Highlights from the 51st Annual Meeting of the European Association for the Study of Diabetes

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This CME program is supported in part through 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 monograph is supported in part through 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. It is understood that supporters will in no way control the content of this program.

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This CME Activity was planned and produced in accordance with the ACCME Essentials.
October 2015

Dear Colleague:

Time restraints prevented many of you from attending the 51st Annual Meeting of the European Association for the Study of Diabetes (EASD) which was held a few weeks ago in Stockholm, Sweden. 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 three 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: October 2015 to July 31, 2016.

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,

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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.
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• Recognize the interrelationship between insulin resistance, hyperglycemia, inflammation, and atherosclerosis in patients with Type 2 diabetes.
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• 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.
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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 EASD conference concludes, a Diabetes 2015 booklet (containing all of the newsletters, a program highlights summary from the program co-editors, a course evaluation form, and a sample post-test) and post-test will 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™.
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In this issue of the Diabetes 2015 monograph, we summarize important new diabetes information that was presented at the 51st Annual Meeting of the European Association for the Study of Diabetes (EASD) in Stockholm, Sweden.

During a much anticipated symposium at the Annual Meeting of the EASD, investigators presented results of the landmark EMPA-REG Outcome trial, which randomized 7,020 Type 2 diabetes patients with overt cardiovascular (CV) disease (i.e., documented coronary, cerebrovascular, or peripheral vascular disease) and eGFR >30 mL/min/m² to the SGLT-2 inhibitor, empagliflozin, or placebo. The top-line study results were announced a few weeks ago, but the magnitude of the reported benefits on the primary major adverse cardiovascular outcomes (MACE) endpoint and other outcomes were embargoed until the symposium at the EASD and simultaneously published in the New England Journal of Medicine.

Dr. John Lachin, PhD from George Washington University, Washington, DC, described the statistical design of the trial. EMPA-REG Outcome was designed initially as a non-inferiority study to demonstrate that patients randomized to either of 2 empagliflozin doses (10, 25 mg) had CV outcomes that were no different than those assigned to placebo, each strategy prescribed upon background standard-of-care for not only glucose control but also that of blood pressure and lipids. The study design employed a hierarchical model for sequential testing and was adequately powered to demonstrate superiority once the non-inferiority threshold had been met, a standard approach used in such trials. Importantly, all major CV endpoints were independently adjudicated. Statistical analyses were between the pooled group of both empagliflozin doses versus placebo.

Dr. Christoph Wanner from the University of Wurzburg, Germany, discussed the baseline characteristics and biochemical and physiological changes during the trial. Mean HbA1c decreased by about 0.6% in the empagliflozin groups during the first 12 weeks of the trial (when changes in background anti-hyperglycemic therapy were not allowed). By trial end, the mean difference between groups was 0.3% for HbA1c, 4 mmHg for systolic blood pressure, and 2 kg for weight.

Dr. Silvio Inzucchi from Yale University then revealed the CV outcomes of the study. The primary endpoint of 3-point MACE (i.e., the composite of CV death, non-fatal MI, and non-fatal stroke) was reduced by 14% in the pooled empagliflozin group (HR 0.86 [95% CI: 0.74, 0.99]; p=0.0382). Other statistically significant between-group differences included a 38% reduction in CV death (HR 0.62 [95% CI: 0.49, 0.77]; p<0.0001), 35% reduction in heart failure hospitalizations (HR 0.65 [0.50, 0.85]; p=0.0017), and 32% reduction in all-cause mortality (HR 0.68 [0.57, 0.82]; p<0.0001). Discussants underscored that the EMPA-REG Outcome trial is the first large trial to demonstrate significant CV benefits with a diabetes medication in a high-risk population. Wrapping up the symposium, Dr. Bernim Zinman from the University of Toronto noted that the number needed to treat one CV death over 3 years was 39, which compares favorably to results from some statins and ACE inhibitor trials in a high-CV risk population. Importantly, the findings of this study were demonstrated upon a background of high use of evidence-based CV therapies, such as statins, RAS inhibitors, and aspirin. Dr. Hertzel Gerstein, McMaster University, noted that strikingly early separation of the event curves suggests that the effect of study drug was likely not meditated through the modest effects on glucose, weight, and blood pressure. Instead, he speculated that osmotic diuresis may have resulted in a better hemodynamic status, perhaps treating early heart failure or preventing heart failure.

Nonalcoholic fatty liver disease (NAFLD) is especially prevalent in patients with Type 2 diabetes and is frequently associated with elements of the metabolic syndrome such as obesity, dyslipidemia, and insulin resistance. A symposium, entitled “Liver in Focus,” was devoted to this topic. Professor Hannele Yki-Jarvinen, University of Helsinki, described NAFLD as a heterogeneous disease with various etiologies: (1) metabolic (obesity, metabolic syndrome, diabetes); (2) genetic, and; (3) combination of metabolic, genetic, and ethanol use. NAFLD is the most common form of chronic liver disease, with obesity being its most common cause. Yki-Jarvinen provided rationale for why diabetologists should be interested in NAFLD including its predictive value for Type 2 diabetes, predictive value for CV disease independent of obesity, and its strong association with cirrhosis and hepatocellular carcinoma. She recommended screening of patients with metabolic syndrome or Type 2 diabetes for NAFLD. Specifically, hepatic enzymes, steatosis biomarkers (e.g., fatty liver index, NAFLD Liver Fat Score, SteatoTest™), and/or ultrasound should be part of the routine work up. She cautioned that ~50% of Type 2 diabetes have NAFLD despite normal ALT levels, therefore, fibrosis biomarkers are recommended as well (e.g., NAFLD Fibrosis Score, FIB-4 calculation). Dr. Yki-Jarvinen’s closed by saying “Think of the liver every time you see a patient with Type 2 diabetes!”

Dr. Kenneth Cusi, University of Florida, discussed treatment of NASH, stating that targeting adipose tissue and altering glucose and/or lipid metabolism should be the primary approach. To date, the most promising data are from studies of the thiazolidinedione (TZD), pioglitazone, and the GLP-1 receptor agonist (RA), liraglutide. However, long-term, larger studies are needed before either can be routinely recommended. There are several investigational agents under evaluation with the most notable being: obeticholic acid*, a farnesoid X receptor agonist; GFT-505*, a PPAR-alpha/delta agonist; and cenicriviroc*, a dual CCR2/CC5 receptor antagonist. Dr. Cusi closed with recommendations to actively employ screening and the need for the development of a long-term treatment approach. In a related poster presentation, Tang and colleagues from China completed a comprehensive analysis of randomized (n=19) and non-randomized (n=14) trials of 1,156 Type 2 diabetes patients with liver disease to identify the comparative efficacy of anti-hyperglycemic medications on NAFLD (abstract 726). The TZDs when utilized for 12 to 72 weeks were associated with the greatest reduction in hepatic fat content compared with placebo, metformin, and glibenclamide. The GLP-1 RAs also had beneficial effects after 26-50 weeks. Neither metformin alone for 16 to 48 weeks nor dapagliflozin for 24 weeks had an impact. From this extensive review of the literature, the researchers suggested that in patients with Type 2 diabetes and NAFLD, the TZD* and GLP-1 receptor agonist* drug classes appear to have the most promise for treating NAFLD, and randomized controlled trials are warranted.

Presentations made at the EASD 2015 Scientific Sessions focused on new roles for GLP-1 RAs. Several studies evaluated the agents in combination with insulin in Type 1 and Type 2 diabetes (abstract 74, abstract 114). Baron and US colleagues reported the results of a double-blind, randomized trial involving ITCA 650*, an osmotic mini-pump system, placed subdermally, designed to deliver continuous subcutaneous release of exenatide (abstract 12). 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 evaluated non-glycemic actions of the GLP-1 RAs, such as impact on heart rate (abstract 16). CV outcomes (abstract 937), and hepatic fat content (abstract 13). Development of IDeGluR™ (the combination of basal insulin degludec* and the GLP-1 RA liraglutide as one injectable) for Type 2 diabetes continues (abstracts 834 and 836), with the goal of preventing progression to the more complex basal-bolus insulin therapy.

Innovations in insulin therapy continue to be studied, as well. These included the basal insulin, peglispro*, which has a two to three day half-life and preferential hepatic action due to its large molecular size (abstracts 3 and 40) and a faster insulin aspart (abstract 39). Research on “closing the loop” continues (abstract 987), the results of a small study suggesting that prolonged home use of unsupervised day-and-night insulin pump married to a glucose sensor under free-living conditions in adults with Type 1 diabetes may be feasible, conferring improved glucose control and reduced exposure to hypoglycemia without increasing total daily insulin exposure.

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.
The number of available agents to manage hyperglycemia in patients with Type 2 diabetes has increased dramatically over the past two decades (Table 1). With sulfonylureas and insulin being the only options available until 1995, we now have 12 individual glucose-lowering classes of drugs. Indeed, the array of options can be a bit dizzying at times. What advantages do the newer and, of course, much costlier drugs actually provide? Do they lower glucose better or more safely? These are important questions. Although the bulk of research presented at this week’s EASD meeting in Stockholm focused on new or emerging agents, a few presentations that caught our eyes pertained to traditional diabetes drugs.

The sulfonylureas have been available since the early 1950s. Original agents like chlorpropamide and tolbutamide have been replaced by glyburide, glipizide, and glimepiride. They are still frequently used throughout the world as either monotherapy or in combination with metformin. Sulfonylurea drugs are insulin secretagogues; they inhibit K-ATP channels on beta cells, depolarizing them, resulting in calcium influx and hormone secretion. Unfortunately, their action is not glucose-dependent and they are therefore associated with the risk of hypoglycemia. Although these drugs appear to be safe for the cardiovascular (CV) system in clinical trials (UKPDS, ADVANCE, BARI-2D), there remains a lingering concern regarding the possibility that this class could result in more cardiac events in such a predisposed population. This worry relates to the risk of severe hypoglycemia, which is associated with not only adrenergic activation but also, more recently, repolarization abnormalities in the heart itself and in the activation of pro-inflammatory cascades. Another possibility is a deleterious effect on “ischemic preconditioning”, the heart’s self-protective mechanism that minimizes ischemic damage when blood supply to the myocardium is threatened.

In this vein, Baxter and Canadian colleagues conducted a Bayesian meta-analysis of 91 randomized clinical trials that included 36,573 patients and 26 observational studies with 1,553,856 patients

### Table 1. Currently Available Type 2 Diabetes Medication Classes

<table>
<thead>
<tr>
<th>Oral agents</th>
</tr>
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<tbody>
<tr>
<td>Sulfonylureas*</td>
</tr>
<tr>
<td>– glyburide, glipizide, glimepiride</td>
</tr>
<tr>
<td>Biguanides*</td>
</tr>
<tr>
<td>– metformin</td>
</tr>
<tr>
<td>Thiazolidinediones*</td>
</tr>
<tr>
<td>– pioglitazone, rosiglitazone</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
</tr>
<tr>
<td>– acarbose, miglitol</td>
</tr>
<tr>
<td>Meglitinides</td>
</tr>
<tr>
<td>– repaglinide, nateglinide</td>
</tr>
<tr>
<td>DPP-4 inhibitors*</td>
</tr>
<tr>
<td>– sitagliptin, saxagliptin, linagliptin,alogliptin</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
</tr>
<tr>
<td>– colesvelam</td>
</tr>
<tr>
<td>Dopamine agonists</td>
</tr>
<tr>
<td>– Bromocriptine</td>
</tr>
<tr>
<td>SGLT-2 inhibitors*</td>
</tr>
<tr>
<td>– canagliflozin, dapagliflozin, empagliflozin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin*</td>
</tr>
<tr>
<td>– various formulations</td>
</tr>
<tr>
<td>GLP-1 receptor agonists*</td>
</tr>
<tr>
<td>– exenatide, liraglutide, albiglutide, dulaglutide</td>
</tr>
<tr>
<td>Amylinomimetics</td>
</tr>
<tr>
<td>– pramlintide</td>
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</tbody>
</table>

*Most commonly prescribed drugs.
of MI for sulfonylureas compared to all other therapies combined. As for stroke, the trial meta-analysis demonstrated increased risk with sulfonylureas when compared to DPP-4 inhibitors (HR 9.40 [3.27, 41.9]). GLP-1 agonists (45.40 [1.99, 362.7]), thiazolidinediones (TZDs) (1.75 [1.20, 2.69]), and even insulin (1.46 [1.01, 2.14]). Reliable stroke data were not available from the observational studies. The conclusion was that this class of drugs is associated with increased CV risk as compared to most other therapies. The investigators suggested that their data might inform revision of prevailing treatment guidelines that still include these insulin secretagogues as reasonable options in some patients.

While we find these data provocative, a few points are necessary to clarify. First, some of the hazard ratios reported by the investigators seem unbelievably high, such as those versus GLP-1 agonists and SGLT-2 inhibitors. Second, we would emphasize that the safety of the sulfonylureas has been demonstrated when they are tested in individual, large clinical trials. In the UKPDS, for example, the drugs were associated with a non-significant 15% decreased risk of MI. Accordingly, we remain unconvinced that these extremely cost effective drugs should be abandoned from treatment guidelines. However, their adverse effects need to be taken into consideration when designing individualized approaches for the management of hyperglycemia. We would add that we don’t believe them to be good options in patients with active coronary artery disease and recommend stopping them at once if hypoglycemia occurs more than rarely after optimal dosage titration.

Another noteworthy secretagogue study was presented by Thai investigators, focusing on patients who fail sulfonylurea therapy (abstract 217). Their goal was to determine if sulfonylureas were still useful as glucose-lowering drugs in that setting. This is, of course, a common clinical conundrum: Should the drug be stopped if it is no longer working? Kunavisarut et al. studied 25 patients on maximal doses of a sulfonylurea and metformin who had an HbA1c ≥8%. Beta-cell function and insulin resistance/sensitivity status were measured by plasma glucose and insulin response to an oral glucose tolerance test (OGTT). This was performed 3 times: while the patient was receiving maximum dose of the sulfonylurea at baseline, after discontinuation for 4 weeks, and at 2 weeks after the reintroduction of the same drug at a lower dose (25% of the maximum recommended). During each study, plasma glucose and insulin levels were measured at 0, 30, 60, 90, and 120 minutes. Beta-cell function was determined by using the equation of area under the curve (AUC) of the insulin concentration divided by AUC of the glucose concentration. Insulin sensitivity and insulin resistance were measured by the Matsuda index and the homeostatic model of insulin resistance (HOMA-IR), respectively. All patients were maintained on the same metformin dose during the entire study.

The patients in this study had an extensive history of diabetes (mean duration, 12 years; range, 4-38). Beta-cell function both at the baseline study (maximum sulfonylurea dose) and at the follow-up study (reduced dose) was significantly higher than that during the time off the drug (p<0.001). This suggested that this therapy is still able to stimulate insulin secretion in patients who were no longer responding optimally. There was no difference in the Matsuda or the HOMA-IR measurements, indicating no significant effect of the sulfonylureas on insulin response, consistent with many other studies. The investigators felt that their data implied that sulfonylurea therapy is still useful and need not be stopped when patients progress to insulin therapy.

We feel the investigators may have over-reached a bit with this conclusion for two reasons. First, their patients may not all have required insulin. A third oral agent has become the standard approach in patients failing two agents in combination so long as hyperglycemia is not severe. Secondly, when transitioning to insulin, just because beta-cell function remains under some sulfonylurea control does not mean that the oral agent needs to be continued. By adjusting the insulin dose it is possible, perhaps probable, that the same quality of glycemic control can be achieved with insulin-metformin instead of the more complex insulin–sulfonylurea-metformin. In fact, several studies have reported increased hypoglycemia rates when insulin secretagogues are used in combination with insulin. So, caution is advisable.

Another traditional diabetes agent is, of course, metformin. This drug remains the most popular treatment for Type 2 diabetes in the US and much of the world. Its only widely recognized frequent side effect is diarrhea, affecting up to 50% of patients early in the treatment course. Less than 5%, however, cannot tolerate the drug long-term. Concerns about lactic acidosis have been muted in recent years with the realization that this specific complication is extremely rare and typically occurs because of another disease state such as overwhelming infection or CV collapse, usually in the setting of advanced renal dysfunction. In fact, studies have suggested that the overall lactic acidosis rate in metformin-treated patients is the same as in diabetic individuals not taking the medication. Because it is rarely cleared, however, chronic kidney disease is a contraindication to therapy, although the specific cut-points for stopping the drug are controversial and vary from country to country. In the US, prescribing guidelines prescribe its use when the serum creatinine reaches or exceeds 1.5 mg/dL in men and 1.4 mg/dL in women. In Europe, eGFR-based thresholds are used instead. In the UK, for example, the drug is continued when the eGFR reaches 60 mL/min/1.73m², reduced in dose (typically by half) at 45, and stopped only when the eGFR hits 30.

With chronic therapy, metformin has been associated with a modest reduction in circulating B12 levels over time, a less recognized side effect whose potential clinical impact is unknown. This is likely related to reduced vitamin absorption. Given the propensity of patients with longstanding diabetes to develop peripheral neuropathy, reduced B12 could be important. There are few data confirming any specific harmful effects of metformin on neurological function however. Out and Dutch colleagues analyzed data and blood from the HOme trial, in which 390 insulin-treated patients with Type 2 diabetes had 850 mg metformin or placebo added to their regimen up to three times daily for one year (abstract 220). The investigators specifically analyzed the association between metformin therapy and changes in HbA1c, methylmalonic acid (MMA) levels (a marker of the actual physiological impact of low B12 levels, increasing as B12 supply is reduced), and the Valk Score, a validated neuropathy measure. They utilized structural equation modeling (SEM) analysis to estimate the likelihood of either MMA levels or HbA1c control to be mediating changes in the Valk Score, so as to assess the overall effect of metformin on clinical neuropathy. Fifteen patients with known B12 deficiency at baseline or taking B12 supplements were excluded.

The investigators found that metformin was associated with an increase of MMA by the end of the study (0.04 μmol/L [95% CI: 0.02, 0.06; p=0.001]) as compared to placebo. There were no measurable differences in the neuropathy score, however, after 52 months between the metformin and placebo groups. In the mediation analysis, the effect of metformin on the neuropathy score was distinguished into a benefit from HbA1c lowering combined with a harm from the higher MMA. The investigators therefore concluded that not only does metformin reduce B12 concentrations and increase MMA, but that this may be associated with a significant underlying worsening of the neuropathy score.
While we find this analysis interesting, it’s hard to argue with the main finding of this study—no differences in the neuropathy score in the metformin-treated patients irrespective of what happened to their MMA. Of course, the findings may have been different following more long-term exposure to the drug. So, we feel that, irrespective of the findings of Out et al., it is reasonable to supplement such patients with oral vitamin B12 supplements (which has been demonstrated to result in higher B12 levels in metformin-treated patients). The relative cost effectiveness of tracking plasma B12 and MMA concentrations and intervening as needed or simply recommending prophylactic supplements in all chronic metformin users is not known.

Individualizing Type 2 diabetes treatments is key for successful and safe lowering of blood glucose levels. Unfortunately, we have little data to predict which drugs work best in which patient and who might be at the greatest risk for adverse effects of certain therapies. Shields et al. from the UK used their national Clinical Practice Research Datalink (CPRD) database to assess HbA1c responses to adding a second anti-hyperglycemic agent after metformin monotherapy (abstract 841). They assessed HbA1c levels over 12 months in 8,748 patients prescribed a sulfonylurea and 8,876 patients prescribed a TZD, and then used linear regression to explore the relationships between clinical phenotype and glycemic response, adjusted for baseline HbA1c. The analysis was then repeated for a large randomized clinical trial, ADOPTo (A Diabetes Outcome Progression Trial), which compared the monotherapy durability of the TZD, rosiglitazone (n=1,456), versus the sulfonylurea, glyburide (n=1,441), versus metformin. In CPRD, women appeared to respond better to TZDs (-0.2% greater HbA1c reduction compared to men, p<0.0001), and fared worse with sulfonylureas (-0.2% lesser response, p<0.0001). Patients who were obese appeared to respond better to a TZD (-0.2% greater HbA1c reduction compared to non-obese, p<0.0001) and non-obese patients responded better to sulfonylureas (-0.2% higher HbA1c response, p<0.0001). Of note, combining clinical features led to even greater response differences. For example, obese women experienced about a 0.4% greater HbA1c response to TZDs and non-obese men, approximately a 0.3% better response compared with sulfonylureas. Effect sizes were very similar when the ADOPTo data were queried post-hoc. The investigators concluded that patient clinical phenotypes may help to predict response to second-line glucose-lowering therapies, and that this information might be used to determine optimal treatment options at an individual level. We agree and appreciate the robustness of these data, taking advantage of information from both a healthcare database (where decisions to use certain medications are unknown) and a clinical trial (where treatment assignment is completely randomized). However, since side effects play such an important role in selecting and adherence to a diabetes medication, it is unclear how impactful this information might be. In an era where there is so much emphasis on new and more expensive diabetes drugs, a comprehensive understanding of older, very effective medications is important, although important safety issues must be considered.

**Table 2. Liraglutide versus Placebo in Patients with Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liraglutide (n=46)</th>
<th>Placebo (n=44)</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%) at 12 weeks</td>
<td>-0.7 (-0.8, -0.5)</td>
<td>-0.3 (-0.5, -0.1)</td>
<td>-0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c (%) at 26 weeks</td>
<td>-0.6 (-0.8, -0.5)</td>
<td>-0.5 (-0.6, -0.3)</td>
<td>-0.1</td>
<td>0.146</td>
</tr>
<tr>
<td>Body weight (kg) at 12 weeks (kg)</td>
<td>-5.02 (-5.84, -4.20)</td>
<td>-0.07 (-0.92, 0.78)</td>
<td>-4.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body weight (kg) at 26 weeks</td>
<td>-5.89 (-6.97, -4.82)</td>
<td>+0.23 (-0.63, +1.08)</td>
<td>-6.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Daily insulin dose (units) at 12 weeks</td>
<td>+3.15 (+1.20, +5.10)</td>
<td>+11.77 (+7.91, +15.63)</td>
<td>-8.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Daily insulin dose (units) at 26 weeks</td>
<td>+4.04 (+1.94, +6.15)</td>
<td>+13.61 (+9.2, +17.30)</td>
<td>-9.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate (beats per minute) at 26 weeks</td>
<td>+4.74 (+2.93, +6.55)</td>
<td>+0.24 (+2.35, +2.83)</td>
<td>+4.50</td>
<td>0.005</td>
</tr>
</tbody>
</table>

p<0.0001, and total daily insulin doses were reduced by 18.1 units in the liraglutide group and 2.3 units with placebo (p<0.0001). Rates of symptomatic and asymptomatic non-severe hypoglycemia did not differ between the groups. No patients experienced severe hypoglycemia. The investigators concluded that the addition of liraglutide to daily insulin therapy was an effective treatment option to improve glycemic control, while reducing body weight and daily insulin requirements without increasing hypoglycemia.

In a similar study, this time in patients with Type 1 diabetes*, Deiggaard and Danish co-investigators randomized 100 patients already on intensive insulin therapy to receive either liraglutide 1.8 mg daily or placebo over 26 weeks (abstract 114).
Baseline HbA1c was 8.8% in each group; body weight and total daily insulin doses were similar as well (93-94 kg and 60-61 units, respectively). Interestingly, at 12 weeks, HbA1c was reduced in the liraglutide group compared with placebo, but ultimately, this parameter was not different at week 26. The liraglutide group did maintain weight loss and reduced insulin dose for the full duration of the study (Table 2). Hypoglycemia rates did not differ between groups, however, there was an increase in heart rate and higher frequency of adverse gastrointestinal effects in the liraglutide group. Overall, we find these results not very encouraging for the future use of these agents in patients with Type 1 diabetes.

A group of researchers from Sweden, the US, and Austria utilized continuous glucose monitoring (CGM) to assess glycemic variability with weekly dulaglutide in comparison with daily glargine, each in combination with the prandial insulin analogue, lispro, in patients with Type 2 diabetes as a sub-study of the AWARD-4 trial (abstract 76). The hypothesis was that less glycemic variability due to dulaglutide would lead to lower risk of clinical hypoglycemia. Patients deemed uncontrolled on conventional insulin regimens (mean HbA1c 8.6%, BMI 32.9 kg/m²) were randomized to receive weekly dulaglutide 0.75 mg or 1.5 mg or daily glargine. According to findings from CGMS® iPro®, there were no significant differences for any of the three groups based on percent of time within glycemic range (70-180 mg/dL) at either baseline, 26, or 52 weeks with the exception of the dulaglutide 1.5 mg group at week 26 (i.e., change from baseline in percent time within range was 34.9 for dulaglutide versus 24.7 with glargine; p < 0.05). The primary advantage of dulaglutide was decreased percent of time less than 70 mg/dL at week 52 (1.3% with 1.5 mg, 1.1% with 0.75 mg, 4.5% with glargine; each p < 0.05 versus glargine). The investigators suggested that the results of their study are consistent with the lower risk of clinical hypoglycemia observed with dulaglutide in the overall AWARD-4 study. Further analysis will be required to detail the causal relationship between changes in glycemic variability and hypoglycemic episodes.

With weekly GLP-1 RAs (albiglutide, dulaglutide) now commercially available, several studies this week evaluated even longer-acting formulations. Interim data from a 16-week study using a novel, ultra long-acting (half-life ~158 hours) GLP-1 RA, HM11260C,* was presented by Del Prato and international colleagues (abstract 113). Patients with Type 2 diabetes (mean age 56 years, BMI 32.1 kg/m², diabetes duration of nearly 8 years) suboptimally controlled on stable doses of metformin were randomized to one of three doses of HM11260C or placebo. Each of the three doses (8, 12, and 16 mg) of the investigational agent resulted in clinically meaningful improvements of glycemic control and weight loss, with change in HbA1c statistically significant for the 8 mg/month dose (-1.26% vs. 0.30% for placebo, p=0.0002). The percent of patients achieving an HbA1c target <7% was 73.3% with 8 and 16 mg doses, 64.3% with 12 mg, and 22.2% with placebo. Percent change in body weight ranged from -2.2 to -2.8% with HM11260C in comparison to -1.2% with placebo at 4 months. A common adverse event was mild to moderate gastrointestinal distress. No increase in heart rate occurred, as has been found with other GLP-1 RAs (see below). While only preliminary, these data appear promising for a once-monthly dose of GLP-1 RA and, of course, more detailed and longer-term studies are under way.

Another interesting long-acting GLP-1 RA is ITCA 650,* an osmotic mini-pump system placed subdermally, designed to deliver continuous subcutaneous release of exenatide over one year. Baron and US co-investigators reported results from a 39-week randomized, double-blind, placebo-controlled trial in Type 2 diabetes (abstract 112). Patients were randomized 1:1:1 to receive ITCA 650 40 mcg/day or 60 mcg/day for 26 weeks (after 13 weeks at an initial dose of 20 mcg/day), or placebo. Mean reduction of HbA1c from baseline was significantly greater (p=0.001) for both doses of ITCA 650 versus placebo (40 mcg/day: -1.1% [95% CI: -1.3, -0.7]; 60 mcg/day: -1.2% [-1.4, -0.8]). The higher dose resulted in more significant weight loss and a higher percentage of patients achieving HbA1c <7%. Common adverse events were of a gastrointestinal nature, as seen with all GLP-1 based therapy, but fewer patients discontinued ITCA 650 for this reason. Overall, ITCA 650 was deemed effective in consistent drug delivery over 39 weeks, offering meaningful improvements in both glycemic parameters and body weight.

In addition to the studies evaluating glycemic control, several addressed non-glycemic actions of the GLP-1 RAs such as impact on CV parameters and outcomes and hepatic fat content. For example, international researchers, Lorenz et al., examined the differential effects of a number of GLP-1 RAs on 24-hour averaged heart rate in both patients with Type 2 diabetes and healthy volunteers (abstract 16). A literature review of publications reporting 24-hour time-averaged heart rate monitoring was conducted and data analyzed. Shorter acting agents such as exenatide twice daily and lixisenatide daily resulted in a smaller and shorter increase in heart rate (1-3 beats/minute ranging from 1-12 hours), whereas the longer-acting drugs (e.g., liraglutide, albiglutide, and weekly exenatide) were associated with a larger (6-9 beats/minute) and more prolonged effect. Dulaglutide was the exception as its increase in heart rate (1-3.5 beats/minute) was similar to the shorter-acting agents, but it still persisted at night. Only one head-to-head trial was evaluated: lixisenatide* (short-acting) had smaller increases in heart rate from baseline in comparison with liraglutide (longer-acting) and the greatest difference between the two occurred at nighttime. The clinical consequences of these effects with regard to CV events remain to be determined. Any drug that increases heart rate might raise some concerns in higher-risk patients.

Drug-related CV safety and long-term outcomes associated with medications used to manage diabetes are of great interest, with post-marketing surveillance required by regulatory agencies as new medications are approved. Anyanwagwu et al. from the University of Nottingham, UK evaluated CV events and all-cause mortality when insulin versus a GLP-1 RA is added to failed dual therapy with metformin and a sulfonylurea (abstract 937). Utilizing a retrospective cohort from the UK General Practices via The Health Initiative Network (THIN) databases, the risk of a CV composite outcome was determined in patients with Type 2 diabetes (n=2003) between 2006 and 2014. The two

Figure 1. Estimated Probability of Survival when Insulin or GLP-1RA is Added to Dual Therapy with Metformin and a Sulfonylurea

<table>
<thead>
<tr>
<th>Year</th>
<th>Met + SU + GLP-1</th>
<th>Met + SU + Ins</th>
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<tr>
<td>0</td>
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<td>0.25</td>
</tr>
<tr>
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<td>0.50</td>
</tr>
<tr>
<td>2</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* = osmotic mini-pump system
** = continuous subcutaneous release of exenatide
groups were taking metformin + sulfonylurea + insulin (n=1584) or metformin + sulfonylurea + GLP-1RA (n=419). Follow-up was five years (total of 6614 person-years) and propensity score matching analysis and Cox proportional hazard models were used. HbA1c reduction was similar in both groups (-1.3% with insulin versus -1.0% with a GLP-1 RA, p=0.156), however, the number of CV events was significantly greater in the group receiving insulin: 231 vs. 11 (44.5 vs. 7.7 per 1000 person-years adjusted HR: 0.27 [95% CI: 0.14-0.53] in favor of GLP-1 RA therapy, p<0.0001). Weight gain was also highest in the insulin group (+1.8 vs. -3.9 kg, p<0.0001). The investigators declared that patients in routine clinical practice demonstrate a much greater risk of CV events with add-on therapy, p<0.0001). The investigators reported that future risk of chronic liver disease, including cirrhosis as well as hepatocellular carcinoma, discovering new treatment modalities is imperative. We therefore find these data very compelling although, of course, longer-term data are necessary so that we may be able to establish a baseline), 21 overweight but healthy males (40.3±2.5 years; BMI 31±1.0 kg/m2) were randomized to a hyperenergetic (25% excess) high-fat diet (38% carbohydrate, 47% fat, 15% protein) or high-carbohydrate diet (65% carbohydrate, 20% fat, 15% protein) for 2 weeks. The investigators reported that excess energy consumption over this relatively short time frame increased liver fat content, as determined by 3T H1 magnetic resonance spectroscopy (Figure 2), triglycerides, apolipoprotein A (HDL), and apolipoprotein B (non-HDL).

**Nutrition Nuggets**

The impact of dietary constituents and eating habits on metabolic variables was the focus of several presentations this week.

**High Protein Diet**

Markova et al. from Germany randomized 30 Type 2 diabetes patients (age 65±6 years, BMI 30.5±3.6 kg/m2, HbA1c 7.0±0.6%) to a 6-week isocaloric high-protein diet (30% protein, 40% carbohydrates, 30% fat) of animal origin (meat and dairy foods) or plant origin (abstract 701). They noted that a high-protein diet improved glucose metabolism, i.e., HbA1c (animal-derived: -0.58%, p<0.05; plant-derived: -0.41%, p<0.001) and decreased liver fat content dramatically (-43.6% [p<0.001] and -37.1%, [p<0.001], respectively, independent of the origin of the protein. Insulin sensitivity (from hyperinsulinenic euglycemic clamps) improved significantly only in the animal protein group, however. High-protein diet had no adverse effects on kidney parameters. Actually, patients in the plant protein group experienced significantly reduced plasma creatinine (-7.79 µmol/l, p<0.01) and increased glomerular filtration rate (from 75.95 to 88.15 ml/min/1.73m 2, p<0.001). After dietary intervention, the investigators observed increased phosphorylation of some proteins of the Akt/mTOR pathway in subcutaneous adipose tissue (AMPK, Erk1/2, and 4E-BP1 -2-fold higher in the animal protein group; Bad and PDK1 significantly increased in the plant protein group), suggesting a differential modulation of intracellular signaling pathways.

**High-Fat Diet**

Chee et al. of the UK furthered our understanding of the effects of carbohydrate versus fat overfeeding on liver fat content and lipid metabolism in healthy overweight males (abstract 703). After 1 week of ingesting an isocaloric diet (to establish a baseline), 21 overweight but healthy males (40.3±2.5 years; BMI 31±1.0 kg/m2) were randomized to a hyperenergetic (25% excess) high-fat diet (38% carbohydrate, 47% fat, 15% protein) or high-carbohydrate diet (65% carbohydrate, 20% fat, 15% protein) for 2 weeks. The investigators reported that excess energy consumption over this relatively short time frame increased liver fat content, as determined by 3T H1 magnetic resonance spectroscopy (Figure 2), triglycerides, apolipoprotein A (HDL), and apolipoprotein B (non-HDL).
There were no significant changes, however, in body mass, visceral fat, insulin resistance (HOMA-IR), fasting insulin, fasting glucose, free fatty acids, total cholesterol, or liver function after 2 weeks of overfeeding. Compared with fat overfeeding, the high carbohydrate diet led to a greater increase in liver fat content (p=0.06; Figure 2). There were no other differential effects between diets based on measures of lipid metabolism or insulin resistance. The investigators concluded that the metabolic effects of excess energy consumption per se are greater than any differential effects of fat versus carbohydrate overfeeding.

**Rate of Eating**

Ohkuma et al. from Japan conducted a meta-analysis of 21 cross-sectional studies to evaluate the association between eating rate and obesity (abstract 707). Mean BMI was 1.78 kg/m² greater (95% CI, 1.53-2.04 kg/m²) among individuals who ate quickly as compared to those who ate slowly. The risk of obesity was more than 2-fold higher among rapid eaters (pooled odds ratio = 2.15; 95% CI: 1.84, 2.51). Three longitudinal studies also showed that a faster eating rate was associated with increased BMI and a higher risk of incident obesity over time.

With an overwhelming focus on pharmacological therapies for diabetes, it is important to realize the profound impact that nutrition has on metabolism. Each patient with diabetes should be offered a consultation with a registered dietician for advice on how to optimize his or her nutritional status.

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

**Glucagon Nasal Spray**

Sherr and collaborators from the US (7 study sites) examined the utility of intranasal (IN) glucagon for treatment of hypoglycemia in youth with Type 1 diabetes (abstract 42). A 3 mg intranasal dose of glucagon has been shown to effectively reverse hypoglycemia in adults with Type 1 diabetes. By way of background, intramuscular (IM) glucagon, in weight-adjusted 0.5 and 1.0 mg doses, is the only currently available pharmacologic treatment for severe hypoglycemia outside of the hospital setting. Unlike current IM emergency kits, needle-free dry-powder IN glucagon does not require reconstitution prior to administration.

In a double-blind study of 45 youth with Type 1 diabetes, those between 4 years and <12 years of age were randomized to 2 mg and 3 mg IN glucagon on two separate days, in random order, or a single weight-based dose of IM glucagon. Patients between 12 and <17 years of age received 1 mg IM glucagon at one session and 3 mg IN glucagon at another session, in random order. Glucagon was given after blood glucose was lowered to <80 mg/dL during a controlled, clamp procedure. The primary efficacy outcome, a ≥25 mg/dL rise in plasma glucose from nadir, was met within 10-20 minutes after all IM and IN doses of glucagon, with the exception of one (6-year-old) patient who immediately blew his nose following a 2 mg IN dose and in whom lack of absorption was documented by low peak glucagon (324 pg/mL). Time to peak and peak glucagon levels were similar following both IM and IN administration. Transient nausea (with or without vomiting) occurred during 67% of IM sessions vs. 42% of IN sessions (p=0.06). The investigators concluded that a single 3 mg IN glucagon dose can be safely and effectively used to treat hypoglycemia in pediatric Type 1 diabetes patients (4-<17-years) given the transient nature of adverse effects when they occur.

**Uric Acid and Diabetic Kidney Disease**

Diabetes is the major cause of chronic kidney disease (CKD). Recent evidence suggests that increased serum uric acid is a risk factor for loss of renal function and development and progression of CKD in patients with Type 1 diabetes. Studies presented this week further evaluated this association in both Type 1 and Type 2 diabetes.

Pacak and coworkers from the Czech Republic assessed the prognostic value of baseline uric acid and variability in selected genes involved in the regulation of uric acid metabolism for diabetic kidney disease (DKD) progression in 422 Type 2 diabetes patients over a median (IQR) follow-up of 47 [27-79] months (abstract 1102). The investigators evaluated two separate end-points. The first was DKD progression. This was defined as the decline of glomerular filtration rate (GFR) to <60 ml/min/1.73 m² during the follow-up period for those with GFR ≥60 at baseline; or the development of overt proteinuria in normo- and microalbuminuric patients at baseline; or, the progression of CKD by at least one stage for those with CKD 3 and 4 at baseline). In these analyses, all-cause mortality was employed as a competing risk. The second was major cardiovascular event (MACE), defined as fatal or non-fatal MI or cerebrovascular event, limb amputation, or revascularization, here with non-CV death as a competing risk. Analyses included survival analysis, competing risk analysis, and Cox regression.

All complications occurred at a very high rate in this cohort. The cumulative incidence of DKD progression was an impressive 54.4%, with MACE occurring at a 32.2% rate, and total mortality extremely high at 43.8%. Hyperuricemia at baseline (7.1 mg/dL in men, 6.1 mg/dL in women, or treatment with allopurinol) was a significant risk factor for both DKD progression and MACE (p<0.00001 and p=0.0021, respectively; log-rank test). An observation in this non-interventional study was a lack of protective effect with allopurinol with respect to DKD progression.

In a related study, Pilemann-Lyberg and coworkers from Denmark performed a post hoc analysis of data from a prospective, double-blind, clinical intervention study (losartan 100 mg) of diabetic nephropathy progression in Type 1 diabetes to evaluate the effect of serum uric acid on change in GFR (abstract 1103). At baseline, mean ± SD uric acid was 5.7 ± 1.7 mg/dL and GFR 87 ±23 ml/min/1.73m²; geometric mean (IQR) of uric acid excretion rate (UAER) was 1023 (631-1995) mg/24 hours. After adjustment for known progression factors (gender, HbA1c, systolic blood pressure, cholesterol, baseline GFR, and baseline UAER) in a linear regression model, uric acid was significantly associated with decline in GFR in this cohort of patients with Type 1 diabetes and nephropathy (r²=0.35, p=0.011). In backward elimination, uric acid was a significant predictor together with UAER and baseline GFR (r²=0.26, p=0.0031).

These findings suggest the need for larger, prospective studies of uric acid’s role in the development/progression of DKD. There is actually an ongoing large prospective clinical trial that will assess the potential impact of uric acid lowering with allopurinol to prevent renal function loss in patients with Type 1 diabetes (NCT02017171).

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

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The epidemic of Type 2 diabetes warrants strategic studies into the genetic susceptibilities and developmental programming that lead to the two main determinants of hyperglycemia: insulin resistance and progressive beta cell failure. This lofty task is only accomplished through detailed, metabolic characterization of people known to be at risk for Type 2 diabetes, as well as mechanism-driven research to probe differences between various metabolic subtypes. This is all in the hopes of preventing the onset of disease through targeted interventions in high-risk individuals.

At this year’s EASD meeting, the distinguished Claude Bernard Lecture was given by Dr. Hans-Ulrich Haring from the University of Tubingen, Germany, who for over 20 years has studied a cohort of over 3,000 people at risk for Type 2 diabetes, with the purpose of phenotyping pre-diabetes. His group’s cohort has a mean age of 45 years at the time of enrollment, with risk factors including prior gestational diabetes, obesity, or a positive family history of diabetes. Based on an OGTT, the subjects were characterized as having diabetes (Type 2), impaired fasting glucose and/or impaired glucose tolerance (IFG/IGT), or normal glucose tolerance. Over the years, subsets of this cohort have participated in several studies, including a lifestyle intervention program (TULIP) of 400 subjects with OGTTs at baseline, 1 year, and 8 years after intervention. While the 1-year data showed an initial improvement in insulin sensitivity with lifestyle intervention, by 8 years, unfortunately, insulin sensitivity worsened.

In a search to find the underlying reasons for this persistent disease progression, studies were completed to examine the contributions of genetics, ectopic fat, and altered brain regulation to diabetes risk. Within the Tubingen cohort, the effect of genetics on diabetes risk was found to be modest, with only a few gene variants indicating an increased risk. However, for subjects in his cohort with a variant TCF7L1 allele, impaired glucose stimulated insulin secretion was realized, an important downstream physiological consequence contributing to disease progression.

In contrast, the study of ectopic fat proved a higher yield in predicting diabetes risk. Using MRI and MR spectrometry scans from more than 2000 subjects, Dr. Haring and colleagues realized that visceral fat, including the presence of ectopic fat within liver cells, was the primary indicator of whether an obese person was ‘metabolically unhealthy.’ However, even within this group, some subjects were more insulin sensitive than others. They further characterized a ‘metabolically benign’ fatty liver, in which a specific pattern of fatty acid metabolism did not lead to the usual lipotoxicity and its consequences. A single nucleotide polymorphism in the patatin-like phospholipase 3 (PNPLA3) gene may play a role in a protective pattern of fatty acid metabolism. The subjects with insulin resistance, fatty liver, and lipotoxicity had evidence of microinflammation, thought to be a result of signaling through the Toll-like receptor, TLR4, in hepatocytes. Further work showed that fetuin A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance, and plasma levels of fetuin A correlate well with insulin resistance.

But what about the connection to beta cell failure? Dr. Haring next described how ectopic fat can actually accumulate in the islets of the pancreas, near the beta cells, which his group discovered by imaging and through histological human islet studies. This site-specific fat accumulation is associated with macrophages, likely due to the fat secretion of monocyte chemoattractant protein-1 (MCP-1) and cytokines IL-6 and IL-8 that promote macrophage recruitment and activity. Also, in a model of cross-talk between organs, fetuin A, which is synthesized by the lipotoxic liver, stimulates fat cells in the pancreatic islet to secrete these pro-inflammatory molecules. In this model, the key to preventing beta cell functional decline may actually be treatment directed at fatty liver. Consistent with this hypothesis, in a previous exercise intervention trial, 50% of people with fatty liver responded very well in terms of reducing...
liver fat and improving insulin secretion. However, 25% of participants in this study did not improve at all with exercise, indicating a resistant phenotype that may require drug therapy to reduce hepatic steatosis. The mechanism behind this resistant phenotype is unknown but under active investigation.

Finally, in an exciting new direction of research, Dr. Haring addressed the role of the brain in determining peripheral insulin sensitivity, and the efforts underway to understand how gestational diabetes (GDM) may alter fetal brain programming toward an insulin resistant and obesogenic phenotype that may actually begin in utero. New advances in MR technology, known as fetal magnetoencephalography (fMEG) enable assessment of fetal brain function during pregnancy. Initial studies comparing fetal brain activity during pregnancies in women with GDM versus normal glucose tolerance showed that fetuses of GDM women had slower brain response time to an auditory stimulus during an OGGT. These findings add even further support to the goal of tight glucose control during pregnancy.

Understanding the subphenotypes in pre-diabetes may define the success of Type 2 diabetes prevention. Whether it is tight glucose control during pregnancy or exercise prescriptions for fatty liver disease, an individualized approach in characterizing and treating pre-diabetes is an important investment in holding back the tide of obesity-driven Type 2 diabetes.

**SGLT-2s: “New Kid on the Block”**

Sodium glucose co-transporter (SGLT)-2 inhibitors are the newest class of antihyperglycemic drugs for the management of Type 2 diabetes. They promote urinary excretion of glucose via inhibition of SGLT-2 in the proximal nephron, resulting in a reduction of glucose reabsorption and a lowering of the renal threshold for glucose excretion—an insulin-independent phenomenon. Canagliflozin, dapagliflozin, and empagliflozin are all now approved in the US. Presentations made this week at the 2015 EASD Annual Meeting focused on the long-term non-glycemic effects of SGLT-2 inhibition, efficacy and safety in combination with insulin and other antihyperglycemic agents, and the concept of dual SGLT-1/SGLT-2 inhibition.

**Renal Function and Albuminuria**

Hypertension and albuminuria are risk factors for CV and renal disease in patients with Type 2 diabetes, and control of glycemia, blood pressure, and albuminuria are important to reducing risk of these sequelae.

Interested in the effect of SGLT-2 inhibition on albuminuria and estimated glomerular filtration rate (eGFR), Heerspink et al. from the Netherlands and Sweden pooled data from 2 studies of Type 2 diabetes patients with micro- or macroalbuminuria and hypertension on stable angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy, who were assigned to dapagliflozin 5 mg (n=87), 10 mg (n=167), or placebo (n=189) (abstract 185). They determined that dapagliflozin reduces albuminuria on top of renin-angiotensin system blockade in hypertensive patients with diabetes. At 12 weeks, dapagliflozin resulted in greater reductions from baseline versus placebo in albuminuria. The mean difference (95% CI) versus placebo for albumin:creatinine ratio (ACR) was -35.2 mcg/mg (-49.5, -16.8) with dapagliflozin 5 mg and -33.2 mcg/mg (-45.4, -18.2) for dapagliflozin 10 mg. There was a decrease in eGFR with dapagliflozin (-1.5 and -3.1 mg/mL/1.73 m², respectively), which was reversed 1 week after the last dose. The ACR-reducing effect was also present after adjustments for changes in HbA1c, systolic blood pressure (SBP), and eGFR. There were no serious renal-related adverse events in any group.

**Blood Pressure Effects**

Cooper and multinational collaborators evaluated the effect of CKD on blood pressure modulation and weight loss with the SGLT-2 inhibitor empagliflozin. The investigators pooled data from 5 trials in which 2,286 patients with Type 2 diabetes were randomized to empagliflozin 25 mg or placebo for 24 weeks, as monotherapy or add-on therapy (abstract 751). Data were adjusted for differences in baseline SBP body weight, HbA1c, region, treatment, study, and baseline eGFR.

Among patients with normal renal function, or stage 2 or 3 CKD, the SGLT-2 inhibitor significantly reduced HbA1c, SBP, and body weight, as compared to placebo. As expected, improvements in HbA1c and body weight with empagliflozin were reduced with decreasing baseline eGFR, since glucose excretion requires reasonably intact filtration. However, placebo-corrected reductions in SBP were maintained irrespective of baseline renal function. The mean difference (95% CI) with empagliflozin vs. placebo was -3.2 (-4.9, -1.5) mmHg for eGFR ≥ 90 mL/min/1.73 m² (normal renal function) -4.0 (-5.4, -2.6) mmHg for eGFR 60 to <90 (CKD stage 2), -5.5 (-7.6, -3.4) mmHg for eGFR ≥ 30 to <60 (CKD stage 3), and -6.6 (-11.4, -1.80) mmHg for eGFR <30 (CKD stage 4). The investigators concluded that their study findings suggest that SBP modulation with empagliflozin may involve pathways other than urinary glucose excretion such as diuretic effects, weight loss, reduced arterial stiffness, or direct vascular effects.

**Weight Loss**

Stenlöf and coworkers from Sweden and the US reported on the long-term effects of SGLT-2 inhibition on weight loss in Type 2 diabetes patients, resulting from mild osmotic diuresis and net caloric loss (abstract 739). The investigators evaluated weight change in two randomized, double-blind, studies of canagliflozin 100 mg and 300 mg. Study 1 tested the drug versus glimepiride as add-on to metformin in a 52-week core period, followed by a 52-week extension (n=1,450, mean age 56.2 years, HbA1c 7.8%, body weight 86.6 kg). Study 2 was versus placebo in older patients (55-80 years) on various background antihyperglycemic therapies in a 26-week core period, followed by a 78-week extension (n=714, mean age 63.6 years, HbA1c 7.7%, body weight 89.5 kg). Both doses of canagliflozin led to body weight reduction in a greater proportion of Type 2 diabetes patients compared with the sulfonylurea (SU) or placebo over 104 weeks. Most canagliflozin-treated patients (80-90%) experienced body weight reductions, and a greater proportion achieved ≥5% and ≥10% weight loss, versus the comparator. In Study 1, the proportions of patients with ≥5% body weight reduction with canagliflozin 100 mg and 300 mg and SU were 33%, 43%, and 6%, respectively, at Week 52 (Figure 3A), and 35%, 40%, and 7%, respectively, at Week 104. In Study 2, the proportion of patients with ≥5% body weight reduction with canagliflozin 100 mg and 300 mg and placebo was 24%, 28%, and 4%, respectively, at Week 26 (Figure 3B), and 28%, 33%, and 11%, respectively, at Week 104. The proportion of patients with weight loss ≥10% was low across groups in both studies, but higher with canagliflozin versus comparator.
Combination with Insulin

Gaal and multinational investigators conducted a post hoc analysis of 1,718 Type 2 patients (mean age 63 years; HbA1c 8.3%; eGFR, 74.9 mL/min/1.73 m²; Type 2 diabetes duration 16.6 years; insulin dose 83 IU/day) with a history or high risk of CV disease enrolled in the CANgliflozin cardioVascular Assessment Study (CANVAS) (abstract 745). Study patients received canagliflozin 100 or 300 mg or placebo once daily, in addition to insulin ≥30 IU/day, for 18 weeks. Consistent with its insulin-independent mechanism of action, the SGLT-2 inhibitor improved glycemic control, as well as body weight and SBP, and was generally well tolerated compared with placebo, across tertiles by baseline insulin dose. Relative to placebo, canagliflozin 100 mg (-0.64%, -0.70%, -0.59%) and 300 mg (-0.71%, -0.77%, and -0.72%) provided reductions in HbA1c at week 18 that were similar across tertiles of baseline insulin dose (≥54 IU/day, 54-<90 IU/day, and <90 IU/day, respectively). The incidence of documented hypoglycemic episodes was higher with canagliflozin 100 mg and 300 mg compared with placebo across tertiles, and the incidence of severe hypoglycemia episodes was low across groups in all tertiles.

Combined with a DPP-4 inhibitor or GLP-1 RA

Woo and CANVAS coworkers reported that the addition of a SGLT-2 inhibitor to DPP-4 inhibitor or GLP-1 RA leads to reductions in HbA1c and body weight (abstract 186). Of the 4,330 Type 2 diabetes patients enrolled in CANVAS, 316 patients were taking a DPP-4 inhibitor (mean baseline HbA1c 8.1%, body weight 90.7 kg) and 95 were taking a GLP-1 RA (mean baseline HbA1c 8.1%, body weight 108.8 kg). As noted above, patients were randomized to one of two canagliflozin doses or placebo. In the DPP-4 inhibitor subgroup, a greater proportion of patients had reductions in both HbA1c and body weight at week 18 with canagliflozin 100 mg and 300 mg versus placebo (65.3%, 78.1%, and 29.2%, respectively; placebo-subtracted differences [95% CI] of 36.2% [22.2, 50.2] and 48.9% [35.9, 62.0]). Likewise, a greater proportion of patients in the GLP-1 RA subgroup had reductions in both HbA1c and body weight at week 18 with canagliflozin 100 mg and 300 mg versus placebo (82.4%, 85.7%, and 24.1%, respectively; placebo-subtracted differences of 58.2% [34.9, 81.6] and 61.6% [37.8, 85.3]). There are no published randomized trials yet with SGLT-2 inhibitors and GLP-1 RAs, so these essentially observational data from CANVAS are of some interest.

Dual SGLT-1 and SGLT-2 Inhibition

CEFalu and US colleagues hypothesized that dual inhibition of both SGLT-1 (to reduce glucose absorption in the gastrointestinal tract, with an increase in incretins) and SGLT-2 (to reduce renal glucose reabsorption) may provide additional benefit above that achieved with SGLT-2 inhibition alone when used as adjunctive therapy to insulin in Type 1 diabetes. Sotagliflozin (LX4211) is a dual inhibitor of SGLT1 and SGLT2.*

The investigators conducted a double-blind study in which they randomized 33 patients with Type 1 diabetes (ages 21-57 years, duration of diabetes 3-42 years, screening HbA1c 7.0%-9.0%), treated with insulin pump or multiple daily injection therapy, to sotagliflozin 400 mg or placebo once daily to treated with insulin pump or multiple daily injection therapy, to sotagliflozin 400 mg or placebo once daily

Table 3. Effects of Sotagliflozin Added to Insulin in Type 1 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=17</th>
<th>Sotagliflozin n=16</th>
<th>p-value Sotagliflozin vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c change from baseline (%)</td>
<td>-0.06</td>
<td>-0.55</td>
<td>0.002</td>
</tr>
<tr>
<td>Daily bolus insulin change from baseline assessed at days 3-27 (%)</td>
<td>-6.4</td>
<td>-32.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Daily basal insulin change from baseline assessed at days 3-27 (%)</td>
<td>+0.2</td>
<td>-2.4</td>
<td>0.53</td>
</tr>
<tr>
<td>Total daily insulin change from baseline assessed at days 3-27 (%)</td>
<td>-0.7</td>
<td>-15.3</td>
<td>0.029</td>
</tr>
<tr>
<td>Mean body weight change from baseline assessed at day 29 (kg)</td>
<td>+0.5</td>
<td>-1.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Post-meal urinary glucose (g/3 hr) at day 29</td>
<td>9.2</td>
<td>29.1</td>
<td>0.025</td>
</tr>
<tr>
<td>PYY post-meal AUC change from baseline assessed at day 29 (pmol/L*h over 3 hr)</td>
<td>-0.7</td>
<td>+6.0</td>
<td>0.018</td>
</tr>
</tbody>
</table>
daily for 29 days (abstract 182). Sotagliflozin improved glycemic control among the study patients, significantly reducing HbA1c, daily bolus and total daily insulin dose, postprandial blood glucose, and body weight, and increasing the anorectic hormone, PYY (Table 3), with no increase in hypoglycemia risk. Larger studies of a longer duration are needed to confirm these findings.

While all these data are of some interest, there is palpable excitement in Stockholmsmassan convention center for Thursday’s presentation of the results of the EMPA-REG OUTCOME trial, the first large CV trial with an SGLT-2 inhibitor (empagliflozin) to report. Be sure to read our next edition to update you on those findings!

### New Insulins on the Horizon

Insulin therapy remains imperfect, owing to non-physiological delivery systems, variable absorption, and pharmacokinetic properties that vary from formulation to formulation. These issues superimposed upon the variability in patients’ nutritional intake and physical activity from day to day make the control of glucose through injections or infusions of this life-saving hormone very challenging. At the 2015 EASD Annual Meeting, many presentations concerned new types of insulin products and delivery devices, most still investigational.

**Peglispro: A Novel Basal Insulin**

Insulin peglispro, a pegylated basal insulin in late-stage clinical development, has demonstrated hepato-preferential action and reduced peripheral effects in muscle and fat. Results of studies of peglispro in both Type 1 and Type 2 diabetes patients were presented in Stockholm this week.

Garg and coworkers from the US, Europe, and Japan randomized 455 patients with Type 1 diabetes (51% female, HbA1c <12%) to bedtime peglispro (n=295) or glargine (n=160), each with prandial insulin lispro (abstract 3). At week 26, HbA1c reduction was greater with peglispro compared with glargine (treatment difference -0.37%; 95% CI: -0.50%, -0.23%) and more peglispro-treated patients reached HbA1c targets (Table 4). In addition, peglispro led to modest weight loss, possible related to its differential effects in liver vs. peripheral tissues. The nocturnal hypoglycemia rate was lower, but the total and severe hypoglycemia rates were higher with peglispro. There were significant between-group differences based on insulin dose (i.e., basal dose higher and bolus and total dosages lower in the peglispro group). While triglycerides were significantly increased with peglispro versus glargine, LDL-C and HDL-C were not. Of some concern, however, was the fact that more peglispro-treated patients experienced an increase in ALT >3 x ULN (4.5% vs. 0.7%, p=0.041) and injection site reactions (25% vs. 0%, p<0.001). No patients met Hy’s Law criteria for acute, severe drug-induced liver injury. Peglispro, interestingly, increased liver fat content, assessed by MRI, in a subset of patients and this is an additional concern that needs to be addressed.

In a double-blind study, Davies et al. from the US, UK, and Hungary randomized insulin-naïve patients with Type 2 diabetes to evening dosing of peglispro (n=1003) or glargine (n=535), added to oral antihyperglycemic drugs (OAD) (abstract 40). Peglispro-treated patients experienced a greater reduction in HbA1c at week 52 compared to glargine-treated patients (-1.6 vs. -1.3%; A=0.3% (95% CI: -0.40, -0.19)), with more patients at HbA1c goal of <7.0%: 58% vs. 43%, p<0.001. Within-day and between-day glycemic variability were significantly lower for peglispro, as was the incidence of nocturnal hypoglycemia (0.30 ± 0.02 vs. 0.40 ± 0.03 events/patient/30 days, p<0.001), whereas the rate of total hypoglycemia was similar between the groups. More patients had HbA1c <7% without nocturnal hypoglycemia with peglispro than with glargine (26% vs. 15%, p<0.001). At week 52, weight gain was less with peglispro (2.1 ± 0.2 vs. 2.6 ± 0.2 kg, p=0.046), but insulin dose was higher (0.45 ± 0.01 vs. 0.42 ± 0.01 U/kg, p=0.022). Thus, peglispro was titrated to a higher dose than glargine with similar total hypoglycemia rates, lower HbA1c, and less weight gain.

**Table 4. Peglispro vs. Insulin Glargine in Type 1 Diabetes Patients**

<table>
<thead>
<tr>
<th></th>
<th>26 weeks</th>
<th>78 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glargine</td>
<td>Peglispro</td>
</tr>
<tr>
<td>HbA1c (%)b</td>
<td>7.4 ± 0.1</td>
<td>7.1 ± 0.0</td>
</tr>
<tr>
<td>HbA1c &lt;7% (n of patients)</td>
<td>27.5</td>
<td>44.9</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)b</td>
<td>160.2 ± 5.4</td>
<td>138.6 ± 0.4</td>
</tr>
<tr>
<td>Body weight change (kg)b</td>
<td>0.7 ± 0.3</td>
<td>-1.2 ± 0.2</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia (RR)c,d</td>
<td>2.7 ± 0.2</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>Total hypoglycemiaa</td>
<td>12.4 ± 0.6</td>
<td>16.0 ± 0.4</td>
</tr>
<tr>
<td>Severe hypoglycemiaa</td>
<td>16.2 ± 5.9</td>
<td>39.0 ± 7.4</td>
</tr>
<tr>
<td>Basal daily insulin (U)b</td>
<td>25.9 ± 0.8</td>
<td>29.2 ± 0.7</td>
</tr>
<tr>
<td>Bolus daily insulin (U)b</td>
<td>35.0 ± 1.4</td>
<td>26.9 ± 1.1</td>
</tr>
<tr>
<td>Total daily insulin (U)b</td>
<td>59.7 ± 1.9</td>
<td>53.3 ± 1.6</td>
</tr>
<tr>
<td>Between-day glucose variability (mg/dL)b</td>
<td>59.3 ± 2.4</td>
<td>52.5 ± 1.8</td>
</tr>
<tr>
<td>ALT (IU/L)b</td>
<td>21.0 ± 1.3</td>
<td>29.4 ± 0.9</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.96 ± 0.06</td>
<td>1.24 ± 0.04</td>
</tr>
<tr>
<td>LFC (N) (2 studies)</td>
<td>(64) (118)</td>
<td>(11) (26)</td>
</tr>
<tr>
<td>LFC (%)</td>
<td>3.0 ± 0.3</td>
<td>5.4 ± 0.2</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; LFC = liver fat content; LSM = least squares mean; RR = relative rate peglispro/glargine; ULN = upper limit of normal.

* p<0.5 , ** p<0.01, *** p<0.001
peglispro and decreased with glargine (11 ± 2 vs. -7 ± 3 mg/dL, p<0.001). HDL- and LDL-cholesterol were not different between groups. More peglispro-treated patients had ALT ≥3 x ULN (2.3% vs. 0.6%, p<0.012; no Hy’s Law cases). Liver fat content (assessed by MRI) was unchanged from baseline with peglispro (-0.6 ± 0.5%, p=0.232) and decreased with glargine (3.1 ± 0.7%, p<0.001; p=0.002 between groups). Injection site reactions were more common with peglispro (3.5% vs. 0.6%, p<0.001), the majority being lipohypertrophy (2.1% vs. 0.4%, p=0.007). Adjudicated CV events were similar between the peglispro and glargine groups.

We conclude that this insulin has some promise as a new basal formulation but that there remain some safety issues to understand and further explore.

**Faster Insulin Aspart?**

In a double-blind, crossover study, Bode et al. from the US and Denmark randomized 43 adults with Type 1 diabetes, who underwent blinded continuous glucose monitoring (CGM), to 14 days of continuous subcutaneous insulin infusion (CSII) of a ‘faster-acting’ insulin aspart and CSII of ordinary insulin aspart (abstract 39). The faster aspart formulation resulted in a significantly greater glucose-lowering effect than aspart, as reflected in lower mean change in prandial glucose response 2 hours after a standardized meal test (individualized insulin dosing by bolus calculator) (ΔPG0–2h): (54.5 vs. 72.4 mg/dL; mean difference [95% CI]: -17.8 [-35.1; -0.54]). These findings were confirmed by CGM for all meals, and all less time spent with interstitial glucose levels (i.e., ≤70 mg/dL per 24 hours) (2.03 vs. 2.45 hours; mean difference [95% CI]: -0.42 [-0.72; 0.11]). No new safety findings were observed for this investigational product.

**Basal Insulin and GLP-1 Agonist in One Injectable?**

Due to the progressive nature of Type 2 diabetes, most patients will require treatment intensification, many requiring insulin in combination with an oral agent(s). In this regard, results of several studies of a new combination injectable, insulin degludec (a new basal insulin available in Europe) plus li raglud t e, a GLP-1 RA (IDegLira), added to OADs, were presented this week, each showing that IDegLira significantly benefited glycemic control.

In a 26-week open-label trial, Linjawi and multinational investigators randomized insulin-naive Type 2 diabetes patients with poor glycemic control despite maximum dose GLP-1 RA therapy (li raglud t e QD or exenatide BID) plus OADs (i.e., metformin ± pioglitazone ± sulfonylurea) to the combination product QD (n=292) or continuation of (i.e., unchanged) GLP-1 RA therapy (n=146), each added to baseline OADs (abstract 834). IDegLira led to significant reduction in mean HbA1c (Table 5). The majority (75%) of IDegLira-treated patients achieved Hba1c <7% (vs. 36% on unchanged GLP-1 RA; p<0.001). Fasting plasma glucose and 9-point self-measured blood glucose (SMBG) profiles improved significantly more with IDegLira than unchanged GLP-1 RA (Table 5). Weight increase and confirmed hypoglycemia were more common with the combination product. Mean IDegLira dose at 26 weeks was 43 U insulin degludec/1.55 mg li raglud t e. Importantly, this formulation’s dose is adjusted predominately based on the insulin component, given the fixed ratio. The maximum dose is the maximum daily approved amount of the li raglud t e component. So, the precise dose of the GLP-1 RA will totally depend on what dose of degludec is reached.

**Table 5. Liraglutide ± Insulin Degludec in Type 2 Diabetes Patients**

<table>
<thead>
<tr>
<th>Observed Change from Baseline to 26 Weeks</th>
<th>IDegLira</th>
<th>Unchanged GLP-1RA</th>
<th>Estimated Treatment Difference [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>-1.3 (0.8)</td>
<td>-0.3 (0.9)</td>
<td>-0.94 [-1.11; -0.78]</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL), mean (SD)</td>
<td>-53.6 (41.0)</td>
<td>-10.8 (49.3)</td>
<td>-47.5 [-54.5; -40.5]</td>
</tr>
<tr>
<td>Mean of 9-point SMBG profile (mg/dL), mean (SD)</td>
<td>-39.6 (34.2)</td>
<td>-10.8 (43.2)</td>
<td>-32.0 [-38.3; -25.7]</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>+2.0 (3.9)</td>
<td>-0.8 (3.0)</td>
<td>2.89 [2.17; 3.62]</td>
</tr>
<tr>
<td>Hypoglycemia, observed rate/ patient-year of exposure</td>
<td>2.82</td>
<td>0.12</td>
<td>Estimated rate ratio (95% CI); negative binomial regression 25.4 (10.6; 60.5) p&lt;0.001</td>
</tr>
</tbody>
</table>

* ANCOVA analysis; IDegLira—Unchanged GLP-1RA.
† plasma glucose <55.8 mg/dL or severe (reported for 1 patient in the IDegLira group) during treatment period.

**Figure 4. Mean HbA1c Over Time in Type 2 Diabetes: IDegLira vs. Glargine**

Mean observed values with error bars (standard error mean) based on full analysis set and LOCF imputed data — ADA/EASD HbA1c, target <7.0%; AACE HbA1c target <6.5% AACE=American Association of Clinical Endocrinologists; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes.

-3.20 kg [-3.77, -2.64], p<0.001). Significantly more (all p<0.001) IDegLira-treated patients achieved prespecified endpoints of: Hba1c <7% (71.6% vs. 47.0% with glargine; estimated odds ratio [95% CI] 3.45 [2.36; 5.05]); Hba1c <7% without hypoglycemia (54.3% vs. 29.4%; 3.24 [2.24; 4.70]); and, Hba1c <7% without hypoglycemia and no weight gain (38.8% vs. 12.2%; 5.53 [3.49; 8.77]). The investigational product was to some degree ‘insulin sparing;’ the mean 26-week dose was 41 units of the degludec component versus 66 units with glargine (p<0.001).
Closing the Loop

Developing a mechanized artificial pancreas is the goal of many investigators who are pursuing a fully integrated insulin pump communicating with a glucose sensor (CGM). In an open-label, 3 center crossover study, Thabit et al. from the UK, Germany, and Austria randomized 33 adults with Type 1 diabetes on insulin pump therapy (18 males, age 40.0 ± 9.4 years, HbA1c 8.5 ± 0.6%, duration of diabetes 20.9 ± 9.3 years) to two 12-week periods of sensor augmented pump (SAP) therapy at home, under normal conditions with or without day-and-night closed-loop insulin delivery utilizing a model predictive control algorithm to direct insulin delivery (abstract 987). All patients underwent 5 to 6 weeks of training and optimization on SAP beforehand. The order of interventions was random with a 4-week washout between study periods. The proportion of time when sensor glucose was in target range (70 to 180 mg/dL) was significantly increased during closed-loop compared to SAP control (p<0.001; Table 6). Mean glucose and time spent hypoglycemic were significantly reduced during closed loop, this being achieved without changing the total daily insulin dose delivery (p<0.57). These findings suggest that prolonged home use of unsupervised day-and-night closed loop under free living conditions in adults with Type 1 diabetes may be feasible, conferring improved glucose control and reduced exposure to hypoglycemia without increasing total daily insulin exposure.

We look forward to ongoing research in the area of insulin management, where advances in technology will hopefully make life easier for our patients.

Table 6. Glucose Control Over 12 Weeks: Sensor-Augmented Pump Without (Control) or With Closed-Loop

<table>
<thead>
<tr>
<th>Time spent at glucose levels (%)</th>
<th>Closed-loop (n=32)</th>
<th>Control (n=33)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 to 180 mg/dL</td>
<td>67.7 ± 10.6</td>
<td>56.8 ± 14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;180 mg/dL</td>
<td>29.2 ± 11.4</td>
<td>38.9 ± 16.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;70 mg/dL</td>
<td>2.9 (1.4, 4.5)</td>
<td>3.0 (1.8, 6.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean glucose (mg/dL)</td>
<td>156.6 ± 19.8</td>
<td>167.4 ± 28.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total daily insulin delivery (U)</td>
<td>48.8 ± 16.1</td>
<td>48.1 ± 15.4</td>
<td>0.57</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Pre-intervention</td>
<td>7.6 ± 3.1</td>
<td>7.6 ± 3.0</td>
</tr>
<tr>
<td>Post-intervention</td>
<td>7.3 ± 3.0</td>
<td>7.6 ± 3.2</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or median (IQR)

Fatty Liver Disease in Type 2 Diabetes

Nonalcoholic fatty liver disease (NAFLD) is especially prevalent in patients with Type 2 diabetes and is frequently associated with elements of the metabolic syndrome such as obesity, dyslipidemia, and insulin resistance. Clinical presentation may range from simple elevation of hepatic aminotransferase levels in asymptomatic patients to clinical steatohepatitis, cirrhosis, hepatocellular carcinoma, and complete organ failure. An entire morning symposium, entitled “Liver in Focus,” was devoted to this topic.

Professor Hannele Yki-Jarvinen, University of Helsinki, discussed diagnosis of NAFLD. She announced, with great excitement, that the first joint guideline endorsed by the EASL (European Association for the Study of the Liver), EASD, and IASO (International Association for the Study of Obesity) on NAFLD and diabetes is soon to be published. Dr. Yki-Jarvinen described NAFLD as a heterogeneous disease with various etiologies: (1) metabolic (obesity, metabolic syndrome, diabetes); (2) genetic; and, (3) combination of metabolic, genetic, and ethanol use. NAFLD is the most common form of chronic liver disease, with obesity being its most common cause. There are two well-described gene variant forms: (1) PNPLA3 I148M (more common) and (2) TMGS2 E167K (less common) strongly associated with the development of NAFLD. Each is independent of obesity and not associated with insulin resistance. She provided rationale for why a diabetologist should be interested in NAFLD including its predictive value for Type 2 diabetes, predictive value for CV disease independent of obesity, and its strong association with hepatocellular carcinoma.

Yki-Jarvinen recommended screening of patients with metabolic syndrome or Type 2 diabetes for NAFLD. Specifically, hepatic enzymes, steatosis biomarkers (e.g., fatty liver index, NAFLD Liver Fat Score, SteatoTest™), and/or ultrasound should be part of the routine work up. She cautioned that ~50% of Type 2 diabetes have NAFLD despite normal ALT levels, therefore, fibrosis biomarkers are recommended as well (e.g., NAFLD Fibrosis Score, FIB-4 calculation). Routine testing for gene variants is not recommended. Genetic carriers have elevated hepatic fat content and increased prevalence of nonalcoholic steatohepatitis (NASH), which may be an indication for further study. Dr. Yki-Jarvinen’s closing remark was an emphatic: Think of the liver every time you see a patient with Type 2 diabetes!

Dr. Kenneth Cusi, University of Florida, US, closed the symposium with his presentation, “Novel Treatment of NAFLD: Current Approaches and Future Directions.” He first discussed NASH in the context of the prevalence of prediabetes and Type 2 diabetes. A recent survey estimated that nearly half of the US population has either pre-diabetes or diabetes (JAMA 2015). Given the strong association between NAFLD and diabetes, this is of grave concern. Secondly, he discussed the approach to treatment stating that targeting adipose tissue and altering glucose and/or lipid metabolism should be the primary approach. Dr. Cusi shared data from some initial trials involving drugs currently on the market. To date, the most promising data are from the TZD, pioglitazone;* and the GLP-1, liraglutide.* However, long-term, larger studies are needed before either can be routinely recommended. There are several investigational agents under evaluation with the most notable being: obeticholic acid,* a farnesoid X receptor agonist; GFT-505,* a PPAR-alpha/delta agonist; and cenicriviroc,* a dual CCR2/CC5 receptor antagonist.

With respect to the future, in Cusi’s opinion, pioglitazone should play a significant role. Of course, the risk versus benefit ratio must be evaluated. He indicated there are emerging pharmacogenetic
data that identify those who are most likely to respond. He also shared a preliminary treatment algorithm for pioglitazone use based on adiponectin levels. Dr. Cusi closed with recommendations to actively employ screening and the need for the development of a long-term treatment approach.

Related to the content of the morning symposium, Tang and colleagues from China completed a comprehensive analysis of clinical trials involving Type 2 diabetes and liver disease to identify the comparative efficacy of anti-hyperglycemic medications on NAFLD (abstract 726). Both randomized (n=19) and non-randomized (n=14) trials involving 1,196 subjects that reported relative changes in hepatic fat content and liver histology were included in the meta-analysis. The TZDs when utilized for 12 to 72 weeks had no impact. Neither did dapagliflozin * for 24 weeks. The researchers also noted that although weight loss has been identified as a known treatment intervention for NAFLD, drug therapy with the TZDs still improved hepatic fat content and liver histology in the presence of significant weight gain when compared with placebo and metformin. Additionally, it was observed that improvements in triglycerides, HbA1c, and inflammation were associated with amelioration of NAFLD. From this extensive review of the literature, the researchers suggested that in patients with Type 2 diabetes and NAFLD, the TZD * and GLP-1 RA * drug classes appear to have the most promise and randomized controlled trials are warranted. We would remind our readers that no drug in these drug classes are formally approved for this indication.

### Table 7. Reduction of Hepatic Fat Content with Anti-Hyperglycemic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Hepatic Fat Content Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td>Placebo</td>
<td>-22.27%* (-26.98, -17.56)</td>
<td>0.000</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Metformin</td>
<td>-27.88%* (-47.41, -8.35)</td>
<td>0.005</td>
</tr>
<tr>
<td>Thiazolidinediones (TZD)</td>
<td>Glibenclamide (GLB)</td>
<td>-35.7% (TZD) / -7.7% (GLB)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exenatide (EX) + pioglitazone (P)</td>
<td>Pioglitazone</td>
<td>-61% (EX+P) / -41% (P)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*weighted mean difference

### Sensory Neuropathy in Pre-Diabetes

Putz and associates from Hungary and the UK investigated risk factors for sensory neuropathy in 75 patients with IGT and 40 age- and gender-matched healthy controls (abstract 1027). Prevalence of sensory neuropathy (assessed by two diagnostic devices known as Neurometer and Medoc, was very high at 58% in subjects with IGT and 10% in controls. Glycemia (120-minute glucose level) was determined to be a risk factor for sensory neuropathy in subjects with IGT (OR: 1.78; 95% CI: 1.20, 2.63), independently of all other known risk factors.

### Type 2 Diabetes Poorly Controlled With Insulin: Patient vs. Physician Viewpoints

Notwithstanding advances in insulins, management of insulin-dependent diabetes can be improved by informing physicians that their perceptions of diabetes control may differ from those of their patients. Understanding this can improve physician/patient communication.

According to a web-based survey conducted by Brod and multinational coworkers, patients with uncontrolled Type 2 diabetes and physicians caring for them may have divergent perceptions of diabetes control, including how they define it, its obstacles, and the impact of uncontrolled glucose levels (abstract 890). Respondents to the survey included 1,012 adults with suboptimally controlled Type 2 diabetes (physician confirmed HbA1c >8%) and treated with basal insulin and 300 physicians in Sweden (n=240 patients and 100 physicians), Switzerland (n=152 patients and 100 physicians), and the UK (n=620 patients and 100 physicians). In defining control, physicians were significantly more likely than patients to indicate that HbA1c (85% vs. 79%, p<0.05), complications from diabetes (89% vs. 75%, p<0.001), and frequency/severity of hypoglycemia (93% vs. 69%, p<0.001) are very/extremely important for deciding whether or not diabetes is well-controlled. Patients, on the other hand, were significantly more likely than physicians to report that a wide range of other factors were very/extremely important (each p<0.001), including energy levels (75% vs. 33%), insulin units/day (78% vs. 29%), how predictable life is (72% vs. 29%), and how much one has to think about diabetes (68% vs. 31%). Physicians were significantly more likely than patients to think about control over the last 3 months (60% vs. 19%, p<0.001) and less likely than patients to consider the last week or more recently (7% vs. 51%, p<0.001). Patients reported more obstacles making control very/extremely difficult compared to physicians (each p<0.01), including stress (75% vs. 54%), medication side effects (70% vs. 56%), other health issues (71% vs. 45%), family obligations (61% vs. 33%), and lack of patient support groups (56% vs. 11%). And, patients were significantly more likely than physicians to consider uncontrolled diabetes as very/extremely interfering in different aspects of their lives (each p<0.001), including general health (70% vs. 51%), energy level (71% vs. 36%), mood/emotions (63% vs. 33%), how much one accomplishes during the day (62% vs. 23%), keeping appointments/commitments (63% vs. 17%), making plans (62% vs. 16%), completing daily chores (60% vs. 21%), and family responsibilities (60% vs. 18%).

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

**Silvio E. Inzucchi, MD**

**Robert S. Sherwin, MD**

Editors, Yale University, New Haven, Connecticut
The highly anticipated results of the EMPA-REG Outcome trial were announced today to an overflowing crowd in the Hellerstrom Auditorium at the 2015 EASD Annual Meeting in Stockholm. In seeming preparation for this presentation, a symposium one day earlier focused on the impact of diabetes therapy on CV complications. Chaired by Professor Lars Ryden from the Karolinska Institute here in Sweden, the session featured differing views from around the world concerning a very important topic.

Leading off the morning was Dr. Stefano Del Prato from Pisa, Italy who addressed whether glycemic targets actually matter as related to CV disease. Briefly, stated, his answer was a qualified “Yes.” Clearly, the impact of glycemic control on microvascular outcomes is large and well substantiated. In contrast, the association between glucose control and cardiac events remains highly controversial, with most studies showing a neutral effect from achieving an HbA1c of about 7% and large meta-analyses suggesting perhaps, at most, an ~15% reduction in non-fatal MI—but no effect on CV or overall mortality. In fact, some studies have suggested some degree of harm if overly aggressive strategies are undertaken in high-risk patients with Type 2 diabetes. Dr. Del Prato proceeded to describe the still perplexing relationship between hypoglycemia and macrovascular complications, concluding that severe hypoglycemia most likely identifies a vulnerable group of patients and may not necessarily be the direct cause of CV events. He did, however, leave open the possibility that, in certain individuals, it might.

The next speaker, Craig Currie PhD from Cardiff, Wales addressed whether specific glucose lowering drug strategies mattered. He presented highly controversial and mainly observational studies from large UK databases that suggest an increased mortality rate in patients using sulfonylurea agents as well as insulin—which he ascribed directly to hypoglycemia. Dr. Currie had mostly positive comments about pioglitazone and its demonstrated benefits to modestly reduce major adverse cardiovascular events (MACE)* in the PROactive study (also interestingly in the 15% range). He also pointed to the suggested benefit on macrovascular outcomes in meta-analyses of clinical trials using DPP-4 inhibitors or GLP-1 receptor agonists.” He acknowledged, however, the neutral results of several recent large cardiovascular outcomes trials (CVOTs) with these agents and looked forwarded to the following day’s results from the first SGLT-2 inhibitor CVOT. Dr. Currie underscored the findings from multiple observational databases that the optimal HbA1c for overall mortality may actually be somewhere between 7.0 and upwards of 8.5%, although he acknowledged the benefit of reducing HbA1c to the lower end of this scale to prevent microvascular disease. He also reminded the audience of the over-riding benefit of blood pressure and lipid control in this population.

In the question and answer period, several audience members took exception to Dr. Currie’s implication that insulin was an unsafe therapy for Type 2 diabetes, making the point that the observational data that he utilized cannot control for all confounders. Indeed, these confounders may be driving the increased risk drawn from the data—i.e., sicker patients tend to use insulin and sicker patients tend to die more often than healthier patients.

To wrap up the morning’s symposium, Dr. Darren McGuire from the University of Texas at Dallas provided the audience a historical overview of large CVOTs in diabetes, being encouraged by regulatory agencies in late 2008 after several glucose lowering agents were found to be associated with new risks not originally considered during development. He pointed to the rosiglitazone controversy primarily, but also apparent risks that emerged with several other compounds, including aleglitazar,* taspoglutide,* and fasiglifam.* Dr. McGuire emphasized that the
series of absolutely neutral CVOTs (e.g., TECOS, SAVOR, EXAMINE, ELIXA) should have been entirely expected since they were meant to prove safety and therefore designed as “non-inferiority” trials. He concluded his remarks by summarizing that these large trials are critical to get at key safety questions beyond glucose control and have already yielded very important results, such as the heart failure signal with saxagliptin in SAVOR.

The EMPA-REG Outcome Trial

These discussions provided a convenient launching pad for Thursday’s main event—release of the results of EMPA-REG Outcome. The current EASD president, Professor Andrew Boulton, and session moderator, Professor Mark Walker, both from the UK, welcomed the audience to the anticipated unveiling of the results from the first CVOT with an SGLT-2 inhibitor, empagliflozin. The top-line results had actually been announced a few weeks ago, but the magnitude of the reported benefits on the primary MACE endpoint and other outcomes were embargoed until the presentation time and simultaneously published in the New England Journal of Medicine.

The first speaker was Dr. Bernie Zinman from the University of Toronto who provided background and context. As mentioned above, large CVOTs are now mandated for all new diabetes drugs by regulatory agencies, specifically the US FDA. So, EMPA-REG Outcome was designed initially as a non-inferiority study to demonstrate that patients randomized to either of 2 doses (10, 25 mg) empagliflozin had CV outcomes that were not different than those assigned to placebo, each strategy prescribed upon background standard of care for not only glucose control but also that of blood pressure and lipids. The study was then adequately powered to demonstrate efficacy on CV outcomes if non-inferiority had been met (summarized below).

Dr. Zinman described the potential of the SGLT-2 inhibitor class, which allows glucose excretion from the urine, thereby lowering blood glucose without promoting hypoglycemia, while also decreasing body weight (through calorie losses) and blood pressure (via osmotic diuresis). The drug class has also been associated, however, with volume contraction, orthostatic symptoms, transient increase in serum creatinine, and modest increases in LDL-cholesterol. Accordingly, the true impact of these agents on CV events could not necessarily be easily predicted.

The next speaker, Dr. John Lachin PhD from George Washington University, Washington, DC proceeded to describe the statistical design of the trial. Inclusion criteria included Type 2 diabetes with overt CV complications (i.e., documented coronary, cerebrovascular, or peripheral vascular disease) and eGFR ≥ 60 mL/min/1.73 m². The study population consisted of 7020 patients, who, as anticipated, had a 99% prevalence of overt CV disease. The study design employed a hierarchical model for sequential testing for superiority once the non-inferiority threshold had been met, a standard approach used in such trials. The primary outcome was 3-point MACE, namely the composite of CV death, non-fatal MI, and non-fatal stroke. A key secondary outcome was 4-point MACE, which was an expanded MACE to include hospitalization for unstable angina. Other prespecified secondary outcomes included components of the primary outcome, as well as hospitalization for heart failure. Routine safety parameters were also collected, including changes in renal function, genitourinary infections, diabetic ketoacidosis (DKA), and fractures.

Table 8. Baseline Characteristics: EMPA-REG Outcome Trial

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>63.2 (8.8)</td>
<td>63.0 (8.6)</td>
<td>63.2 (8.6)</td>
</tr>
<tr>
<td>Male</td>
<td>1680 (72.0%)</td>
<td>1653 (70.5%)</td>
<td>1683 (71.9%)</td>
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<tr>
<td>HbA1c, %</td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
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<td>Body mass index, kg/m²</td>
<td>30.7 (5.2)</td>
<td>30.6 (5.2)</td>
<td>30.6 (5.3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.6 (19.1)</td>
<td>85.9 (18.8)</td>
<td>86.5 (19.0)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>105.0 (14.0)</td>
<td>104.7 (13.7)</td>
<td>104.8 (13.7)</td>
</tr>
<tr>
<td>Time since diagnosis of Type 2 diabetes, years</td>
<td>≤5 423 (18.1)</td>
<td>406 (17.3)</td>
<td>434 (18.6)</td>
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<tr>
<td></td>
<td>&gt;5 to 10 571 (24.7)</td>
<td>585 (24.9)</td>
<td>590 (25.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 1339 (57.4)</td>
<td>1354 (57.7)</td>
<td>1318 (56.3)</td>
</tr>
<tr>
<td>Glucose-lowering medication</td>
<td>Metformin</td>
<td>1734 (74.3%)</td>
<td>1729 (73.7%)</td>
</tr>
<tr>
<td></td>
<td>Sulfonlyurea</td>
<td>992 (42.5%)</td>
<td>985 (42.0%)</td>
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<td></td>
<td>Thiazolidinedione</td>
<td>101 (4.3%)</td>
<td>96 (4.1%)</td>
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<tr>
<td></td>
<td>Insulin</td>
<td>1135 (48.6%)</td>
<td>1132 (48.3%)</td>
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<tr>
<td></td>
<td>Mean daily dose, U</td>
<td>65 (50.6)</td>
<td>65 (47.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>135.8 (17.2)</td>
<td>134.9 (16.8)</td>
<td>135.6 (17.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76.8 (10.1)</td>
<td>76.6 (9.8)</td>
<td>76.6 (9.7)</td>
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<tr>
<td>Heart rate, bpm*</td>
<td>70.7 (0.2)</td>
<td>71.0 (0.2)</td>
<td>70.5 (0.2)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>84.9 (35.3)</td>
<td>86.3 (36.7)</td>
<td>85.5 (35.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44.0 (11.3)</td>
<td>44.7 (12.0)</td>
<td>44.5 (11.8)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m² (MDRD)</td>
<td>73.8 (21.1)</td>
<td>74.3 (21.8)</td>
<td>74.0 (21.4)</td>
</tr>
<tr>
<td>Any CV risk factor</td>
<td>2307 (99.9%)</td>
<td>2333 (99.5%)</td>
<td>2324 (99.2%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1763 (75.6%)</td>
<td>1782 (76.0%)</td>
<td>1763 (75.3%)</td>
</tr>
<tr>
<td>History of MI</td>
<td>1083 (46.4%)</td>
<td>1107 (47.2%)</td>
<td>1083 (46.2%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>563 (24.1%)</td>
<td>594 (25.3%)</td>
<td>581 (24.8%)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>553 (23.7%)</td>
<td>533 (22.8%)</td>
<td>549 (23.4%)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>479 (20.5%)</td>
<td>465 (19.8%)</td>
<td>517 (22.1%)</td>
</tr>
<tr>
<td>Heart failurea</td>
<td>244 (10.5%)</td>
<td>240 (10.2%)</td>
<td>224 (9.5%)</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>2221 (95.2%)</td>
<td>2227 (95.0%)</td>
<td>2219 (94.7%)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>1868 (80.1%)</td>
<td>1896 (80.9%)</td>
<td>1902 (81.2%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1498 (64.2%)</td>
<td>1530 (65.2%)</td>
<td>1526 (65.2%)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>1864 (79.9%)</td>
<td>1926 (82.1%)</td>
<td>1894 (80.9%)</td>
</tr>
<tr>
<td>Statins</td>
<td>1773 (76.0%)</td>
<td>1827 (77.9%)</td>
<td>1803 (77.0%)</td>
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<tr>
<td>Anticoagulants and antiplatelets</td>
<td>2090 (89.6%)</td>
<td>2098 (89.5%)</td>
<td>2064 (88.1%)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1927 (82.6%)</td>
<td>1939 (82.7%)</td>
<td>1937 (82.7%)</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

a Based on narrow standardized MEDORA query “cardiac failure”

Note: Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug. For heart rate, data are mean (SE).

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Importantly, all major CV endpoints were independently adjudicated. The statistical analysis was between the pooled group of both empagliflozin doses versus placebo.

Dr. Christoph Wanner from the University of Wurzburg, Germany, was the next presenter, discussing the baseline characteristics (Table 8) and biochemical and physiological changes during the trial. Consistent with the known effects of this compound, mean HbA1c decreased by about 0.6% in the empagliflozin groups during the first 12 weeks of the trial when changes in background anti-hyperglycemic therapy were not allowed. Subsequently, the differences between the groups decreased; by the end of the trial, the mean HbA1c difference was just 0.3%. Mean changes in systolic blood pressure and weight between the groups averaged about 4 mmHg and 2 kg, respectively.

Next came the CV outcomes. Dr. Silvio Inzucchi from Yale University revealed that the primary endpoint (3-point MACE) was reduced in the pooled empagliflozin group (Figure 5A; HR 0.86 [95% CI: 0.74, 0.99], p=0.0382). As for components of the 3-point MACE, CV death was reduced by an impressive 38% (Figure 5B; HR 0.62 [95% CI: 0.49, 0.77], p<0.0001). The cumulative incidence curves for the individual doses, each representing one-half of the active therapy group, were essentially superimposable, indicating consistent benefit across doses. The two other components, non-fatal MI (HR 0.87 [0.70, 1.09]) and non-fatal stroke (HR 1.24 [0.92, 1.67]) were not significantly altered by therapy, however (Figure 6).

Dr. Inzucchi then proceeded to present subgroup analyses. There was some heterogeneity for the primary MACE outcome, specifically nominally significant heterogeneity for age above versus below 65 (suggestion of lesser effect in younger patients) and for baseline HbA1c above and below 8.5% (suggestion of lesser effect in the most hyperglycemic.) None of these findings could be considered significant after correction for multiple comparisons. In contrast, tests for heterogeneity for all subgroups analyzed for CV death (the prime driver of 3-point MACE) were all non-significant, indicating a robust effect of similar benefit across age, gender, race, baseline HbA1c, BMI, and renal function categories.

The next result was the secondary outcome of heart failure hospitalization (Figure 5C), an increasingly important outcome in patients with diabetes. It is also of growing interest amongst clinical trialists because certain diabetes drugs have been associated with increasing risk of heart failure over the past several years. This too, however, was reduced by empagliflozin (HR 0.65 [0.50, 0.85; p=0.0017]).

Finally, in clinical CV trials, if CV mortality is reduced, there is sometimes an apparent compensatory increase in non-CV mortality, rendering the effect of the intervention on all-cause mortality neutral. In EMPA-REG Outcome, however, the HR for all-cause mortality was 0.68 (0.57, 0.82 p<0.0001), again, owing predominately to the effect on CV mortality, which was not substantially attenuated by the non-CV mortality HR of 0.84 (0.60, 1.16).

The final data presentation was by Dr. David Fitchett, also of the University of Toronto, who focused on safety and tolerability. Briefly, the active therapy groups experienced an approximate 4-fold greater incidence of genital infections (likely fungal). This complication occurred in about 1 in 20 patients on active therapy. There was no increase in complicated urinary tract infections or pyelonephritis, but there was a greater number of adverse events categorized as urosepsis (3 vs. 6 vs. 11 in the placebo, 10 mg and 25 mg empagliflozin groups, respectively). Of recent interest has been the potential for DKA and bone fractures with some SGLT-2 inhibitors. These adverse events, as well as symptoms that would suggest volume depletion, were actually similar in all groups in the EMPA-REG Outcome trial.

To wrap up the presentation, Dr. Zinman returned to the stage to put the results of EMPA-REG Outcome into perspective. He summarized the striking results, and noted that this is the first large trial to demonstrate significant CV benefits with a diabetes medication in a high-risk population. Dr. Zinman then calculated that the number needed to treat to prevent one CV death over 3 years was 39, which compares favorably to results from some statins and ACE inhibitor trials in a high-CV risk population. Importantly, the findings of this study were demonstrated upon a background of high use of evidence-based CV therapies, such as statins, RAS inhibitors, and aspirin. He closed with a provocative question: What effect will these results have on clinical practice guidelines?

Providing independent commentary on the trial was Dr. Hertz Gerstein, McMaster University. The central impression of Dr. Gerstein was that the EMPA-REG Outcome Trial was an important one, especially after many negative diabetes/CVD trials. He feels that the strikingly early separation of the event curves suggests that the effect of the study drug was likely not mediated through glucose or blood pressure. Instead, he felt that the osmotic diuretic aspect to this agent may have resulted in a better hemodynamic status, perhaps treating early heart failure or preventing heart failure. Of course, this is all speculation, and Dr. Gerstein noted that the best trials often raise more questions than they answer. He gave strong support to the need
for these large CV outcome trials in diabetes, mentioning that it is only through studies such as EMPA-REG Outcome that we are able to develop more effective and safer treatment strategies for our patients with diabetes.

In the question and answer period, several audience members asked “Why?” — that is, what is the underlying reason for the surprising findings? No firm conclusions could be made but, as mentioned by Dr. Gerstein, the effect is unlikely to be mediated through glucose control, given the experience in other trials with this parameter. Also, the effects on body weight and systolic BP were modest and also unexpected to result in such a large CV benefit.* Further analysis of the EMPA-REG database will be conducted to determine if clues emerge regarding which effect may have mediated the benefit. This will clearly be a point of active debate over the next few years and will likely lead to a series of mechanistic studies on possible direct cardiac benefits and effects of the drug on sodium balance and renal function. To close the Q&A period, Professor Klaus Malmberg, the famous cardiologist from the Karolinska Institute in Stockholm congratulated the study group on its conduct of this highly successful trial and also reminded the audience that this was a landmark investigation with potentially paradigm-shifting results. We agree, but we are equally unsure as to the mechanisms at play. This will certainly be a fertile ground for future study.

The Perils of Hypoglycemia

Hypoglycemia is a worrisome side effect of insulin and other medications used to manage diabetes. Until recent years, its life-threatening effects and impact on the CV system have not been a prominent focus of investigation. The publication of several large diabetes CV trials in 2008–2009 (ACCORD, ADVANCE, VADT) has taught us that with intensive glycemic control of Type 2 diabetes, hypoglycemia is much more likely to occur and CV events are not prevented. In some cases, it may also be associated with excess mortality.

In a symposium entirely devoted to Every Day Consequences of Hypoglycemia, Dr. Simon Heller of the UK discussed, “Who is at Risk from the Cardiovascular Effects of Hypoglycemia?” He gave a brief history of the relationship between hypoglycemia and CV risk, noting that it is a relatively new concept, a awareness emerging from the aforementioned clinical trials and their subsequent meta-analyses. Several of these have concluded that severe hypoglycemia is associated with a higher risk of cardiovascular disease (CVD), although a cause and effect could not be proven (BMJ, 2013). Heller himself proposed that perhaps hypoglycemia itself may have been responsible for offsetting CV benefits in the studies deemed neutral. He described the pathophysiological CV consequence of hypoglycemia including: inflammation (increased inflammatory markers), blood coagulation abnormalities (increased activation of platelets, macrophages), the sympathoadrenal response of increased epinephrine (resultant rhythm abnormalities and hemodynamic changes), and endothelial dysfunction (decreased vasodilation), providing clinical and experimental data supporting these changes in both Type 1 and Type 2 diabetes patients. He emphasized that asymptomatic nocturnal hypoglycemia is common, prolonged, and associated with arrhythmias in patients with Type 2 diabetes at risk for CV and that experimental hypoglycemia causes cardiac repolarization in patients, some of whom are more sensitive to these changes than those without diabetes. Although rare, hypoglycemia can cause fatal cardiac arrhythmias in young patients with Type 1 disease. Heller appeared convinced that there is a cause and effect link between hypoglycemia, particularly when severe, and CV complications.

The association of hypoglycemia and CVD was the topic of several other oral and poster presentations. Nurses and US colleagues utilized the Humedica Research Database to identify sulfonylurea users to examine a potential relationship between baseline hypoglycemia by severity and CVD (abstract 125). Using ICD-9 codes and free text clinical notes with reference to hypoglycemia and its synonyms, events were categorized as serious, mild-moderate, or unknown. Frequency and seriousness of events were then assessed as determinants of CVD outcomes. The cohort included 82,321 eligible patients receiving a sulfonylurea between January 2009 and March 2014. Of these, 4,922 (6%) had at least one hypoglycemic event in the year prior to cohort entry. These patients were then followed for CVD-related outcomes (median: 164 days; 25th and 75th percentiles: 20 days and 601 days, respectively). During this time period, CVD (any diagnosis) was observed in 47%, acute myocardial infarction (AMI) in 2% and a diagnosis of congestive heart failure (CHF) occurred in 15%. Frequency of severe hypoglycemia was positively associated with both CHF and AMI (CHF: RR per episode=1.69 [CI 1.55, 1.84]; AMI: RR=1.66 [CI 1.31, 2.09]). Mild-moderate hypoglycemia was more strongly associated with CHF than with AMI (CHF: RR=1.48 [CI 0.93, 2.34]; AMI: RR=0.96 [CI 0.63, 1.53]). This was also true for mild-moderate hypoglycemia of unknown seriousness (CHF: RR=1.43 [CI 1.37, 1.48]; AMI: RR=1.19; [CI 1.06, 1.35]). From this analysis, the investigators suggested that CVD and its association with hypoglycemia may be dependent on the degree of hypoglycemia as well as CVD subtype. Of course, a retrospective analysis of electronic health records relying on free text documentation has its limitations and, thus, prospective trials are needed to confirm these relationships. Moreover, the establishment of an association in an observational study cannot determine whether that relationship is cause and effect. In fact, most data to date suggest that the propensity to hypoglycemia may merely identify sicker and more vulnerable patients.
Despite this uncertainty, some have ascribed hypoglycemia-related mortality to QTc interval prolongation and subsequent lethal arrhythmias in both Type 1 and Type 2 diabetes. Makrilakis, et al. from Greece examined the relationship between hypoglycemic episodes and QTc prolongation (identified by CGMS and continuous ECG monitoring, respectively) in patients with Type 2 diabetes (n=40; mean HbA1c 7.5%; diabetes duration 18 years; BMI 30 mg/kg²) during their everyday lives (abstract 878). Hypoglycemia was defined as blood glucose <70 mg/DL lasting for ≥20 minutes. Mean QTc intervals during hypoglycemia episodes were compared to mean QTc intervals during the period prior to the episode. Of the 26 episodes documented in 16 patients, 13 occurred during the night. Mean QTc values were significantly longer during hypoglycemia than during normoglycemia (QTc: 443.4±51.4 vs. 424.5±61.5 msec; p=0.012). However, when assessed temporally, QTc prolongation during hypoglycemia was only significantly different from normoglycemia for nighttime occurrences (nighttime comparison QTc: 459.6±55.7 vs. 417.6±86.1 msec; p=0.003; daytime comparison QTc: 427.2±42.8 vs. 431.3±18.9 msec, p=0.58). From these data, the researchers confirmed that prolongation of the QTc interval is associated with severe hypoglycemia, in particular during overnight episodes.

Dr. Merlin Thomas, Melbourne, Australia, in his presentation, “Kidney Disease and Risk of Hypoglycemia”, addressed the resultant risk of hypoglycemia in those with impaired renal function. He noted that CKD is an all too common companion of diabetes with nearly one-third of patients experiencing a decrease in GFR. He also stated CKD is a mislabeled disease in that it is much more than a kidney problem, it is a systemic problem. Thomas described CKD as a key risk factor for hypoglycemia in this population. As GFR decreases, the risk of hypoglycemia increases for numerous reasons: reduced renal gluconeogenesis; impaired counter-regulatory response; increased half-life of both endogenous and exogenous insulin; drug accumulation (e.g., sulfonlylureas); and misinterpretation of HbA1c as its reliability/validity decreases in renal disease.

Dr. Thomas also commented that hypoglycemia is not only more common, but also more dangerous in those with diabetes; thus, patient management often is a challenge. Of all the therapeutic options available, he recommended use of the DPP-4 inhibitors as a safe and effective means for glycemic control given little to no risk of hypoglycemia and therapeutic efficacy is maintained even in the setting of decreasing GFR. While some DPP-4 inhibitors require dosage adjustment with declining renal function, once properly titrated, any of the available agents work well. Future strategies, pending controlled clinical trial data, might include liraglutide* given its hepatic clearance and early adoption of “smart” insulins and closed loop technologies.* Dr. Thomas’ closed by saying that, despite the associated risk of hypoglycemia and CKD, good options are available to successfully manage the majority of patients such that glycemic control should not be compromised.

German researchers, Wohland et al. evaluated seasonal variations of severe hypoglycemia in patients with Type 1 and Type 2 diabetes (abstract 951). In this prospective, population-based, observational trial, cases of severe events from a large tertiary care hospital in rural Germany were analyzed. Severe hypoglycemia was defined as a symptomatic event requiring treatment with intravenous glucose or glucagon and confirmed by a blood glucose value of <50 mg/DL. Seasons were defined by meteorological conditions. There were 206 patients with Type 1 diabetes and 493 with Type 2, accounting for 405 and 558 episodes, respectively. The majority of patient characteristics evaluated (age, HbA1c, creatinine clearance, impaired awareness of hypoglycemia) were significantly different between those with Type 1 and Type 2 diabetes. The prevalence of severe hypoglycemia in Type 1 patients was increased during spring and summer versus fall and winter (spring 27.7% vs. fall 21.5%, p=0.04; summer 28.6% vs. fall, p=0.02; summer vs. winter 22.2%, p=0.04). Yet HbA1c and insulin dose did not vary significantly by season for patients with Type 1. Among patients with Type 2 diabetes, there was little difference in prevalence of severe hypoglycemia by season: spring 26.0%, summer 25.1%, fall 23.5%, winter 25.3%), but Type 2 patients had higher HbA1c values in the spring compared with the fall (7.0%±1.6 vs. 6.6% ±1.0). From these data, the researchers theorized that the seasonal variation of severe hypoglycemia in Type 1 diabetes patients may be due to short-term lifestyle changes (increased physical activity or alcohol consumption) and proactive seasonal changes in insulin therapy may prevent events. Whereas in Type 2 patients, there appears to be no seasonal effect for this risk.
There were less numerous presentations on DPP-4 inhibitors at this week’s EASD meeting. Whether this represents decreased enthusiasm for the class, in light of now three neutral CV outcome trials (SAVOR-TIMI, EXAMINE and, most recently, TECOS), or simply natural scientific evolution once a pharmacological category has been on the market for nearly a decade is not clear. Nonetheless, the DPP-4 inhibitors remain extremely popular clinically, owing predominately to their good tolerability and overall perceived safety. They specifically are not associated with adverse effects like many other drug classes, such as hypoglycemia, weight gain, edema, or gastrointestinal symptoms.

Two presentations were of interest. The first involved an investigational weekly DPP-4 inhibitor, omagliptin. Weekly dosing of drugs is not uncommon, with bisphosphonates for osteoporosis being the first type of chronic medication able to be prescribed in this fashion. Their need to be taken on an empty stomach and frequent exacerbation of reflux symptoms made them ideal for less frequent administration. In diabetes, there are now two weekly GLP-1 receptor agonists (albiglutide, dulaglutide), the rationale being to minimize the number of injections required over the course of a year. The need for a weekly oral agent that is otherwise well tolerated and can be taken with or without food is not intuitively obvious. Yet, patients with Type 2 diabetes are frequently on very complex medication regimens, and anything that minimizes dosing frequency may improve adherence and thereby result in improved clinical outcomes.

Gantz and colleagues reported results from a non-inferiority clinical trial comparing omagliptin 25 mg weekly compared to sitagliptin 100 mg daily (abstract 110). Omagliptin’s long biological half-life allows for dosing every 7 days. The study involved 642 patients who were randomized to one of the two DPP-4 inhibitors and tracked for 24 weeks. Baseline HbA1c was about 7.5%. By the end of the trial, both agents had reduced HbA1c similarly, between 0.4-0.5% (Table 9). Non-inferiority was confirmed. The type and number of adverse events were similar between the groups.

Another interesting DPP-4 presentation was a post-hoc analysis of a sitagliptin trial during which it was discovered that use of the drug in combination with basal insulin actually leads to a reduction in hypoglycemia rates, despite the fact the HbA1c levels were lower (abstract 805). Similar findings have been reported with linagliptin, and, if real, this effect may relate to enhanced responsiveness of glucagon secretion as a defense against hypoglycemia. In this study, 658 patients with Type 2 diabetes who were intensively titrated on glargine and metformin were randomized to sitagliptin or placebo. The sitagliptin group experienced a further 0.45% reduction in HbA1c and a 4.7-unit decrease in the insulin dose. The investigators sought to determine, in this analysis, whether the lower insulin dose may have influenced their findings regarding less hypoglycemia. So, Engel and colleagues stratified patients into quartiles based on the amount of change in insulin dose. The placebo-adjusted changes in HbA1C by quartile were similar: -0.33%, -0.62%, -0.47%, and -0.47%, respectively. In those patients with the smallest insulin dose reduction (increment ≤6 units), no difference in hypoglycemia incidence was seen (Table 10). However, in the other 3 quartiles, despite equivalent insulin dose reductions, sitagliptin patients still had significantly less frequent hypoglycemia. Based on these findings, the investigators concluded that factors other than the difference in insulin dose were responsible for the reduced hypoglycemia.

The DPP-4 inhibitors remain part of most treatment algorithms for Type 2 diabetes and appear to be safe and well tolerated, although somewhat modest in their glucose-lowering power. They have become particularly popular in combination with metformin. One last point we’d like to make about these medications: The US Food & Drug Administration released a warning (http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm) last week about rare reports of severe joint pains in patients using this class. A total of 33 cases between 2006 and 2013 have been reported, mostly involving sitagliptin—likely due to the fact that 80% of DPP-4 prescriptions have been for this specific compound. The symptoms usually resolved within one month of drug discontinuation and in several cases, rechallenge led to a recurrence. The etiology of this potential side effect is not known but it is important for clinicians to be aware.

### What’s New with the DPP-4 Inhibitors?

**Table 9. Glycemia Effect of DPP-4 Inhibitors**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Mean</th>
<th>Week 24 Mean</th>
<th>Difference (95% CI)</th>
<th>Change from Baseline LS Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omagliptin 25 mg</td>
<td>7.52</td>
<td>6.99</td>
<td>-0.47 (-0.55, -0.38)</td>
<td>-0.03 (-0.15, 0.08)</td>
</tr>
<tr>
<td>Sitagliptin 100 mg</td>
<td>7.49</td>
<td>7.01</td>
<td>-0.43 (-0.51, -0.35)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 10. Hypoglycemia by Insulin Dose in Type 1 Diabetes Patients on Sitagliptin**

<table>
<thead>
<tr>
<th>Insulin Dose (U/day)</th>
<th>Change from Baseline</th>
<th>Mean</th>
<th>Mean</th>
<th>Sitagliptin</th>
<th>Placebo</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st quartile &lt;6</td>
<td>0.2</td>
<td>-0.8</td>
<td>37%</td>
<td>(37/100)</td>
<td>30.8%</td>
<td>6.2% (-7.9, 19.9)</td>
</tr>
<tr>
<td>2nd quartile 6 - 14.3</td>
<td>11.1</td>
<td>10.6</td>
<td>15.7%</td>
<td>(13/83)</td>
<td>31.8%</td>
<td>-16.2 (-30.0, -2.5)</td>
</tr>
<tr>
<td>3rd quartile 14.3 - 32</td>
<td>22.7</td>
<td>22.6</td>
<td>25.6%</td>
<td>(20/78)</td>
<td>45.3%</td>
<td>-19.6 (-33.0, -5.3)</td>
</tr>
<tr>
<td>4th quartile &gt;32</td>
<td>49.1</td>
<td>53.7</td>
<td>20.0%</td>
<td>(13/65)</td>
<td>37.5%</td>
<td>-17.5 (-31.0, -2.8)</td>
</tr>
</tbody>
</table>

Severe hypoglycemia is obviously of major concern for all our patients on certain therapies for their diabetes, particularly insulin. It is important for us to understand the risk factors predisposing patients to severe events and develop management strategies to minimize their frequency. It is also important to educate our patients about recognizing symptoms of hypoglycemia and appropriately treating episodes when they occur.
The prevalence of gestational diabetes mellitus (GDM) is increasing worldwide, with rates from 7.0% in North America to as high as 12.9% in the Middle East, in a map shown by Dr. Culuiin Zhang of the NIH. She reported that pre-pregnancy obesity is the strongest risk factor for GDM, and obesity is a modifiable risk factor that needs to be addressed systematically. By examining the results of former studies on GDM risk factors, she created a statistical model to assess population attributable risk. For women with a BMI >25 kg/m², 40% of the risk of GDM can be attributed to weight (95% CI: 15, 58). Interventions such as reducing pre-pregnancy weight to less than a BMI of 25, exercise of 30 minutes per day, a healthy diet, and smoking abstinence during pregnancy can significantly reduce the risk of GDM.

The aggressive targeting of hyperglycemia in pregnancy has dramatically reduced the rates of perinatal morbidity and mortality over several decades. However, studies continue to report that even milder hyperglycemia has a negative impact on neonatal and delivery outcomes. Dr. Kun from Hungary showed compelling retrospective data that the new GDM diagnostic criteria adopted by the WHO in 2013 are identifying women at risk for pregnancy and neonatal complications, even in the lower glucose range (abstract 148). In a universal screening program over a 3-year period, 4677 pregnant women received a 75-g OGGT, and 445 of these women would now be diagnosed with GDM despite remaining untreated during their pregnancy since they were not identified under the older criteria.

When compared with the women with normal glucose tolerance (NGT), untreated women with GDM had offspring with a higher incidence of macrosomia (>4000 g, OR 1.64, 95% CI: 1.23, 2.20), despite similar maternal weight gain in pregnancy (13.1±0.3 vs. 13.0±0.1 kg, p=NS). They also had higher rate of hypertension in pregnancy (OR 1.44, 95% CI: 1.02, 2.03), induced delivery (OR 1.34, 95% CI: 1.10, 1.64), forceps or vacuum use (OR 1.31, 95% CI: 1.08, 1.60), and acute cesarean section (OR 1.34, 95% CI: 1.10, 1.64). No differences in the risk of pre-eclampsia or malformations were found.

Most cases of GDM can be managed with lifestyle interventions, so its important to assess which women may need glucose lowering agents to maintain goal glycemia in pregnancy. Scheuneman and colleagues from the Netherlands presented their findings about predictors of the need for drug therapy in their GDM population of 820 women, mean age 32±5 years and BMI 27.7 (IQR 24.0-31.9) kg/m² (abstract 147). In their study, GDM was diagnosed by a 75-g OGGT if a fasting glucose was >126 mg/dL or a 2-hour glucose >140 mg/dL. Insulin was the only therapy offered, and was required in 360 (44%) women with doses ranging from 2 to 80 U (median 22; IQR 12-42 U). Using a logistic regression analysis, the strongest predictor for insulin therapy was a fasting glucose of >99 mg/dL (RR 6.81; CI: 4.03, 11.5, p<0.001). Other significant predictors included prior GDM, a prior newborn with birthweight >4500 g or >95th percentile, first-degree relative with Type 2 diabetes, multiparity, Mediterranean ethnicity, pre-pregnancy BMI >30 kg/m², and elevations of both fasting and 2-hour glucose during OGGT.

Dr. Marja Vaarasmaki from Finland discussed the alternatives to insulin therapy for GDM. In a review of comparison trials using metformin,* glibenclamide,* or insulin, metformin is winning favor over sulfonylureas as the choice of oral therapy in mild GDM. When metformin was used as first-line therapy, it was comparable to insulin in glycemic control and neonatal outcomes, and had the benefit of a reduction in maternal weight gain. While most professional guidelines such as the ADA and ACOG still recommend the use of insulin as first-line therapy for GDM, the UK’s National Institute for Health and Care Excellence (NICE) is recommending metformin. The main concern of metformin use in pregnancy is the lack of formalized long-term safety data for offspring, although there is no evidence of teratogenicity and its first reported use in pregnancy was in 1979, indicating decades of at least limited experience without obvious concerning health signals.

In summary, the epidemic of obesity is driving the prevalence of GDM. Interventions to target pre-pregnancy obesity and lifestyle in early pregnancy will likely be the best forms of GDM prevention. Prevention is important given the robust data on neonatal and maternal complications in the setting of GDM. However, the looming concern still to be addressed is the contributions of maternal obesity and dysregulated metabolism to the development of obesity and Type 2 diabetes in the next generation.

CVD Update

There continues to be an enormous focus on the CV complications of diabetes. At this week’s EASD meeting, the Karolinska Institute group from Stockholm, Sweden presented observational data on the relationship between glucose abnormalities and outcomes after acute coronary syndrome (ACS) (abstract 1155). A total of 1062 consecutive patients, 781 men and 281 women, aged 32-80 years, who were admitted to their coronary care unit with ACS between 2006-2008 were analyzed. Each patient classified as IFG or IGT or newly diabetic during OGGT were analyzed together as ‘dysglycemia.’

Mortality and reinfarction rates were studied during a mean follow-up time of 4.0 (±0.8) years, with clinical outcome data obtained from national Swedish registries. Those with known diabetes experienced a significant increase (p<0.001) in death already detectable at 14 days as compared to the dysglycemic and NGT groups but also extending to both 1 year (12% vs. 2% and 0%) and as well as 3 years (25% vs. 5% and 3%). Reinfarction was also significantly more common (p<0.001) at the end of follow-up in those with diabetes compared to the other two groups (28% vs. 17% and 12%). The composite endpoint of mortality or reinfarction was significantly higher (p<0.001) in patients with known diabetes (44% vs 22% and 15%). This specific composite was also statistically significantly more frequent in those with dysglycemia as compared to NGT. The investigators concluded that a majority of patients admitted for ACS have disturbed glucose metabolism and that both diabetes as well as newly discovered dysglycemia are associated with worse outcomes as compared to those with normal glucose metabolism. Whether this finding relates to hyperglycemia itself (unlikely) or to other associated factors is not clear but deserving of further study.

Other Karolinska investigators examined the relationship between Type 1 diabetes and coronary artery disease, an area with a paucity of good studies, most attention having been paid to Type 2 diabetes. Matuleviciene et al. also took advantage of the excellent National Diabetes Registry in Sweden to amass data on a large group of patients (n=33,886) with Type 1 diabetes (abstract 1195). Each patient was matched to 5 individuals from the general population...
(n=169,223.) The investigators then compared those with Type 1 diabetes who had no history of MI to controls both with and without a history of MI. Outcomes examined included MI, CV death, and all-cause mortality, using Cox regression adjusted for age and gender. The mean age of the patients with Type 1 diabetes (with and without MI) and the controls without MI was about 35 years. In the MI group from the general population (n=966), the mean age was 62.5 years. Follow-up averaged nearly 8 years. Hazard ratios (HRs) for MI and CV death for the Type 1 patients with no history of MI versus the healthy control group were 4.6 (95% CI: 4.31, 4.95) and 3.09 (2.78, 3.42), respectively; that for all-cause mortality was 2.70 (2.56, 2.86). The age-adjusted HRs for the patients with Type 1 diabetes without MI versus controls with a history of MI were 1.20 (1.02, 1.42), 0.93 (CI 0.75,1.14), and 1.29 (1.12,1.50).

The investigators concluded that patients with Type 1 diabetes without a history of MI actually have a higher risk of future MI and all-cause mortality and a similar risk of CV death compared to non-diabetic individuals with a prior history of MI. These data underscore the need to aggressively manage CV risk factors in our patients with Type 1 diabetes.

So Many Posters, So Little Time....

**FINDRISC Score as Predictor of Diabetes**

Ribeiro and associates from Portugal identified 1,024 subjects who were determined to be non-diabetic (i.e., “normal” or “prediabetes”) based on both fasting glycemia and/or 2-hour OGTT in a nationwide study of diabetes prevalence (PREVADIAB) (abstract 369). The investigators followed these individuals for 5 years, at which time the OGTT was repeated and HbA1c was measured to evaluate glycemia. 3.8% were diagnosed with diabetes by their physicians during the intervening 5 years, while an additional 5.0% were shown to have undiagnosed diabetes based on the testing performed in PREVADIAB. While no individual with a Finnish Diabetes Risk (FINDRISC—see Table 11) score <7 in the original PREVADIAB study progressed to diabetes, 25.9% of individuals with a higher risk score (>20) developed diabetes within 5 years. Baseline HbA1c was also shown to be related to diabetes incidence, but with a similar sensitivity only at ≥6.3%, very close to the ADA diagnostic threshold of 6.5%. In terms of diabetes detection, applying this HbA1c diagnostic criterion did not add significantly to that based on OGTT measures; only 25.5% of participants found with undiagnosed diabetes were detected by HbA1c. The investigators concluded that FINDRISC, a noninvasive and inexpensive tool, is adequate to evaluate risk of diabetes development in the general population, and that glycemic measures, not solely HbA1c, are needed to monitor diabetes incidence in high-risk individuals.

**Table 11. Type 2 Diabetes Risk Calculator for Physicians**

<table>
<thead>
<tr>
<th>Score</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 points</td>
<td>Low to moderate risk 1-17% chance of developing diabetes within 10 years. We recommend not screening for Type 2 diabetes.</td>
</tr>
<tr>
<td>15-20 points</td>
<td>High risk 33% chance of developing diabetes within 10 years. We recommend screening every 3-5 years with HbA1c.</td>
</tr>
<tr>
<td>21+ points</td>
<td>Very high risk 50% chance of developing diabetes within 10 years. We recommend annual screening with HbA1c.</td>
</tr>
</tbody>
</table>

*a Source: Finnish Diabetes Risk Score (FINDRISC) questionnaire by Adjunct Professor Jaana Lindström, Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland and Professor Jaakko Tuomilehto, Center for Vascular Prevention, Danube-University Krems, Krems, Austria*
1. Which of the following antihyperglycemic agents is most suitable for diabetes patients with advanced chronic kidney disease?
   a. metformin
   b. sulfonylurea
   c. DPP-4 inhibitor
   d. SGLT-2 inhibitor

2. Which of the following statements about metformin is false?
   a. Current treatment guidelines for Type 2 diabetes recommend metformin as first-line therapy (i.e., monotherapy).
   b. Up to half of patients will experience diarrhea early in a treatment course, although most tolerate metformin on a long-term basis.
   c. Patients treated with metformin may benefit from an oral B12 supplement.
   d. Metformin causes weight gain.

3. Interventions for non-alcoholic liver disease among patients with Type 2 diabetes are limited. According to data presented at the 2015 EASD Annual Meeting, all of the following, with one exception, showed a favorable effect on liver fat content. Which of the following does not decrease liver fat content?
   a. weight loss
   b. GLP-1 receptor agonist, liraglutide
   c. thiazolidinedione, pioglitazone
   d. metformin

4. A meta-analysis of cross-sectional studies revealed that rapid eating increases the risk of obesity by more than 2-fold.
   a. true
   b. false

5. While intranasal glucagon has been shown effective in reversing hypoglycemia among adults with Type 1 diabetes, a study presented at the 2015 EASD Annual Meeting showed that intranasal glucagon is not an effective treatment for hypoglycemia in pediatric patients with Type 1 diabetes.
   a. true
   b. false

6. Evidence suggests that increased serum uric acid is a risk factor for development/progression of chronic kidney disease in patients with Type 1 and Type 2 diabetes.
   a. true
   b. false

7. Which of the following is not observed when a GLP-1 receptor agonist is added to poorly controlled insulin-treated Type 2 diabetes patients?
   a. HbA1c reduced
   b. weight loss
   c. increased rate of severe hypoglycemia
   d. decreased total daily insulin dose

8. According to findings from multiple observational databases involving patients with Type 2 diabetes, the optimal HbA1c for overall mortality is <6.5%.
   a. true
   b. false

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

10. Other than a lower HbA1c, each of the following may be expected during treatment with SGLT-2 inhibitors as monotherapy or with metformin, except
    a. decreased albuminuria
    b. decreased blood pressure
    c. weight loss
    d. hypoglycemia

11. Severe hypoglycemia is associated with a lower risk of cardiovascular disease.
    a. true
    b. false

12. As glomerular filtration rate decreases, the risk of hypoglycemia increases in insulin treated patients with diabetes.
    a. true
    b. false

13. Evidence suggests that the use of a DPP-4 inhibitor in combination with insulin leads to a reduction in hypoglycemia, despite reduction in HbA1c.
    a. true
    b. false

14. The FDA recently released a warning about rare reports of severe joint pain in patients using GLP-1 receptor agonists.
    a. true
    b. false

15. Since 2008, the US FDA has mandated that any new medication for Type 2 diabetes must demonstrate _____ before approval.
    a. cardiovascular benefit
    b. cardiovascular safety
    c. no hypoglycemia
    d. cost-effectiveness

16. Which of the following was not observed among untreated women with gestational diabetes mellitus, as compared with women with normal glucose tolerance?
    a. higher incidence of macrosomia
    b. higher incidence of hypertension during pregnancy
    c. higher incidence of fetal malformations
    d. higher incidence of acute cesarean section

17. Among persons admitted to a critical care unit for acute coronary syndrome, the composite endpoint of death or reinfarction was significantly higher in those with diabetes or newly discovered dysglycemia (impaired fasting glucose or impaired glucose tolerance), as compared to those with normal glucose metabolism.
    a. true
    b. false

18. In a case-control study, patients with Type 1 diabetes and no history of MI were found to have a higher risk of future MI and all-cause mortality than non-diabetic individuals with a history of MI.
    a. true
    b. false

19. In a study of patients who were uncontrolled by maximum doses of metformin and sulfonylurea, investigators determined that sulfonylureas still stimulated insulin secretion.
    a. true
    b. false

20. In the EMPA-REG outcome trial of Type 2 diabetes patients with overt cardiovascular disease, all of the following outcomes, except _____, were observed with the SGLT-2 inhibitor, empagliflozin.
    a. The primary endpoint, a composite 3-point MACE (major adverse cardiovascular events), comprised of CV death, non-fatal MI, and non-fatal stroke, was statistically significantly reduced (-14%) by empagliflozin versus placebo.
    b. A statistically significant treatment benefit with empagliflozin (versus placebo) was observed based on a 35% reduction in heart failure hospitalizations.
    c. All-cause mortality was significantly reduced (-32%) by empagliflozin.
    d. As compared to placebo, patients treated with empagliflozin had equal incidence of genital infections.
**Diabetes 2015 Evaluation**  
**Volume 32**

The post-test and evaluation must be completed **on-line** (not by US mail or fax) at www.cme.yale.edu.

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: October 2015 to July 31, 2016.

Diabetes 2015 Test - Volume 32

1. (a) (b) (c) (d)  
2. (a) (b) (c) (d)  
3. (a) (b) (c) (d)  
4. (a) (b)  
5. (a) (b)  
6. (a) (b)  
7. (a) (b) (c) (d)  
8. (a) (b)  
9. (a) (b) (c) (d)  
10. (a) (b) (c) (d)  
11. (a) (b)  
12. (a) (b)  
13. (a) (b)  
14. (a) (b)  
15. (a) (b) (c) (d)  
16. (a) (b) (c) (d)  
17. (a) (b)  
18. (a) (b)  
19. (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 32

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: ________________________________

This CME program is sponsored by Yale School of Medicine, New Haven, CT.