient for those on higher doses of insulin, and preliminary work has demonstrated a smoother absorption profile than conventional glargine. In these randomized, open-label studies, a total of 977 and 953 people took Gla-300 and Gla-100, respectively, for 12 months. By the end of the study, doses were titrated to similar mean amounts (Gla-300: 0.89±0.39 vs. Gla-100: 0.78±0.38 U/kg/day), and both groups had significant lowering of HbA1c from baseline (-0.91±0.03 vs. -0.80±0.03%). Gla-300-treated diabetics had slightly lower mean HbA1c by 0.10% (95% CI: -0.18 to -0.02, p=0.02) and less weight gain (0.85±0.11 vs. 1.25±0.11 kg) with a mean difference of -0.4 kg (95% CI: -0.71 to -0.09 kg; p=0.01). The risk for hypoglycemia was similar between the groups, although Gla-300 treatment was associated with a marginally lower risk of hypoglycemic events <70 mg/dL at night (RR 0.82; 95% CI: 0.67 to 0.99) and fewer patients with hypoglycemic events <54 mg/dL at anytime (RR 0.86; 95% CI: 0.78 to 0.95).

Oral insulin is making another entrance as an investigational pre-prandial, adjunct therapy to subcutaneous insulin in people with Type 1 diabetes. Other than the obvious, an advantage of the oral ORM-D-0801* insulin is its direct delivery into the portal vein following its release from enteric-coated capsules in the GI tract. This should allow better hepatic exposure to control glucose production to a greater degree than subcutaneous injections. Kidron and colleagues presented continuous glucose monitoring data from an RCT phase 2 study in which a ORM-D-0801 8 mg tablet or placebo was administered three times daily, 45 minutes before meals for 7 days to 15 and 10 people with Type 1 diabetes, respectively (abstract 1058-P). While postprandial excursions were not reported, the ORM-D-0801-treated patients required less rapid-acting insulin, reaching a mean daily difference of -5.9 units on day 7, compared to placebo. Fasting plasma glucose levels were lower than baseline but with marked variability for ORM-D-0801 and placebo (-60.2±63.3 vs. -10.2±55.7 mg/dL, respectively). On day 7 of treatment, an equal number of hypoglycemic events <60 mg/dL requiring clinical intervention were reported in both cohorts.

These developments are of interest, but require extensive additional investigations. If successful, they would represent incremental advances in insulin therapy. The only ‘game-changer’ might be a ‘smart insulin’ that is able to respond to ambient glucose concentrations. There were no presentations at the 2015 ADA Scientific Sessions on this topic, however.

For all of the sophisticated insulins in development, one of the keys to glycemic success with this form of therapy is to surmount clinical inertia and to recognize those patients that must transition from oral agents. Empowering our patients to make this transition in a positive fashion, to develop a comfort level with self-titration, and to be able to address the various barriers to its use are critically important. Working in conjunction with a diabetes educator in this regard can be enormously helpful. In a symposium on adherence to insulin therapy, Stewart Harris, MD, MPH from Ontario, Canada emphasized keeping regimens as simple as possible with a step-wise approach to insulin intensification, and enabling patients to gain confidence with glycemic monitoring and insulin titration. Start low, and go slow (refer to Figure 3, Issue 1)!
Exploration continues into the glucagon-like peptide 1 (GLP-1) receptor agonist (RA) class, including development of newer compounds, investigation into alternative indications, and understanding their long-term safety.

Dr. Kathleen Dungan from Ohio State University initiated a Sunday afternoon symposium addressing this important drug class with her presentation entitled “Differentiating Current and Emerging GLP-1 RAs.” Dungan began by identifying GLP-1 RAs which are available or near approval (Table 11). Several head-to-head trials compare individual agents, providing some differentiation. In general, the drugs can be divided into intermittent (exenatide twice daily and lixisenatide) or continuous (all others) activation of GLP-1 receptor. The intermittent drugs have a more favorable impact on postprandial glucose and delayed gastric emptying, whereas the continuous agents tend to have better effects on HbA1c and fasting plasma glucose (FPG) lowering. Dungan went through each of the head-to-head trials identifying parameters favored by each drug. All of the agents have a significant impact on HbA1c, favorable weight loss profile, and minimal risk of hypoglycemia. Specific drug selection will likely be most influenced by third party payer status.

Innovation in drug delivery of the GLP-1 RAs is underway. Rosenson and US colleagues reported the results of a phase 3 trial involving ITCA 650, an osmotic mini-pump system, placed subdermally, designed to deliver continuous subcutaneous release of exenatide (abstract 276-OR). After the initial placement, the device provides drug at a precise predetermined rate for up to 12 months. Patients with Type 2 diabetes (HbA1c ≥ 7.5 to ≤ 10%) managed on diet/exercise or oral agents were randomized to receive ITCA 650 40 mcg/day, 60 mcg/day, or placebo. Drug delivery rates were designed to deliver exenatide at 20 mcg/day for 13 weeks, then either 40 or 60 mcg/day for an additional 26 weeks. HbA1c values were significantly improved from baseline for each dose versus placebo: ITCA 650 60 mcg/day (-1.2% [97.5% CI: -1.37, -0.80, p = 0.001] and ITCA 650 40 mcg/day (-1.1% [-1.29, -0.71; p = 0.001]). Of note, the greatest reduction in HbA1c (1.7%) was observed in patients not receiving sulfonylureas and managed on metformin alone. Weight loss was progressive and dose dependent (Figure 12). GI symptoms were the most common adverse event, consistent with prior experience with this drug class, and diminished over time. If approved, this innovative delivery device may be a choice for patients who find difficulties with adherence and routine subcutaneous injections.

Late last year, the FDA approved high-dose liraglutide, marketed as Saxenda™, as a treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity. Sun Kim, MD, Stanford, addressed the role of GLP-1 RAs for the treatment of obesity. The magnitude of weight loss differs between patients with diabetes (~ 2-3 kg) versus those without (~ 5-6 kg), which is thought to be attributed to a greater focus on lifestyle changes in the latter group. Dose-related increases in weight loss also occur. Liraglutide 1.8 mg achieves ~ 5-6 kg loss, and the 3 mg dose about 7 kg in the non-diabetes patient. The majority of patients maintain weight loss at the two-year mark when managed with liraglutide 3 mg. Nausea is increased with the higher dose of 3 mg, occurring early in treatment. Kim shared that patients either learn to tolerate the side effect or discontinue therapy. The mechanism of action for liraglutide-induced weight loss is likely both peripheral (delayed gastric emptying) and central (appetite suppression, decreased intake, and increased satiety). Liraglutide may be superior to other GLP-1 RAs for weight loss given its ability to penetrate the central nervous system.

Dr. Jane Reusch, Denver, Colorado closed the symposium providing an update on the safety of GLP-1 RAs. She prefaced her comments by stating that there are 350 million cases of diabetes worldwide. Thus, the discussion of safety is one of risk versus benefit given the prevalence of diabetes and obesity. Reusch began with assessing CV risk and whether the GLP-1 RAs impact CV outcomes. The results of ELIXA (lixisenatide safety) are summarized in this issue (page 1), whereas the results of LEADER (liraglutide) are anticipated later this year or early 2016. Three others, SUSTAIN (semaglutide), EXCEL (exenatide) and REWIND (dulaglutide) are expected to close in 2016, 2018, and 2019, respectively.

Animal data suggest that GLP-1 RAs may have a potential benefit on myocardial function, so they might be useful in patients with heart failure.” However, the SAVOR trial found that the DPP-4 inhibitor, saxagliptin, increased risk for heart failure hospitalizations. Whether saxagliptin-induced circulating GLP-1 is related to this event and the implications for GLP-1 RAs are not yet known. Acute pancreatitis is another safety concern. Despite the FDA/EMA joint position statement suggesting otherwise, Reusch shared a recent publication involving liraglutide. A comparison of liraglutide users (n = 6345) versus matched controls (n = 1846) revealed that acute pancreatitis occurred in 1.6 versus 0.7 cases per 1000 patient-year-exposures in the controls (Jensen TM, et al. Diabetes Care, 2015). Reusch

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### Table 11. GLP-1 RAs for Type 2 Diabetes

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Brand Name</th>
<th>Dosing Frequency</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>Tanzeum™</td>
<td>Weekly</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity™</td>
<td>Weekly</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Byetta™</td>
<td>Twice daily</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Bydureon™</td>
<td>Weekly</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza™</td>
<td>Daily</td>
<td>FDA, EMA</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Lyxumia™</td>
<td>Daily</td>
<td>EMA</td>
</tr>
<tr>
<td>Semaglutide</td>
<td></td>
<td>Weekly (Subcutaneous)</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Semaglutide</td>
<td></td>
<td>Daily (Oral)</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Tasapoglutide</td>
<td></td>
<td></td>
<td>Haltered (tolerability)</td>
</tr>
</tbody>
</table>

FDA = US Food and Drug Administration, EMA = European Medicines Agency.

### Figure 12. Weight Loss Observed with ITCA 650

![Graph showing weight loss observed with ITCA 650](image)
concluded that although the data are mixed and remain inconclusive, the incidence of acute pancreatitis is very rare. From her perspective, the GLP-1 RAs have multiple benefits, but they must be balanced against their downside—GI symptoms, a possible small signal for pancreatitis, and their exceedingly high cost. The magnitude of the number of patients who benefit from these agents likely outweighs their small risks. She encouraged all practitioners to remain aware and vigilantly monitor the literature for safety issues. The large CV outcome trials underway should settle many of these concerns. Finally, their high cost is another concern.

Many other presentations this week focused on this antihyperglycemic drug category. Kawabe and Japanese co-workers evaluated the impact of a long-acting (liraglutide) and a short-acting (lixisenatide) GLP-1 RA on heart rate in Type 2 patients using a Holter monitor and power spectrum analysis (abstract 282-OR). Assessments were analyzed at baseline and hourly for 24 hours following treatment. The heart rate of patients in the liraglutide group was significantly increased (from a sum of 96,321 to 117,376 bpm, p<0.001) and significant increases occurred every hour during the 24-hour period. Patients in the lixisenatide group demonstrated a non-significant increase (from a sum of 99,618 to 104,426 bpm). All patients in the liraglutide group (22/22) experienced an increase in heart rate, whereas 17/22 in the lixisenatide arm had elevated rate and 5/22 demonstrated a decreased rate. Upon hourly analysis, only 3 of the 24-hour time points were considered as significant for lixisenatide. Following power spectrum analysis, liraglutide and lixisenatide significantly increased heart rate at 24 and 8 time points during the day, respectively. The investigators noted that the findings are consistent with the half-lives of the drugs and not entirely unexpected. Given the potential impact of elevated heart rates on ischemic heart disease and mortality, further investigation of this finding is warranted. The ELIXA results mitigate the concern.

Several abstracts addressed the role of GLP-1 RAs in combination therapy with other antihyperglycemic agents. Of the multiple combinations of glucose-lowering drugs available to us in practice, putting together two incretin-based therapies, DPP-4 inhibitors and GLP-1 RAs, is not recommended. Nauck and colleagues from Germany and Denmark evaluated the short-term impact of combining both classes of incretin mimetic drugs—sitagliptin, a DPP-4 inhibitor, and liraglutide, a GLP-1 RA (abstract 10-OR). Sitagliptin 100 mg or placebo was added to Type 2 diabetes (n=16) patients managed with liraglutide and metformin (≥2 weeks) after an overnight fast 60 minutes before a standard mixed meal. Sitagliptin-treated patients increased intact GLP-1 and GIP by 78.4% and 90.2%, respectively (p<0.0001, when compared with placebo). Despite increasing intact incretin plasma concentrations, total GLP-1 and GIP responses were numerically but not significantly reduced (36.5% and 18.2%, respectively). Also, glucose, insulin, C-peptide, and glucagon levels were unchanged. The investigators hypothesized that GLP-1 receptors may be maximally stimulated by the GLP-1 agonist. Thus, addition of a DPP-4 inhibitor offers little to glycemic parameters even though intact plasma concentrations of the gut hormones are increased. Therefore, as previously thought, combined therapy should be avoided.

There is growing interest in the use of GLP-1 RAs with basal insulins to prevent the need to progress to basal-bolus insulin therapy, which requires 3-4 injections per day and more finger-
hypoglycemia (≤72 mg/dL) demonstrated an increase in QTc during those periods. The change in QTc during hypoglycemia was inversely proportional to the baseline QTc. This prolongation of QT interval during spontaneous hypoglycemia may play a role in life-threatening arrhythmias in high-risk individuals.

Addressing this issue from more of a hematological viewpoint, Kahal and colleagues from the UK and Qatar presented findings of their case-control study examining platelet function immediately and 24 hours following induced hypoglycemia (50.4 mg/dL for 1 hour) in 10 subjects with Type 2 diabetes compared to eight healthy age-matched controls (abstract 353-OR). Data were presented as median (25th/75th percentiles). Platelet sensitivity to prostacyclin (an inhibitor of platelet aggregation and antagonist of thromboxane-mediated vasoconstriction), measured as percentage inhibition in fibrinogen binding, was significantly reduced right after hypoglycemia (38.5% [12.1-51.8]) and also at 24 hours (29.5% [10.3-43.8]), compared to baseline (50.8% [36.8-61.1], p<0.05). Investigators concluded that blood coagulability is enhanced up to 24 hours after being induced through impaired platelet sensitivity to prostacyclin occurring after hypoglycemia.

In light of numerous studies showing increased morbidity and mortality following hypoglycemic events, prediction, with the ultimate aim of prevention, of such events is important. Miller et al. (abstract 389-P) presented the incidence of and risk factors for hypoglycemia in Veteran Affairs Medical Center patients from 2000 to 2009 based on review of inpatient, emergency room, and outpatient encounters. The incidence of hypoglycemia, as identified by ICD-9-CM codes, was noted to be 24%. High risk for hypoglycemia was found with insulin and secretagogue use, particularly long-acting formulations, and in those recently started on these medications or recently discharged from the hospital. Hypoglycemia was associated with high (not low) HbA1c, the presence of metabolic and microvascular complications, longer diabetes duration, but not necessarily with advanced age. Similarly, Kotwal and colleagues from the University of Massachusetts identified potential predictors of hypoglycemia in insulin-treated Type 1 and Type 2 diabetic patients in their cross-sectional study (abstract 392-P). In this study, prior severe hypoglycemic episodes and a lower HbA1c were the strongest predictors in Type 1 patients, while wide glycemic excursions and prior severe episodes were the top predictors in Type 2 patients (Table 12). With the increased risk for complications following hypoglycemic events comes increased utilization of resources. A retrospective, non-interventional study by Goldstein et al. aimed to quantify resource use associated with a severe hypoglycemic event utilizing electronic medical record data. The investigators compared health care utilization per patient per month prior to and after a severe hypoglycemic event (abstract 400-P). The number of patients requiring hospital admission within one month post-event was more than double the number of patients admitted within a month pre-event. Moreover, of those admitted to the hospital, the mean duration of stay was significantly longer during the month post- vs. pre-event (5.59 days vs. 4.37 days, p<0.001). Outpatient visits were 46.8% more common during the month post- vs. pre-event (12,557 vs. 18,441, p<0.001).

The risk for hypoglycemia increases with the use of intensive glucose control regimens in an attempt to prevent long-term microvascular complications. However, there is increasing evidence that demonstrates increased morbidity and mortality associated with hypoglycemia. Along with higher morbidity comes higher utilization of healthcare resources and ultimately higher health care costs. Assuming the majority of hypoglycemic episodes resulted from overly stringent regimens, such events may be preventable by more conservative therapy, perhaps to a range that allows reasonable control while minimizing hypoglycemic events. (However, the link between higher HbA1c and hypoglycemia noted above deserves some consideration, as well.) This is congruent with the recommendation of the ADA and EASD regarding personalization of HbA1c goals based on comorbidities, life expectancy, disease duration, complications, patient attitude and expected treatment efforts, support system, and risk for hypoglycemia (refer to “Management of Hyperglycemia in Type 2 Diabetes”, Issue 1, page 3).

### Table 12. Potential Predictors of Hypoglycemia in Insulin-treated Type 1 and Type 2 Diabetic Patients

<table>
<thead>
<tr>
<th>Type 1 Diabetes Patients</th>
<th>Type 2 Diabetes Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower HbA1c</td>
<td>Glycemic variability</td>
</tr>
<tr>
<td>Previous hypoglycemia</td>
<td>Previous hypoglycemia</td>
</tr>
<tr>
<td>Young age</td>
<td>Lower BMI (only for severe hypoglycemia)</td>
</tr>
<tr>
<td>Longer diabetes duration</td>
<td>Longer diabetes duration</td>
</tr>
<tr>
<td>↑ Number of daily injections</td>
<td>Depression (only for hypoglycemia, not severe hypoglycemia)</td>
</tr>
</tbody>
</table>

### Table 13. The Three-Minute Foot Exam

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Exam</th>
<th>Education (for the high risk foot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of:</td>
<td>Shape (deformity, prominence of metatarsal heads, claw toes)</td>
<td>Daily foot care – self inspection, reporting of new lesions</td>
</tr>
<tr>
<td>– neuropathic symptoms</td>
<td>Neurologic (Ipswich Touch Test)</td>
<td>Shoes – avoidance of barefoot gait, use of appropriate shoes, regular replacement of shoes</td>
</tr>
<tr>
<td>– claudication</td>
<td>Vascular-pulse, temperature</td>
<td>Modification of overall health risk – BP and glycemic control</td>
</tr>
<tr>
<td>– foot lesions</td>
<td>Ulcers</td>
<td>Nails</td>
</tr>
<tr>
<td>History of vascular intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
regarding the number of sites to test and the number of sites missed to be classified as an abnormal result. Furthermore, it is time-consuming to perform.

The three-minute foot exam, as the name suggests, is a much faster and efficient method for evaluating for neuropathy. It consists of three parts, each requiring a minute to perform or complete—history, physical exam, and education (Table 13).

Part of this exam is the Ipswich Touch Test (IpTT), a simple maneuver that involves using one to two seconds of the examiner’s light finger touch over the patient’s first, third, and fifth toes on both feet. Loss of sensation in two or more areas denotes feet that are at risk for ulceration, while loss of sensation in one area is a marker of impairment. It has been shown to be similar to the more time-consuming monofilament exam in predicting risk for ulceration in several studies. In a poster presented this week at the ADA Scientific Sessions, the IpTT was compared with the monofilament test and neuropathy disability score (NDS) in 50 adult diabetic patients (92% with Type 2 diabetes) who were tested using the three methods (abstract 717-P).

### Table 14. Performance of IpTT, Monofilament Exam, and Neuropathy Disability Score (reference)

<table>
<thead>
<tr>
<th>Comparison with NDS</th>
<th>IpTT</th>
<th>Monofilament</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td>PPV</td>
<td>87%</td>
<td>76%</td>
</tr>
<tr>
<td>NPV</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Pearson Chi-square value</td>
<td>34.059</td>
<td>27.086</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Results show similar sensitivity, specificity, and negative predictive value (NPV), but IpTT had a higher positive predictive value (PPV) (Table 14).

When it comes to diagnosing peripheral neuropathy, a thorough examination is key. In studies conducted between 1983 and 1996 regarding foot pressure, the correlation between high foot pressures and ulcers is evident. Pressure abnormalities often precede the appearance of neuropathy, which in turn increases risk for ulcers. Plantar callus formation associated with high pressure is also predictive of ulcer formation. Podotrack™ (PressureStat) is an inexpensive, user-friendly, dynamic pressure print map system that can correctly identify high-pressure sites on the foot. Lastly, Dr. Brand recommended foot temperature monitoring. It is noted that foot temperature increases before skin breaks down. In patients who are regularly monitoring foot temperature, a greater than 3°F difference in temperature between feet is a marker of the need to rest the feet. When rest is provided after such a discrepancy is noted in temperature, the risk of ulcer formation decreases remarkably from 30% to 8%.

Dr. William Ennis of the University of Illinois, another speaker at the plenary session, acknowledged there is a great disparity in access to healthcare, delivery of healthcare, and health education among different ethnicities. These discrepancies translate to disparities in factors affecting wound healing and risk of complications. For example, African Americans have delayed epithelialization, which may ultimately delay wound healing and increase risk for complications. He also highlighted the need to personalize both diagnosis and treatment plan of patients to optimize treatment benefits.

### Table 15. Endpoints Among Hospitalized Type 2 Diabetes Patients Treated with Oral Agents and/or Basal Insulin

<table>
<thead>
<tr>
<th></th>
<th>Oral Agent (n = 1350)</th>
<th>Oral Agent + Basal Insulin (n = 196)</th>
<th>Basal Insulin (n = 4302)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65.5±12.3</td>
<td>60.5±11.5</td>
<td>63.5±12.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.1±7</td>
<td>32.8±8</td>
<td>31.7±8</td>
<td>0.0034</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.9±1.5</td>
<td>8.5±2.2</td>
<td>8.1±2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>153±53</td>
<td>210±77</td>
<td>199±78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission</td>
<td>153±41</td>
<td>194±56</td>
<td>178±48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>80-180 mg/dL, %</td>
<td>979 (81)</td>
<td>80 (46)</td>
<td>2384 (60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;70 mg/dL, %</td>
<td>103 (7.6)</td>
<td>18 (9.2)</td>
<td>479 (11.1)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Length of stay, median in days</td>
<td>5 (3 - 8)</td>
<td>5 (3 - 7)</td>
<td>5 (4 - 9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>8 (0.6)</td>
<td>1 (0.5)</td>
<td>62 (1.4)</td>
<td>0.0301</td>
</tr>
<tr>
<td>Lactic acidosis, n (%)</td>
<td>46 (3.4)</td>
<td>6 (3.1)</td>
<td>271 (6.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute MI, n (%)</td>
<td>21 (1.6)</td>
<td>2 (1.0)</td>
<td>125 (2.9)</td>
<td>0.0088</td>
</tr>
<tr>
<td>Acute kidney injury, n (%)</td>
<td>96 (8.6)</td>
<td>15 (9.1)</td>
<td>620 (15.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

**Should Oral Agents Be Used in the Hospital?**

Pasquell and coworkers from Atlanta, GA, conducted a retrospective study of 5,848 Type 2 diabetes patients admitted to medical and surgical non-ICU wards at 4 teaching medical centers in the US between 2012 and 2013 (abstract 1268-P). The objective was to determine the utilization, efficacy, and safety of oral antihyperglycemic agents among patients in general hospitalized patients. Most experts, we would add, recommend stopping oral agents upon admission and to conduct glucose with insulin, given its greater flexibility. The majority of patients in this study (73.6%) was treated with a basal insulin regimen (glargine or detemir), 23.1% with oral antihyperglycemic drugs, and a minority (3.4%) with both. Among patients on an oral agent, approximately half (51.3%) were treated with metformin, 38.4% with sulfonylurea, and 10.3% with both, for an average of 2.8 days. Patients treated with oral agents had lower HbA1c and lower blood glucose at admission. They also had lower blood glucose and less hypoglycemia, hospital complications (lactic acidosis, myocardial infarction, acute kidney injury), and mortality compared to those treated with basal insulin ± oral therapy (Table 15).

Nonetheless, if the data can be confirmed in a randomized trial, they would have major impact in our approach to managing hyperglycemia in the hospital.
Questions 1-5: For Type 2 diabetes patients who have uncontrolled
glycemia with metformin, identify the agent that is relatively
contraindicated (as dual therapy), given the following patient factors:

1. Patient with height failure
2. Woman with frequent genitourinary infections
3. Patient with prior propensity towards hypoglycemia
4. Patient with gastroparesis
5. Patient whose HbA1c is 2 points above target
   a. sulfonylurea
   b. thiazolidinedione (TZD)
   c. DPP-4 inhibitor
   d. SGLT-2 inhibitor
   e. GLP-1 receptor agonist

6. According to study results reported at the 2015 ADA Scientific Sessions,
   approximately 1 in 5 adolescents and 1 in 4 young adults in the US
   meet criteria for prediabetes.
   a. true
   b. false

7. Which of the following statements about Medical Nutrition Therapy
   is false?
   a. It is the total amount of carbohydrates eaten at a meal, rather
      than the type of carbohydrate, that has the greatest impact
      on postprandial glucose.
   b. Fiber is of vital importance, stabilizing glucose levels and
      helping with satiety.
   c. In those without chronic kidney disease, daily protein intake
      of diabetes patients should be the same as the general
      population (~0.8 grams/kg).
   d. In diabetes patients with no history of heart disease, it is the
      percentage of total calories from fat, rather than the type of
      fat that is important.

8. From age 50, patients with diabetes have approximately 6-8 years
   earlier onset of disability, compared to those without diabetes.
   a. true
   b. false

9. The first step towards a completely ‘closed loop’ insulin pump/glucose
   sensor glucose control system has been the development of which
   special feature of the latest pumps?
   a. rapid augmentation of insulin pump insulin delivery rate
      when glucose begins to climb
   b. automatic insulin pump shut-off when glucose levels
      decrease to a prespecified hypoglycemic range
   c. automatic increase in insulin pump insulin delivery rate
      when patient begins to eat
   d. automatic decrease in insulin pump insulin delivery rate
      when patient’s blood glucose falls under 100 mg/dL

10. In the US, diabetes accounts for substantially more cases of chronic
    kidney disease (GRF 30-59 mL/min) than does hypertension.
    a. true
    b. false

11. Relative to babies born to mothers with gestational diabetes, those
    born to overweight or obese mothers are at 75% decreased risk of
    being overweight by 2 years of age.
    a. true
    b. false

12. One of the many benefits of FDA approval of numerous insulin products
    is that their price has decreased substantially over the last decade.
    a. true
    b. false

13. All of the following pharmacological characteristics, except _____,
    support the potential use of SGLT-2 inhibitors in patients with
    Type 1 diabetes?
    a. mechanism of action independent of insulin
    b. directly augment incretin hormone levels
    c. indirectly enhance insulin sensitivity
    d. additional benefit on blood pressure

14. In a recently conducted head-to-head comparison, visual acuity in
    patients with moderate to severe diabetic macular edema was not
    improved with any of the currently used intravitreously administered
    VEGF inhibitors.
    a. true
    b. false

15. According to a longitudinal, retrospective study, spouses of patients
    with newly diagnosed diabetes are at increased risk of developing
    diabetes, as compared to the general population.
    a. true
    b. false

16. Which of the following antihyperglycemic agents is associated with
    the highest risk for hypoglycemia?
    a. sulfonylureas
    b. DPP-4 inhibitors
    c. metformin
    d. thiazolidinediones

17. Which of the following combinations of glucose-lowering medications
    is not recommended?
    a. metformin + sulfonylurea
    b. metformin + basal insulin
    c. DPP-4 inhibitor + GLP-1 receptor agonist
    d. GLP-1 receptor agonist + SGLT-2 inhibitor

18. Other than a lower HbA1c, each of the following may be expected
    during treatment with SGLT-2 inhibitors, except _____.
    a. decreased urinary albuminuria
    b. decreased blood pressure
    c. weight loss
    d. increased uric acid

19. All of the following, except _____, have been shown to increase the
    risk of hypoglycemia in insulin-treated Type 1 diabetes patients.
    a. lower HbA1c
    b. history of previous hypoglycemia events
    c. young age
    d. history of hypertension

20. With regard to exercise recommendations in patients with diabetes,
    which of the following statements is false?
    a. Adults with diabetes should perform at least 150-minutes/week
       of moderate intensity aerobic physical activity, spread over at
       least 3 days/week with no more than 2 consecutive days
       without exercise.
    b. There is no need to limit exercise in the setting of hypoglycemia.
    c. Adequate amounts of exercise have been shown to decrease
       HbA1c by >0.5%, similar to glycemic reductions achieved
       with many recently developed oral agents.
    d. In an older patient or one with multiple cardiac risk factors, a
       careful cardiovascular history should be taken and consideration
       be given to screening with cardiac stress testing before any
       vigorous exercise program is undertaken.
1. **How would you rate Diabetes 2015 for content?**
   a. very relevant to my practice
   b. interesting but not relevant
   c. uninteresting

2. **How would you rate Diabetes 2015 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 2015 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, abnormal insulin secretion, and derangements in the incretin axis.
   b. Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
   c. Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
   d. Implement strategies for the early diagnosis and treatment of diabetes.
   e. Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
   f. Recognize the interrelationship between insulin resistance, hyperglycemia, inflammation, and atherosclerosis in patients with Type 2 diabetes.
   g. Underscore the importance of lifestyle change, exercise, and dietary interventions in the management of diabetes.
   h. Compare the mechanisms of actions of a growing array of oral and injectable pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper evidence-based role in the management of this disease.
   i. Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
   j. Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
   k. Identify unique management issues among special sub-populations of patients with diabetes.
   l. Discuss the impact of diabetes on healthcare systems.

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 program evaluation, which must be completed on-line at www.cme.yale.edu. 80% constitutes a passing grade. Term of approval: June 2015 to December 31, 2015.

Diabetes 2015 Evaluation - Volume 31

1. (a) (b) (c) (d) (e) 11. (a) (b)  
2. (a) (b) (c) (d) (e) 12. (a) (b)  
3. (a) (b) (c) (d) (e) 13. (a) (b) (c) (d)  
4. (a) (b) (c) (d) (e) 14. (a) (b)  
5. (a) (b) (c) (d) (e) 15. (a) (b)  
6. (a) (b) 16. (a) (b) (c) (d)  
7. (a) (b) (c) (d) 17. (a) (b) (c) (d)  
8. (a) (b) 18. (a) (b) (c) (d)  
9. (a) (b) (c) (d) 19. (a) (b) (c) (d)  
10. (a) (b) 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 2015 Evaluation - Volume 31

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 (k) yes / no (l) 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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