Sodium glucose co-transporter (SGLT-2) inhibitors are the newest addition to an expanding armamentarium of antihyperglycemic drugs for the management of Type 2 diabetes. Canagliflozin, dapagliflozin, and empagliflozin are all now approved in the US. This week, a symposium entitled, “A New Class of Oral Agents: SGLT2 Inhibitors” addressed three major facets of these agents: (1) pharmacology; (2) therapeutic role; and (3) tolerability.

In the first session, “How Do They Work?” Dr. Anna Solini, Italy, reviewed mechanism of action. This class promotes 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. Historically, the role of the kidney in maintaining glucose homeostasis (via glucose filtration and reabsorption) has been underappreciated. Dr. Solini also shared that patients with Type 2 diabetes have higher SGLT-2 expression or upregulation of SGLT-2, resulting in increased renal glucose reabsorption. She also highlighted that SGLT-2 inhibitor action on urinary glucose excretion is dependent upon renal function. Patients with Type 2 diabetes and moderate to poor renal function also have a comparable loss of tubular resorptive capacity. These patients subsequently exhibit proportionally less glucose excretion than their counterparts with preserved renal function. A very attractive component of their mechanism is that SGLT-2 inhibitor activity is entirely independent of β-cell function and insulin action, making these drugs useful at various stages of diabetes.

An additional action is weight loss, likely due to their diuretic effect, at least initially. Chronically, patients experience a true loss of calories due to urinary glucose excretion. Early data demonstrate visceral adipose mass decreases over time. Mild reductions in blood pressure also occur, the mechanism for which is not entirely elucidated. Certainly, osmotic diuresis and decreased plasma volume play a role, but a thiazide-like diuretic mechanism has been postulated as well.

Finally, small but significant decreases in uric acid have been observed due to increased fractional excretion of urate. The mechanism has not been confirmed, but may be due to urate transport by SGLT-2 inhibitors. Dr. Solini closed her presentation stating that the SGLT-2 inhibitors are insulin-independent drugs that provide reversal of glucotoxicity and its related consequences and their efficacy is dependent upon glomerular filtration rate.

As mentioned, glycemic efficacy of the SGLT2 inhibitors should not be linked to baseline β-cell function (BCF) nor to insulin sensitivity (IS). To test this hypothesis, Matthews and international colleagues evaluated baseline BCF and IS using pooled data from placebo- and active-controlled studies involving canagliflozin (abstract 855). The first analysis involved 4 placebo-controlled, 26-week trials (n=2313; baseline HbA1c=8.0%, HOMA2-%BCF [as a measure of BCF]=49, HOMA2-%IS [as a measure of IS]=60). Due to the impact of baseline HbA1c on improvement of control, in addition to dividing patients into HOMA2-%BCF or -2%IS tertiles, they were further categorized by HbA1c values (<7.5%, between 7.5 and 8.5% and ≥8.5%). Glycemic control was evaluated for three subgroups: canagliflozin 100 mg, canagliflozin 300 mg, and placebo. A similar analysis was conducted for the 2 active-comparator, 52-week trials between canagliflozin 300 mg and sitagliptin 100 mg (n=1488, baseline HbA1c=8.0%, HOMA2-%BCF=49, HOMA2-%IS=59). As expected, greater reductions in HbA1c were observed in those patients with higher baseline HbA1c values. In the placebo-controlled and active-comparator trials, reduction in HbA1c with canagliflozin was similar regardless of baseline BCF and IS as measured per HOMA2. In comparison with sitagliptin, greater improvement in glycemic control occurred with canagliflozin, with the greatest differences occurring in patients with higher baseline HbA1c and lower baseline HOMA2-% (Figure 1). According to this investigation, the glucose-lowering effects of the SGLT-2 inhibitors...
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is clearly independent of the baseline degree of insulin deficiency and insulin resistance, two fundamental features of Type 2 diabetes.

With respect to impact of SGLT-2 inhibitors on body weight, Ferrannini and co-investigators from Italy and Germany examined weight loss as a function of degree of urinary glucose excretion (abstract 3). Data from a 90-week clinical trial of daily empagliflozin in patients with Type 2 diabetes (n=86, age 58±9 years, BMI 29.8±4.5 kg/m²) was utilized. Throughout the trial, body weight, estimated glomerular filtration rate (eGFR), and fasting plasma glucose (FPG) were collected at multiple time points (n=11). Time-dependent urinary glucose excretion (UGE) was estimated using the equation, eGFR x FPG. Using a mathematical model (http://bwsimulator.niddk.nih.gov) that simulates the time-course of weight loss for a given change in calorie balance, calorie-to-weight change was calculated. The observed calorie loss based on UGE predicted a weight loss of -8.7±2.4 kg over the 90-week period, yet the observed, weight gain, and other potential side effects when SGLT-2 inhibitors change the landscape? He began by identifying the SGLT-2 inhibitors currently available in the US and EU along with additional agents, ipragliflozin, luseogliflozin, and tofogliflozin, all currently on the market in Japan. Dr. Tsapas shared efficacy and safety data derived from meta-analyses conducted of all clinical trials (≥12 weeks) involving this drug class that were placebo controlled (n=55 trials) or with active comparators (n=15), amounting to approximately 22,000 patients. He proceeded to describe their overall impact on HbA1c, risk of hypoglycemia, weight gain, and other potential side effects when SGLT-2s are used as monotherapy or in combination and how this class compares to other modalities. Overall, HbA1c lowering averaged 0.7-1.0%, comparable or superior to all entities against which the SGLT inhibitors were studied. Patients experienced consistent weight loss and had a low risk of hypoglycemia. Dr. Tsapas methodically presented data supporting use of an SGLT-2 inhibitor along the entire spectrum of indications identified by the ADA-EASD position statement (i.e., monotherapy, combination with one or multiple drugs). His point was that these drugs will and are changing the treatment landscape and, given their insulin-independent actions, could be used at any point in the spectrum of diabetes. Despite his robust endorsement, Dr. Tsapas also provided information on special populations, including those with kidney disease, in whom the drugs are not recommended. Also, long-term outcomes data are still not available, with cardiovascular outcomes trials in progress. There is also some concern regarding slight increases in lipid parameters and mixed data on fracture risk.

The skeletal health issue relates to these agents’ augmentation of urinary calcium excretion. Observational studies have demonstrated that patients with Type 2 diabetes have a higher risk of fractures, which is sometimes linked to drug therapy, and the thiazolidinediones in particular. In a pooled data analysis, Johnsson and researchers from the US and Sweden evaluated data from 21 double-blind, phase 2b/3 studies of dapagliflozin (n=5936) compared with placebo predicted weight loss. The increase in intake was inversely correlated with baseline BMI (partial r=-0.33, p<0.01) and positively correlated with baseline eGFR (partial r=0.30, p<0.01). From these data, the investigators concluded that glucosuria results in an adaptive response of increased energy (i.e., calorie) intake, especially in those patients who have lower BMIs and preserved renal function at baseline. They theorized that weight loss might be even more profound with the SGLT2 inhibitors if concomitant strategies to maintain/reduce calorie intake could be implemented.

In the second symposium session, Dr. Apostolos Tsapas of Aristotle University, Thessaloniki, Greece posed the question, “Will SGLT-2 inhibitors change the landscape?” He began by identifying the SGLT-2 inhibitors currently available in the US and EU along with additional agents, ipragliflozin, luseogliflozin, and tofogliflozin, all currently on the market in Japan. Dr. Tsapas shared efficacy and safety data derived from meta-analyses conducted of all clinical trials (≥12 weeks) involving this drug class that were placebo controlled (n=55 trials) or with active comparators (n=15), amounting to approximately 22,000 patients. He proceeded to describe their overall impact on HbA1c, risk of hypoglycemia, weight gain, and other potential side effects when SGLT-2 inhibitors are used as monotherapy or in combination and how this class compares to other modalities. Overall, HbA1c lowering averaged 0.7-1.0%, comparable or superior to all entities against which the SGLT inhibitors were studied. Patients experienced consistent weight loss and had a low risk of hypoglycemia. Dr. Tsapas methodically presented data supporting use of an SGLT-2 inhibitor along the entire spectrum of indications identified by the ADA-EASD position statement (i.e., monotherapy, combination with one or multiple drugs). His point was that these drugs will and are changing the treatment landscape and, given their insulin-independent actions, could be used at any point in the spectrum of diabetes. Despite his robust endorsement, Dr. Tsapas also provided information on special populations, including those with kidney disease, in whom the drugs are not recommended. Also, long-term outcomes data are still not available, with cardiovascular outcomes trials in progress. There is also some concern regarding slight increases in lipid parameters and mixed data on fracture risk.

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(n=3403) (abstract 804). Although statistical analysis was not provided, dapagliflozin was not associated with any increase in fractures overall and or within high-risk subgroups (i.e., age ≥65 years, age ≥75 years, women >50 years, and eGFR <60 ml/minute).

Although labeling by the FDA and its European counterpart, the EMA, dictates use of these agents mainly in combination with metformin, they have conceivable utility as monotherapy in patients intolerant of metformin. The drug class was not recognized in the 2012 ADA-EASD Position Statement on the Management of Hyperglycemia in Type 2 Diabetes, because their approval was granted subsequent to publication. However, over the past 2 years, the SGLT-2 inhibitors have become increasingly popular and many clinicians are now considering their position in a treatment algorithm as related to other glucose-lowering drugs, mainly as second- or third-line agents. Several investigations have evaluated the role of combination therapy with an SGLT-2 inhibitor and a DPP-4 inhibitor. Researchers from the US and EU, Patel et al. evaluated fixed-dose combinations of empagliflozin with the DPP-4 inhibitor, linagliptin, in patients with Type 2 diabetes as add-on to stable-dose metformin for 52 weeks (abstract 1). In this double-blind, parallel group trial, 686 patients were randomized to one of five groups (2 different fixed combinations of the two drugs [empagliflozin 25mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg] and the individual components, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg). At 52 weeks, both the empagliflozin 25mg/linagliptin 5 mg group and the empagliflozin 10 mg/linagliptin 5 mg group led to significant reductions in HbA1c of -1.21% and -1.04%, respectively, compared to baseline. Reduction in HbA1c from baseline for the individual components were -0.45%, -0.69%, and -0.70% for linagliptin 5 mg, empagliflozin 25 mg, and empagliflozin 10 mg, respectively. The fixed dose combinations also led to statistically significantly higher percentages of patients achieving HbA1c <7%. Combination therapy significantly decreased body weight relative to linagliptin alone, but not when compared to empagliflozin monotherapy.

Based on these results, fixed-dose combinations provide greater glycemic control when compared with the individual agents used as monotherapy and were also noted to be well tolerated.

In a similar combination therapy study, empagliflozin and saxagliptin were evaluated as combination therapy in comparison to each as component monotherapy. Hansen and US investigators conducted a 24-week double-blind trial in which they randomized 534 Type 2 diabetes patients who were poorly controlled on metformin (mean HbA1c 8.9%) to once daily dapagliflozin 10 mg/saxagliptin 5 mg, dapagliflozin 10 mg/placebo, or saxagliptin 5mg/placebo (abstract 4). Combination therapy produced significantly greater reductions in HbA1c versus component therapy (treatment difference versus dapagliflozin -0.27% [95% CI: -0.48%, -0.05%], p<0.02; difference versus saxagliptin -0.59% [95% CI: -0.81, -0.37], p<0.0001). Percent of patients achieving HbA1c <7% also favored combination therapy (difference versus dapagliflozin 19% [95% CI: 10, 28]; difference versus saxagliptin 23% [95% CI: 15, 32]). Rates of urogenital infections (0.6-1.1%) were consistent with previously reported literature, and overall adverse event rates were comparable across groups. We note the relatively small differences in HbA1c between SGLT-2 inhibitor monotherapy and the combination in both trials.

The third speaker of the afternoon symposium, Dr. Jack Sobel, Wayne State University, US, an infectious diseases specialist, addressed the most common of all side effects associated with the SGLT-2 inhibitors in his presentation, “What About Urogenital Infections?” Sobel focused on both urinary tract infections (UTIs) as well genital mycotic infections. He revealed that the prospective data relative to SGLT-2 inhibitor-related genitourinary (GU) infections are lacking as initial drug studies focused on glycemic and metabolic outcomes. Culture and susceptibility data were not an initial focus of clinical trials and there is a paucity of data relative to specific infection rates and identified pathogens.

With respect to UTIs, the epidemiology of patients with diabetes is similar to those without: they are more common in women and frequency of sexual activity increases risk. Diabetes doubles the risk of UTI, not only due to glycosuria but also likely due to other factors such as bladder dysfunction. Patients with diabetes have a greater likelihood of having asymptomatic bacteruria, however, Dr. Sobel was quick to note this does NOT require treatment, even in diabetes (with the exception of pregnancy). Patients on SGLT-2 inhibitors do have a slight, but modest risk of increased bacterial UTIs. These are easily managed, occur with all SGLT-2 inhibitors, and are not a contraindication for use. He recommended that routine urine cultures should not be done as they are likely to reveal asymptomatic bacteruria which, as mentioned, does not require treatment. Antibiotic prophylaxis is generally not indicated, however, it is not entirely clear for patients with recurrent UTIs. In general, this patient population was excluded from the initial SGLT-2 studies.

The primary side effect is an increase in genital mycotic infections. Vulvovaginal candidiasis (VVC) commonly occurs in females with diabetes, regardless of drug therapy, and Candida balanitis is not uncommon in men, especially in males who are not circumcised. Candida glabrata is the primary pathogen for both infections, however, Candida glabrata is a growing concern. C. glabrata is generally not susceptible to standard treatment and very difficult to treat. In addition to diabetes, other risk factors for VVC include hyperglycemia, estrogens (especially topical)/oral contraceptives, sexual behavior, antibiotic use, corticosteroids, immunosuppressive therapy, and of course, treatment with SGLT-2 inhibitors. Use of SGLT-2 inhibitors increases the risk of genital mycotic infections by 3-6-fold. However, most are mild and respond to conventional therapy. The management of genital mycotic infections is the same in patients with/without diabetes. C. albicans is generally responsive to azole therapy. Alternatives such as nystatin or boric acid may be required. Similar to UTIs, Dr. Sobel emphatically stated that asymptomatic colonization should NOT be treated nor should the sexual partner(s) of the patient be treated. Prophylaxis should be reserved only for those patients with persistent, recurrent infections, regardless of SGLT-2 therapy.

Dr. Sobel concluded the presentation stating that future studies involving SGLT-2 inhibitors require study designs that prospectively analyze and evaluate the specific nature (i.e., pathogens) of GU infections associated with these drugs.

The Pitfalls of Hypoglycemia

Many presentations made this week at the EASD 2014 annual meeting addressed the incidence and consequences of hypoglycemia (ADA definitions presented in Table 1) associated with glucose-lowering therapies— particularly insulin and sulfonylureas (insulin secretagogues)— resulting in significant morbidity and at considerable financial cost. Recent data from large cardiovascular studies have linked hypoglycemia to increased cardiovascular events as well, making the prevention of this complication of diabetes therapy of growing importance.

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Silent Hypoglycemia

Simonyi et al. from Hungary determined the incidence of hypoglycemic episodes, most notably asymptomatic events, using continuous glucose monitoring (CGM) in patients with well-controlled Type 2 diabetes treated with a sulfonylurea with or without metformin (abstract 647). The study population was small, and included 10 Type 2 diabetic patients (7 men, mean age 71 ± 10 years, mean duration of diabetes 11 ± 9 years, mean HbA1c 4.9 ± 0.9%) who reported no symptoms of hypoglycemia over the previous two years. Over an average monitoring period of 4 days, 7 of the 10 patients had silent hypoglycemic episodes (interstitial glucose by CGM ≤ 70 mg/dl), lasting 374.5 ± 463.0 minutes on average, with a mean of 4.6 ± 2.6 episodes per patient. Five of the 10 patients had more significant hypoglycemic episodes defined by interstitial glucose ≤ 56 mg/dl, lasting 96.0 ± 156.6 minutes on average, with a mean of 2.0 ± 0.7 episodes per patient. None of the patients reported symptoms of hypoglycemia during monitoring. These data suggest that silent hypoglycemia is common in well-controlled patients with Type 2 diabetes being treated with sulfonylureas.

Risk Factors for Hypoglycemia and its Sequelae

Blonde and multinational CREDIT (Cardiovascular Risk Evaluation in people with Type 2 Diabetes on Insulin Therapy) investigators evaluated the incidence and rate of hypoglycemia based on HbA1c among 2,999 insulin-treated Type 2 diabetes patients (mean duration of diabetes 10.6 ± 7.8 years, BMI 29.3 ± 6.3 kg/m²) in routine clinical practices in Europe, Canada, and Japan (abstract 973). Hypoglycemia events were tracked during the 6 months prior to 1-, 2-, 3-, and 4 year follow-up visits (n = 2272 with 4-year data). Initiation of insulin was associated with a significant improvement in glycemia: mean (SD) HbA1c declined from 9.5 (±2.0)% at the start of insulin to 7.6 (±1.3)% at 4 years. Study patients starting insulin who achieved mean HbA1c < 7% (i.e., target HbA1c) experienced higher incidence and rates (events/patient) of asymptomatic and nocturnal hypoglycemia than those failing to achieve this target (Table 2), with the largest between-group differences apparent in the first year. The mean rate of severe hypoglycemia was low and similar between those who did and did not achieve target HbA1c.

Table 1. ADA/Endocrine Society Classification of Hypoglycemia in Diabetes

- Severe Hypoglycemia: event requiring assistance of another to take corrective action, such as actively administering carbohydrates, glucagon, or take other corrective actions
- Documented Symptomatic Hypoglycemia: event during which typical symptoms of hypoglycemia are accompanied by a measured blood glucose (BG) < 70 mg/dl (3.9 mmol/l)
- Asymptomatic Hypoglycemia: event not accompanied by typical symptoms but with a measured BG < 70 mg/dl (3.9 mmol/l)
- Probable Symptomatic Hypoglycemia: event during which symptoms typical of hypoglycemia are not accompanied by a BG but that was presumably caused by a value < 70 mg/dl (3.9 mmol/l)
- Pseudo-hypoglycemia: event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured BG concentration > 70 mg/dl (3.9 mmol/l) but is approaching that level


Table 2. Impact of Treatment to Target HbA1c on Symptomatic and Severe Hypoglycemia Among Insulin-Treated Type 2 Diabetes Patients

<table>
<thead>
<tr>
<th>Participants</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>At HbA1c target, n</td>
<td>710</td>
<td>685</td>
<td>621</td>
<td>586</td>
</tr>
<tr>
<td>Not at HbA1c target, n</td>
<td>1919</td>
<td>1842</td>
<td>1741</td>
<td>1602</td>
</tr>
<tr>
<td><strong>Symptomatic hypoglycemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anytime, patient, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At HbA1c target</td>
<td>175 (24.6)</td>
<td>155 (22.7)</td>
<td>110 (17.7)</td>
<td>107 (18.3)</td>
</tr>
<tr>
<td>Not at HbA1c target</td>
<td>315 (16.5)</td>
<td>309 (16.8)</td>
<td>274 (15.8)</td>
<td>259 (16.2)</td>
</tr>
<tr>
<td>Anytime, events/person</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At HbA1c target</td>
<td>1.40 ± 4.79</td>
<td>1.35 ± 4.34</td>
<td>1.18 ± 4.49</td>
<td>1.39 ± 4.76</td>
</tr>
<tr>
<td>Not at HbA1c target</td>
<td>0.96 ± 4.65</td>
<td>0.93 ± 4.97</td>
<td>0.75 ± 2.59</td>
<td>0.92 ± 3.58</td>
</tr>
<tr>
<td><strong>Severe hypoglycemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anytime, patient, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At HbA1c target</td>
<td>21 (3.0)</td>
<td>25 (3.6)</td>
<td>21 (3.4)</td>
<td>27 (4.6)</td>
</tr>
<tr>
<td>Not at HbA1c target</td>
<td>29 (1.5)</td>
<td>17 (0.9)</td>
<td>28 (1.6)</td>
<td>17 (1.1)</td>
</tr>
<tr>
<td>Anytime, events/person</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At HbA1c target</td>
<td>0.04 ± 0.26</td>
<td>0.08 ± 0.50</td>
<td>0.10 ± 0.66</td>
<td>0.20 ± 1.17</td>
</tr>
<tr>
<td>Not at HbA1c target</td>
<td>0.03 ± 0.44</td>
<td>0.02 ± 0.23</td>
<td>0.04 ± 0.45</td>
<td>0.04 ± 0.61</td>
</tr>
<tr>
<td><strong>Nocturnal events/person</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At HbA1c target</td>
<td>0.02 ± 0.15</td>
<td>0.03 ± 0.25</td>
<td>0.02 ± 0.15</td>
<td>0.06 ± 0.47</td>
</tr>
<tr>
<td>Not at HbA1c target</td>
<td>0.01 ± 0.35</td>
<td>0.00 ± 0.04</td>
<td>0.01 ± 0.14</td>
<td>0.01 ± 0.10</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD.

Note: Target based on mean HbA1c from 1 month after insulin initiation up to follow-up year values. Hypoglycemia events (during the last 6 months of each yearly follow-up period) were categorized by whether or not the person experiencing the event had mean HbA1c < 7.0% (target) or not at the follow-up visit closest to the event.

Wang and Chinese co-investigators evaluated early warning indicators for nocturnal hypoglycemia (abstract 643). Their study population included 1147 patients with Type 2 diabetes (63% male; mean age 59.2 ± 11.3, range 14-91 years old; mean blood glucose [BG] 134 ± 54 mg/dl) who underwent CGM for 65 to 82 hours. Hypoglycemia, asymptomatic hypoglycemia, and nocturnal hypoglycemia occurred in 37%, 23%, and 18% of patients, respectively. Of 965 hypoglycemic events, 61% were asymptomatic and 49% occurred at night. Nocturnal hypoglycemia

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The Pitfalls of Hypoglycemia

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peaked during the 10 pm to 2 am time frame, the rate 1.7-fold higher than that from 2-6 am (p<0.01). BG 3 hours after dinner correlated to some degree with the rate of nocturnal hypoglycemia (r=-0.955), with half of the events occurring among those who had 3-hour post-meal BG <85 mg/dl.

Separately, 479 participants with BG <85 mg/dl at 3 hours after dinner were randomly assigned to a non-intervention or an intervention group (e.g., insulin dosage reduced before sleep and/or eating 50-100 grams of protein or carbohydrate). Such treatment resulted in apparent prevention of nocturnal hypoglycemia for ~40%: The risk of nocturnal hypoglycemia (RR) was 1.7-fold higher in the non-intervention group (16.8% vs. 9.7%; p<0.01).

Using the ACCORD (Action to Control Cardiovascular Risk in Diabetes) cohort, Seaquist et al. from Minnesota and North Carolina determined that baseline insulin deficiency in Type 2 diabetes, possibly due to islet autoimmunity, is associated with severe hypoglycemia and mortality (abstract 638). In this nested case-control study, a participant who died with at least 1 episode of prior severe hypoglycemia (defined as hypoglycemia requiring assistance) was classified as a case and those who neither died nor had severe hypoglycemia were classified as controls (n=86 and 344, respectively). Each case was matched to 4 controls based on age (±5 years), race, BMI (±2.5 kg/m2), and glycemic intervention. After adjustments for age and BMI, death with at least 1 episode of severe hypoglycemia was associated with baseline insulin deficiency defined by fasting C-peptide <1.35 ng/ml (OR 6.5, 95% CI: 2.6-16.4; p<0.01) and the presence of the diabetes autoimmune marker, glutamic acid decarboxylase (GAD) antibodies (OR 2.4, 95% CI: 1.0-5.4; p=0.04), but not with other related antibodies (tyrosine phosphatase-related islet antigen 2 [IA-2A], insulin [IAA], zinc transporter [Zn-T8]). GAD antibodies were more common in insulin deficient (54.6%) than non-insulin deficient (4.9%) participants. Whether treatments to preserve insulin secretion in this subgroup of patients with Type 2 diabetes may reduce mortality remains an intriguing area for further study.

Consequences of Hypoglycemia

Bagger and Danish coworkers distributed a survey to Danish Diabetes Association members to investigate individual and societal consequences of hypoglycemia (abstract 1042): 3,117 of 9,951 invited individuals with Type 1 (32.2%) or Type 2 diabetes (67.8%) completed the survey. The rates of self-reported severe hypoglycemia were 2.9, 0.6, and 0.1 events per patient-year (PPY) in patients with Type 1 diabetes, insulin-using Type 2 diabetes, and non-insulin-using Type 2 diabetes, respectively. The rates of self-reported mild hypoglycemia in the respective groups were 99.0, 23.2, and 10.9 events PPY. Self-care strategies to avoid hypoglycemia included maintaining higher blood glucose levels (45.7%) and reducing physical activity (15.7%). Few took sick leave as a result of hypoglycemia. Prolonged mental recovery (>4 hours) following an episode of mild or severe hypoglycemia was reported by 8.7% and 31.0%, respectively. Of those holding a valid driver’s license, almost 1 in 10 (9.3%) reported having at least 1 episode of severe hypoglycemia in the last year. Patients who indicated that they had considered under-reporting hypoglycemia to maintain their driver’s license were more likely to have experienced severe hypoglycemia (OR 3.0, 95% CI 2.4-3.8; p<0.0001). Taken together, the study shows a high rate of self-reported severe hypoglycemia among insulin-treated patients who engage in self-care behavior that may compromise glycemic control due to fear of hypoglycemia and under-report hypoglycemic events due to concern about losing driving licensure.

In addition to being a barrier to optimal glycemic control, nocturnal hypoglycemia in patients with Type 2 diabetes decreases awakening response following the event, according to data presented this week by Madsbad from Denmark and the US (abstract 644). In a two-period, single-blinded, crossover study, using the hyperinsulinemic glucose clamp technique, 26 patients with Type 2 diabetes were randomized to two experimental night visits—one normoglycemic (plasma glucose maintained at 90-126 mg/dl) and one hypoglycemic (plasma glucose ~50 mg/dl) for 15 minutes after reaching sleep stage N2 or deeper then brought back to normoglycemia. The impact of nocturnal hypoglycemia on sleep was assessed using polysomnography. There was no difference between the hypoglycemic and normoglycemic nights based on number of EEG-identified arousals or awakenings in the first 4 hours of sleep. However, the number of awakenings was lower on hypoglycemic versus normoglycemic nights during the final 4 hours of sleep (geometric mean: 10 vs. 14, p<0.05) as well as during the entire 8 overnight hours (25 vs. 30, p<0.05)—but not during the first 4 hours of sleep. Total sleep time tended to be slightly longer on the hypoglycemic night (observed means: 366 vs. 349 minutes, p=NS). Statistically significantly higher hormonal counter-regulatory responses (adrenaline, growth hormone, and cortisol) to hypoglycemia were observed as compared with levels during the normoglycemic night. These findings, while representing seemingly modest differences, amplify concerns about nocturnal hypoglycemia, which potentially affect patients’ ability to wake up and respond adequately to hypoglycemia.

Hypoglycemia induces multiple pre-arrhythmic changes (e.g., decreases in serum potassium, intracellular calcium overload), and is therefore a potential risk factor for sudden death due to cardiac arrhythmia. Few data, however, directly link episodes of severe hypoglycemia with pre-arrhythmic conditions, such as QT prolongation. At the EASD annual meeting this week, Mylona and Greek coworkers presented data showing that severe iatrogenic hypoglycemia requiring medical assistance is associated with a both statistically and clinically significant prolongation of QT interval corrected for heart rate by the Bazett formula (QTcB) (abstract 631).

They conducted a prospective, multicenter study of documented iatrogenic hypoglycemia treated in an emergency department, requiring that a 12-lead ECG be obtained simultaneously with or immediately after the management of hypoglycemia, and within 30 minutes after the administration of glucose. After excluding patients who received medications possibly affecting QTc and those with hypokalemia (< 3.5mEq/L), 177 ECGs from hypoglycemic diabetes patients (mean age 72.7±15.7 years, 48.6% women, 9% with Type 1 diabetes) were compared to 91 age- and gender-matched control patients visiting outpatient diabetes clinics of the same hospitals over the same 6-month period. Three cardiologists blindly measured QT and RR intervals. Mean QTcB interval was significantly prolonged in patients compared to controls (440.4±41.5 vs. 413.9±32.5 msec, respectively; p<0.001). A significantly higher proportion of hypoglycemic patients had QTcB >440 msec (49.7% vs. 24.2% of controls; p<0.001); 14 hypoglycemic patients (7.9%) had QTcB >500 msec, compared to no control patient. These data indicate that hypoglycemia severe enough to require emergency department evaluation is linked to pro-arrhythmogenic cardiogram changes.

Hospitalization and Other Resource Utilization

Pilemann-Lyber et al. from Denmark investigated the incidence of hospital admission during 2010-2011 due to severe hypoglycemia (i.e., episodes needing external assistance) among Type 2 diabetes patients being treated with a sulfonylurea (SU) as monotherapy or with other oral
The Pittfalls of Hypoglycemia
Continued from page 5

Albuminuria Predicts Progression to ESRD in Diabetes

Albuminuria in diabetic patients is a known risk factor for adverse renal outcomes, primarily based on surrogate markers including decline in GFR. Babazono et al. from Japan conducted an observational cohort study of 20,884 diabetic patients (59% men, mean age of 55±14 years) to determine whether albuminuria can be used to predict the risk of developing a hard endpoint, the end-stage renal disease (ESRD) (abstract 1191). During a median follow-up period of 5.6 years (up to 18.1 years), 1,033 patients reached the endpoint of eGFR < 15mL/min/1.73 m². The 18-year cumulative incidence of reaching the endpoint, estimated by the Kaplan-Meier method, was 1.9%. These trials included several comparator agents—insulin glargine, biphasic insulin aspart, insulin detemir, and sitagliptin—and mealtime insulin aspart was used in some regimens.

In a related presentation, Heller et al. from the UK and Denmark evaluated resource utilization associated with severe hypoglycemia (defined as episode in which the patient required external assistance for recovery and reported as a serious adverse event). They analyzed three groups: patients with Type 2 diabetes treated with basal insulin plus oral therapy, Type 2 diabetes on multiple daily insulin injections, and patients with Type 1 diabetes treated with basal-bolus insulin (abstract 487). Included in their analyses were data from 14 phase 3 trials of an investigational basal insulin, insulin degludec, or degludec/insulin aspart.

These trials included several comparator agents—insulin glargine, biphasic insulin aspart, insulin detemir, and sitagliptin—and mealtime insulin aspart was used in some regimens. Severe hypoglycemic events often resulted in emergency/ambulance calls and treatment in a hospital setting, and were observed with all insulin regimens. Of 536 total severe hypoglycemic events, 157 (29.3%) required an ambulance/emergency call or treatment in a hospital setting, and were observed with all insulin regimens. Of 536 total severe hypoglycemic events, 157 (29.3%) required an ambulance/emergency call or treatment in a hospital setting, and were observed with all insulin regimens.

So Many Posters, So Little Time....

Table 3. Resource Utilization Associated with Severe Hypoglycemia Among Insulin-Treated Diabetes Patients

<table>
<thead>
<tr>
<th>Diabetes Type – Treatment</th>
<th>Treatment Regimen</th>
<th>Number of Hypoglycemic Events</th>
<th>Treatment without Resource Utilization</th>
<th>Ambulance/Emergency Calls &lt;24 Hours</th>
<th>Hospital/ED Treatment &gt;24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 – basal/bolus insulin</td>
<td>IDeg + IAsp IGlar + IAsp IDet + IAsp IDegAsp + IAsp</td>
<td>420</td>
<td>62.1%</td>
<td>31.0%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Type 2 – basal insulin + oral therapy</td>
<td>IDeg IGlar</td>
<td>21</td>
<td>42.9%</td>
<td>14.3%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Type 2 – multiple daily insulin injections</td>
<td>IDeg + IAsp IGlar + IAsp BiAsp bid IDegAsp qd or bid</td>
<td>95</td>
<td>54.7%</td>
<td>25.3%</td>
<td>23.2%</td>
</tr>
<tr>
<td>All</td>
<td>536</td>
<td>60.1%</td>
<td>29.3%</td>
<td>11.9%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

Table 4. Risk of ESRD by Baseline Urinary ACR

<table>
<thead>
<tr>
<th>Albumin-to-Creatinine Ratio (mg/g creatinine)</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-99</th>
<th>100-299</th>
<th>300-999</th>
<th>1000-2999</th>
<th>≥3000</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 9432) (n = 5362) (n = 2787) (n = 1356) (n = 1008) (n = 622) (n = 317)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-yr cumulative incidence of ESRD</td>
<td>1.9%</td>
<td>5.5%</td>
<td>14.1%</td>
<td>31.8%</td>
<td>71.8%</td>
<td>82.7%</td>
<td>98.1%</td>
</tr>
<tr>
<td>HR Reference</td>
<td>3.3</td>
<td>8.1</td>
<td>20.0</td>
<td>48.9</td>
<td>126.6</td>
<td>372.3</td>
<td></td>
</tr>
</tbody>
</table>

ACR = albumin-to-creatinine ratio; ESRD = end-stage renal disease; HR = hazard ratio.

summarized by baseline urinary albumin-to-creatinine ratio (ACR) (Table 4). After adjustments for gender, age, and baseline eGFR using the Cox proportional hazard model, there was a step-wise increased risk of developing ESRD based on level of albuminuria (each p < 0.001 as compared to the reference group of ACR < 10 mg/g creatinine) (Table 4). Higher levels of albuminuria, even within the normal reference range, were associated with increased risk of ESRD.

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Editors, Yale School of Medicine
New Haven, Connecticut
Important data on diabetes presented at the 50th Annual Meeting of the European Association for the Study of Diabetes come to you in Diabetes 2014, a newsletter CME program that is being offered to you by Yale School of Medicine. After receiving the newsletters by e-mail, please go to www.cme.yale.edu and take the CME quiz. You will qualify for up to 5 AMA PRA Category 1 Credits™ to be issued by Yale School of Medicine.

Diabetes 2014 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the etiologic 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 diabetes, 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.

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Some have amusingly proposed that diabetes is a cardiovascular (CV) disease manifested by hyperglycemia. While such hyperbole confuses the nuances of this relationship, it is quite clear that CV complications are exceedingly common in our patients with both Type 1 and Type 2 diabetes and are often responsible for their demise. Although most scientific investigation in this area has appropriately focused on atherosclerosis and coronary heart disease, heart failure is an increasingly common diagnosis in patients with diabetes. This is likely a reflection of improved survival rates after myocardial infarction in both diabetic and non-diabetic individuals over the past 2-3 decades, a testament to improved CV risk factor control and intensive interventions for acute coronary syndromes. That is, as mortality associated with myocardial ischemic events decreases, more of our patients are living with the consequences of long-term damage to the myocardium. In addition, diabetes is frequently associated with hypertension, which itself increases the risk of heart failure. Finally, a unique and still poorly understood syndrome of ‘diabetic cardiomyopathy’, which likely involves both structural and metabolic changes to contracting myocardial tissue, is responsible for additional cases. Importantly, heart failure is, in part, a disease of aging, and our population is growing increasingly older, with rates of both heart failure and diabetes on the rise. Accordingly, the older diabetic patient with heart failure will be an increasingly common clinical scenario over the coming years. There was significant attention paid to this topic in Vienna this week.

Heart Failure in Diabetes: New Outcomes Data from Sweden

Norhammar et al. from the Karolinska Institute in Stockholm, Sweden compared the prognosis in ischemic heart failure in patients with and without diabetes (abstract 44). They analyzed the Swedish Heart Failure Registry (which covers about 80% of Swedish hospitals) between 2003 and 2011, that includes nearly 35,000 patients. They discovered a striking 25% prevalence of diabetes in their heart failure population—60% of whom have ischemic heart disease as the suspected etiology. In all, 5,265 patients with and 12,408 patients without Type 2 diabetes were identified—each with heart failure in the context of coronary artery disease (CAD). Fifty percent of the entire cohort had been revascularized. The registry allowed the evaluation of 29 demographic, clinical, and treatment variables.

Those with diabetes were slightly younger (75 vs. 77 years), had a higher prevalence of hypertension (59% vs. 45%), but had better preservation of renal function (GFR > 60 ml/min, 44% vs. 38%). Although mean left ventricular (LV) ejection fraction was similar between the two groups, those with diabetes had more advanced heart failure symptoms (NYHA Class III-IV, 53% vs. 46%). Kaplan-Meyer survival curves are shown in Figure 1. The unadjusted odds ratio (OR) for mortality in the diabetic group was 1.32 (95% CI: 1.24-1.41). The investigators then considered age, gender, weight, duration/severity of heart failure, revascularization status, coexisting atrial fibrillation, pulmonary disease, anemia, renal function, and pharmacological treatment.

Figure 1. Kaplan Meyer-Curve of Long-term Survival by Diabetes Status in Patients with Ischemic Heart Failure

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Diabetes & CV Disease: An Update
Continued from page 1

After these adjustments, the OR was 1.71 [1.56-1.86]. The same trends were seen in the diabetic subgroup that had undergone revascularization (unadjusted OR 1.52 [1.39-1.67] and adjusted OR 1.63 [1.45-1.84]). The investigators concluded that diabetes is an independent predictor of long-term mortality in patients with ischemic heart failure, a risk that was not abolished by revascularization.

The same group of investigators, led by Johansson, reported a corresponding analysis from the registry, this time focusing on patients with preserved LV function (abstract 45). This category of heart failure is defined as that existing in a patient with signs and symptoms of heart failure, ejection fraction of >40-50% (depending on the author), and some structural abnormality by cardiology or imaging, such as LV hypertrophy (LVH) and/or diastolic dysfunction. Prior literature has determined that risk factors for this condition include female sex, hypertension, obesity, and diabetes. Notably, most investigators have found a somewhat better prognosis in those with preserved (as opposed to reduced) LV function.

In the Johansson study, patients with LV ejection fraction ≥50%, with (n=1,658) and without (n=5,047) Type 2 diabetes were tracked for a median of 22.5 months. As with the ischemic cardiomyopathy study above, a logistic regression model accounted for baseline differences. In this cohort, the diabetic group was also slightly younger (76 vs. 78 years), and was more frequently afflicted with CAD (47% vs. 36%) and hypertension (68% vs. 52%), but also had more frequently preserved renal function (eGFR >60 mL/min, 45% vs. 38%). The K-M survival curves are displayed in Figure 2—essentially no differences in mortality in the unadjusted analysis (OR 1.02 [0.92-1.15]). However, differences became apparent after adjustment for baseline variables (adjusted OR 1.39 [1.20-1.61]). The investigators concluded that, in patients with heart failure with preserved LV function, diabetes confers additional mortality risk.

These data from Sweden confirm those from prior investigations suggesting that heart failure is a particularly virulent comorbidity in our patients with diabetes. We now need to learn how to potentially reverse these mortality trends. Given the multifactorial nature of heart failure in diabetes, it is unlikely that a single focus of treatment will be successful in this regard.

Impact of Diabetes Therapies on Heart Failure

The potential effect of antihyperglycemic medications on heart failure risk is an emerging area of concern, initially stemming from the experience with thiazolidinediones (TZDs), which increase renal sodium retention and are contraindicated in those with a prior history of heart failure. More recently, in the SAVOR-TIMI trial, the DPP-4 inhibitor saxagliptin was associated with a 27% increased relative risk of heart failure hospitalizations. A contemporaneous trial, EXAMINE, using a different DPP-4 inhibitor, alogliptin, found no such risk, however. A third member of this class, vildagliptin was studied by Evans and US/European colleagues (abstract 888). Although this drug is not marketed in the US, we found the results of this study interesting, shedding further light on a controversial topic.

The investigators conducted a meta-analysis of prospectively adjudicated heart failure events from a pooled database of approximately 17,000 patients participating in 40 Phase 3 randomized vildagliptin clinical trials of a least 12 weeks duration. In these studies, the DPP-4 inhibitor was used as monotherapy or in combination with other antihyperglycemic agents and compared to placebo or other active comparators. All reported heart failure events were prospectively adjudicated by an independent expert committee, and the Mantel-Haenszel relative risk (RR) of confirmed events with vildagliptin vs. non-vildagliptin treatments was calculated. Of note, these trials were conducted long before any concern of heart failure was raised, so patients with NYHA Class I-III symptoms were included.

A total of 9,599 patients were treated with vildagliptin versus 7,847 with other glucose-lowering drugs. Baseline demographics and clinical characteristics were similar between the groups. Over 40% of patients had 2 or more CV risk factors and nearly 20% had a previous history of CV disease. Confirmed heart failure events were similar in number between the groups, at 41 (0.43%) in those randomized to vildagliptin and 32 (0.45%) in patients on other therapies (Figure 3), yielding a RR of 1.08 [95% CI: 0.86-1.70]. From this analysis, it appears that this DPP-4 inhibitor is not associated with any increased heart failure risk. The results conflict with a ‘real world’ analysis recently reported with the most popular DPP-4 inhibitor in the US, sitagliptin, which suggested an increased heart failure hospitalization risk (Weir et al. JCHF 2014).

A similar question was asked by De Berardis and European collaborators, as part of an EU-funded drug safety study. They conducted a meta-analysis of all DPP-4 inhibitor randomized clinical trials to assess their CV safety (abstract 890). A total of 8,168 citations were reviewed, from which 140 manuscripts were selected using pre-defined criteria. The group decided to focus solely on those trials (n=70) that reported at least one CV outcome event. The results of their analysis are disclosed in Table 1.

In the comparison of DPP-4-inhibitor-exposed patients and those receiving placebo, the RR's for a variety of CV disease endpoints were statistically neutral: CV mortality (0.85), MI (0.95), and ischemic stroke (1.04). However, the
investigators found an increased heart failure risk (RR=1.24, 95% CI: 1.03-1.49) in patients treated with DPP-4 inhibitors compared to placebo. In the active comparator studies, all comparisons were not significant, except that, interestingly, DPP-4 inhibitor therapy was associated with a decreased risk of ischemic stroke (RR=0.33, 95% CI: 0.14-0.79).

These results suggest that this newer class of glucose-lowering medication is neutral with regard to CV mortality and traditional CV events, but that, when compared to placebo, may increase the risk of heart failure. Notably, however, given the size of SAVOR-TIMI (16,492 patients), these results were primarily driven by the findings of that study.

We must await the results of two large DPP-4 inhibitor CV safety trials currently ongoing, TECOS (sitagliptin) and CAROLINA (linagliptin) before we know whether the SAVOR-TIMI findings were due to chance or stem from some heretofore unrecognized deleterious effect of this popular class of diabetes drug on cardiac function.

While the numbers are very small, we also found the significantly fewer stroke events in the active therapy group interesting. No diabetes treatment to date, to our knowledge, has been associated with reduced stroke risk, with the exception of pioglitazone in a subgroup analysis from the 2005 PROACTIVE trial (HR=0.53, 95% CI: 0.34-0.85) (Wilcox et al., Stroke 2007;38:865).

Identifying Silent CAD

Kwon et al. from South Korea explored the prevalence of clinically silent CAD in diabetic patients with stroke (abstract 47). They enrolled patients from their institution with acute ischemic stroke but without known CAD between 2008 and 2013. Those with high Framingham Risk Score (FRS) conferring a 10-year CHD event risk rate of ≥20% underwent cerebral and coronary arteriography. A total of 187 patients were studied, and divided into diabetic (59) and non-diabetic (128) groups. The mean age was 64.5±10.9 years and 60.9±10.1 years, respectively. More over, the frequency of reduced CFR was significantly higher (p=0.023) and the prevalence of CAD significantly lower (p=0.020) in the non-diabetic group. Moreover, the frequency of reduced CFR remained significantly lower in non-diabetic patients (p=0.001) (as well as in controls versus albuminuric patients; p<0.001).

Table 1. CV Safety of DPP-4 Inhibitors: Results of a Meta-Analysis

<table>
<thead>
<tr>
<th>Study n</th>
<th>Participant n</th>
<th>RR (95% CI)</th>
<th>Study n</th>
<th>Participant n</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>43,381</td>
<td>0.85 (0.71-1.02)</td>
<td>24</td>
<td>22,064</td>
<td>0.92 (0.50-1.70)</td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>23,494</td>
<td>1.17 (0.90-1.51)</td>
<td>8</td>
<td>7,130</td>
<td>0.83 (0.23-3.00)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>27,553</td>
<td>0.95 (0.84-1.09)</td>
<td>12</td>
<td>5,453</td>
<td>0.70 (0.34-1.43)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>27,224</td>
<td>1.04 (0.84-1.29)</td>
<td>8</td>
<td>7,777</td>
<td>0.33 (0.14-0.79)</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>20,349</td>
<td>1.24 (1.03-1.49)</td>
<td>6</td>
<td>6,180</td>
<td>1.31 (0.50-3.43)</td>
</tr>
</tbody>
</table>

RR=relative risk.

In non-diabetic controls, and normoalbuminuric and albuminuric diabetic patients, the CFR was 3.0±0.8, 2.6±0.8, and 2.0±0.5, respectively (p<0.001), with lower values indicating more microvascular dysfunction. The frequency of reduced CFR (defined as <2.5) was 16.7%, 40.0%, and 83.3% (p<0.001) in the three groups, respectively. Moreover, CAC (median [IQR]) was 0 [0-81], 36 [1-325], and 370 [152-1025] (p<0.001), respectively. After adjustment (age, gender, BMI, 24-hrsystolic blood pressure, heart rate, cholesterol, and smoking status), CFR remained significantly higher (p=0.023) and the prevalence of CAC significantly lower (p=0.020) in the normoalbuminuric versus the albuminuric diabetic group. Moreover, the frequency of reduced CFR remained significantly lower in normoalbuminuric vs. albuminuric patients (p<0.001) (as well as in controls versus albuminuric patients; p<0.001).

Multivariate linear regression was used to identify those variables independently associated with abnormal CFR and CAC. Lower CFR was found to be linked to higher CAC, degree of urinary albumin excretion, age, heart rate, lower HbA1c, and male gender (p<0.047) in the albuminuric group only. In those without albuminuria, the only significant association was to female gender (p=0.024).

It was concluded that in asymptomatic Type 2 diabetes patients without known CAD, the prevalence of coronary microvascular dysfunction was high, especially in those with albuminuria. Interestingly, these results were not entirely concordant with the CAC findings, the latter representing actual atherosclerosis. These data suggest a significant degree of pre-atherosclerotic coronary flow abnormalities in diabetes. Of course, the clinical implications of these findings are not yet known. Prospective studies will be needed to determine their prognostic importance.
This year’s Camillo Golgi Lecture was given by Dr. Solomon Tesfaye of Sheffield Teaching Hospitals in the United Kingdom, a leader in clinical research on diabetic neuropathy. Neuropathy is one of the devastating microvascular complications of diabetes, and, unfortunately, it remains a difficult condition to diagnose and treat. Classically it is a symmetrical, length-dependent sensory and motor polyneuropathy. Unlike retinopathy and nephropathy, the natural history for diabetic neuropathy is poorly understood, and to date there is no reliable screening tool for early disease. In most people, its development is silent, with an insidious progression, resulting in irreversible damage to neural tissues. As a result, diabetic neuropathy is often under-reported by patients, and under-diagnosed by physicians. Importantly, this complication is the leading cause of non-traumatic limb amputation, and is also a condition associated with significant morbidity and mortality.

While the natural history and preventative therapy for both diabetic retinopathy and diabetic nephropathy are reasonably well-characterized and established, our understanding of the pathobiology of neuropathy is substantially less advanced. The onset of retinopathy serves as the inflection point for the 

HbA1c diabetes diagnostic threshold. It is less well-known that the complication of neuropathy significantly precedes retinopathy, being found in ~24% of those with pre-diabetes (Ziegler et al. Diabetes Care 2008; 31(3):464-9). Also, while glycemic control in individuals with Type 1 diabetes was shown to reduce the development of diabetic neuropathy, the relationship with glycemic control is less clear in Type 2 diabetes.

In contrast to retinopathy and nephropathy, diabetic neuropathy does not have a reliable screening test for early diagnosis. Even among a panel of experts, the clinical exam for identifying subclinical neuropathy is not reproducible and actually only helpful once the complication is already well-established. Nerve conduction studies are the closest equivalent to neuropathy’s screening test of microalbuminuria, but this exam is uncomfortable for the patient, and requires significant resources. To further complicate matters, even diabetic patients presenting with painful neuropathy may have normal physical exams and conduction testing! A punch skin biopsy remains the gold-standard means of diagnosis, but this is, of course, even less appealing as a screening modality. Other newer diagnostic tests include corneal confocal microscopy or measurements of sweat gland function in response to heat or low voltage electricity. However, these innovative means of testing sensory and autonomic function have only been evaluated in cross sectional studies, not in longitudinal or randomized control trials.

Our understanding of diabetic neuropathy’s pathogenesis has come a long way since the first reports of low oxygen tension within nerves from diabetic patients nearly 3 decades ago (Newrick, BMJ 1986;293:1053-4). Such nerve hypoxia results from microvascular defects in which capillaries are closed to the normal circulation. As a result of the increased pressure within impaired capillaries, arteriovenous shunts develop, and the blood flow is further diverted away from nerve tissue. Chronic nerve hypoxia leads to a decrease in intraepidermal nerve fiber density and myelinated fiber loss (Malik, Diabetologia 1993;36:454-9). Additionally, in the setting of exercise, blood flow is insufficient to enable an increase in the usual nerve conduction velocity. Other contributions to nerve injury in diabetes may include inflammation, oxidative stress, and a deranged poloy pathway.

Painful neuropathy is mediated by small nerve fibers that regenerate after dying, with their disorganized firing causing pain. However, Dr. Tesfaye emphasized the heterogeneity of pain sensation in different people, with a multitude of factors that contribute to an individual’s pain perception and threshold. As of yet, we don’t have an objective marker for pain, which further complicates diagnosis and treatment.

Diabetic neuropathy is due for a paradigm shift. Dr. Tesfaye emphasized that it is not merely a peripheral neuropathy. Dysfunction also involves the central nervous system. He has found spinal cord atrophy and decreased peripheral gray matter, as measured by MRI, in the brains of individuals with Type 2 diabetes and peripheral neuropathy (Diabetes Care 2014;37:1681-88). The autonomic nervous system is similarly affected and can have protein manifestations, including anhidrosis, gastroparesis, bladder atony, orthostatic hypotension, and cardiac rhythm disturbances.

Treatment options for diabetic neuropathy are primarily symptomatic, with a goal to reduce the symptom severity by 50%. Only duloxetine and pregabalin are FDA-approved for the treatment of neuropathy symptoms. These agents have the strongest evidence for ameliorating discomfort. Other options, which are less evidence-based but may be considered in certain cases, include tricyclic antidepressants, carbamazepine, tramadol, or topical agents such as the substance P depleting capsaicin cream or lidocaine patches. Treatment with nutraceutical anti-oxidants such as alpha-lipoic acid are also under investigation. It should be pointed out that there are no known therapies to reverse diabetic neuropathy once it is established. Depression and functional limitations are closely associated with neuropathy, especially in the setting of chronic pain. Ideally, this disorder should be treated in a multi-disciplinary setting to include diabetes control, podiatry, pain management, physical therapy, and, if needed, psychological counseling.

As we are more aggressive in recognizing and treating pre-diabetes, hopefully, the development of neuropathy may be avoided. But clearly, more research into understanding the natural history and extent of disease may provide insights into better therapeutic options in the future.

Sensor Science

CGM in Daily Use

CGM is increasingly used in Type 1 diabetes patients, mainly in those wearing insulin pumps. These devices provide near continuous information to the patient on current subcutaneous interstitial fluid glucose concentrations, which roughly correlate with plasma levels, especially in steady-state. But is this voluminous amount of information actually used by the patient? Edelman et al. from California developed and extensively beta-tested a 70-question survey to determine current practices among sensor users in real-world settings and what interventions patients make on a daily basis in response to CGM data (abstract 1020). Patients with Type 1 diabetes (n=222) completed the survey—52% male, mean age 46±14 years, duration of diabetes 22±14 years, self-reported HbA1c 6.9%±0.8%. 65% were university graduates or had another advanced degree, 75% used insulin pump and 25% multiple daily injections.

Continued on page 5
Patients wore a CGM device from lunchtime until
breakfast the next day.

CGM levels did not differ between groups at lunchtime but was higher after lunch with PBR vs. BRR, as was glucose level just before exercising (221 ± 62 vs. 171 ± 59 mg/dl, respectively). Mean decrease in glucose during exercise sessions was similar for PBR vs. BRR (BG = -71 vs. -77 mg/dl, CGM = -42.1 mg/dl vs. -34.4 mg/dl). After the initial drop, mean glucose remained stable during the afternoon, at a higher level with PBR vs. BRR. Total glucose area under the curve (AUC) and time spent in the range of 70-180 mg/dl was not significantly different between the approaches, although less time (p=0.057) was spent >180 mg/dl with PBR compared to BRR. Only one hypoglycemia event occurred during exercise (BRR). There was a trend towards fewer hypoglycemic events with PBR in the afternoon (3 events in 3 patients vs. 10 in 6 patients with BRR, p=0.07), with the mean number of events 3.5-fold lower (0.16 ± 0.37 vs. 0.56 ± 0.92). No significant hyperglycemic rebound was observed before dinner and no significant difference in the sensor glucose level at bedtime (176 ± 79 vs. 160 ± 85 mg/dl). Likewise, there was no difference between the two approaches based on nighttime mean glucose, the timing/level of glucose nadir, time spent in or out of the range, or in the number of hypoglycemic events (PBR: 7 events in 5 patients vs. BRR: 10 events in 7 patients, p=0.39). There was also no hyperglycemic rebound the next morning, even in cases of hypoglycemia at night. On the basis of their study results, the investigators concluded that PBR leads to higher glucose but lower risk of hypoglycemia for pump therapy patients who exercise following a meal. An initial decrease in glucose of ~70 mg/dl can be anticipated with either PBR or BRR, and the latter, if chosen, should be initiated at least 30 minutes prior in order to limit hypoglycemia.
Evidence from inpatient (i.e., clinical research unit) feasibility studies shows promising results with full closed-loop systems. Accumulating evidence is now also suggesting clinical utility in the outpatient setting. Thabit et al. from the UK reported data collected in randomized, open-label, crossover studies of overnight closed loop insulin delivery during unsupervised free-living conditions (abstract 194). 40 participants with Type 1 diabetes, including 24 adults (age 43±12 years, HbA1c 8.0±0.9%) recruited at three centers and 16 adolescents (15.6±3.6 years, HbA1c 8.1±0.8%) recruited at one center, underwent training on the study devices followed by two periods, in random order, of sensor-augmented pump therapy in combination with or without overnight closed-loop utilizing a model predictive control algorithm to direct insulin delivery based on CGM data. Each period lasted four weeks in adults and three weeks in adolescents.

Participants initiated closed loop on their own volition on 866 nights (89%). Time spent with sensor glucose in the target range (70-144 mg/dl) between midnight and 8 am increased from 41% during sensor-augmented therapy to 59% during closed-loop (p<0.001; Table 2). Closed loop reduced overnight mean glucose by 14.5 mg/dl (p<0.001), with no difference in overnight glycemic variability, as measured by the standard deviation of sensor glucose. This was accomplished by increased overnight insulin delivery (p<0.001), but without changing the total daily delivery (p=0.84). Time spent above the target range was reduced during closed loop (p<0.001), as was the time spent in hypoglycemia (<70 mg/dl; p=0.014). These preliminary results demonstrate that overnight closed loop insulin delivery at home by adults and adolescents with Type 1 diabetes is feasible, with improved glucose control and reduced risk of nocturnal hypoglycemia. We are puzzled, however, as to why glucose variability did not improve in this study.

While ‘closed-loop’ systems are in early stages of development, major advances in this field made in just the past 2-3 years are extremely encouraging. We hope that fully integrated units will become available for clinical use in the next few years. This would represent a true transformation of insulin therapy for our patients with Type 1 diabetes.

Table 2. Glucose Control With Overnight Closed-Loop Insulin Delivery in Free-Living Conditions Over 3-4 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Overnight Closed-Loop (n=40)</th>
<th>Sensor-Augmented Therapy (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean overnight glucose (mg/dl)</td>
<td>142.2±16.2</td>
<td>156.6±25.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD of overnight glucose (mg/dl)</td>
<td>36.0±5.4</td>
<td>34.2±5.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Time spent overnight at glucose level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-144 mg/dl</td>
<td>59±12</td>
<td>41±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70-180 mg/dl</td>
<td>77±9</td>
<td>62±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;180 mg/dl</td>
<td>38±12</td>
<td>54±17</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;70 mg/dl</td>
<td>1.9 (0.7, 3.5)</td>
<td>2.9 (1.0, 6.4)</td>
<td>0.014</td>
</tr>
<tr>
<td>Insulin delivery overnight (U)</td>
<td>7.0 (5.4, 9.3)</td>
<td>6.0 (4.7, 7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total daily insulin delivery (U)</td>
<td>40.3 (32.9, 52.6)</td>
<td>39.4 (32.6, 55.8)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Data presented are mean± SD or median (interquartile range).

Impact of Two Major Hypertension Drugs on Glycemic Control

Hirst and British colleagues conducted a meta-analysis of 20 randomized, controlled trials (RCTs) that evaluated glycemic control (assessed by fasting blood glucose [FBG] and HbA1c) in people with diabetes mellitus taking either beta-adrenergceptor antagonists (beta-blockers) or diuretics (abstract 1203). Beta-blockers were associated with a mean increase in FBG of 11.5 mg/dl (95% CI: 4.3 to 18.6) and HbA1c of 0.75% (95% CI: 0.30 to 1.20), compared with placebo. Three trials (four comparisons) that studied propranolol showed a ~5-fold larger increase in FBG concentrations than three trials that used other beta-blockers. Diuretics were associated with a mean increase in FBG of 17.3 mg/dl (95% CI: 5.2 to 29.4) and HbA1c of 0.24% (95% CI: -0.17 to 0.65), compared with placebo. The four trials (5 comparisons) that studied thiazide diuretics showed a ~5-fold larger increase in FBG levels than the three trials that used non-thiazide diuretics (p=0.101). There were no significant differences in the numbers of hypoglycemic events or other adverse events between beta-blockers and placebo in three trials. These data may inform the use of beta-blockers and diuretics in patients with diabetes.

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Editors, Yale School of Medicine
New Haven, Connecticut
Important data on diabetes presented at the 50th Annual Meeting of the European Association for the Study of Diabetes come to you in Diabetes 2014, a newsletter CME program that is being offered to you by Yale School of Medicine. After receiving the newsletters by e-mail, please go to www.cme.yale.edu and take the CME quiz. You will qualify for up to 5.0 AMA PRA Category 1 Credits™ to be issued by Yale School of Medicine.

Diabetes 2014 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the contributing 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.
- Undertake 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 diastolic dysfunction, 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.

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That Gut Feeling

Bariatric bypass surgery offers the fastest and most effective means of remission from Type 2 diabetes, but it comes with risks that are directly correlated with the magnitude of weight loss. Professor Helene Hanaire, MD from Toulouse, France presented a summary of recent publications on pathogenic mechanisms and treatment options for hypoglycemia occurring after bariatric surgery—one of its most troublesome adverse effects. After Roux-en-Y gastric bypass, the classical ‘dumping syndrome’ is very common, in which food reaches the small bowel quickly, and mild to moderate hypoglycemia (as well as certain osmotic fluid shifts) may occur 1 to 3 hours after the meal. However, clinical symptoms are rare in this situation. In contrast, less commonly, more severe hypoglycemia with adrenergic and neuroglycopenic symptoms may occur in the post-prandial state, usually developing about one year after the procedure. This degree of hypoglycemia is much more concerning, and Dr. Hanaire emphasized the importance of using strict diagnostic criteria to differentiate it from the milder form associated with dumping.

Fortunately, severe hypoglycemia after gastric-bypass is relatively uncommon, with an estimated prevalence between 0.2% and 0.36% (Kellogg et al. Surg Obes Relat Dis 2008;4:492-9; Marsk et al. Diabetologia 2010;53:2307-11). Severe hypoglycemia has not been found after two other forms of bariatric surgery, gastric banding or vertical banded gastroplasty. Beta cell hyperplasia or nesidioblastosis is a suspected cause, and there are several case reports of the requirement for eventual partial pancreatectomy. However, to advance to this point is thought to be very rare, and recent investigations led to a better understanding of other mechanisms involved and potential less invasive therapies.

Goldfine and colleagues (JCEM 2007;92: 4678-85) initially noted excess levels of insulin, C-peptide, and the incretin hormone, GLP-1, after a glycemic challenge in post-gastric bypass patients. More recently, Salehi and colleagues (Gastroenterology 2014; 146:669-80) demonstrated that GLP-1 mediates both the hypoglycemia and hyperinsulinemia in the post-prandial setting. Post-bypass patients with recurrent hypoglycemia and normal controls underwent a mixed meal tolerance test in addition to either intravenous exendin (a GLP-1 agonist), or saline. Exendin treatment prevented hypoglycemia in all post-bypass patients, in association with lower insulin levels and higher glucagon levels post-prandially. Dr. Hanaire noted that this pathophysiological mechanism may not apply to all patients, since not all patients have high GLP-1 levels although they may still have a hypersensitivity to GLP-1. In another study by Breitman and colleagues (Diabetes Care 2013;36:e57), the site of glucose delivery was found to be important. Differences in glucose curves, insulin, and GLP-1 levels, were seen in obese patients taking an oral glucose challenge versus direct jejunal delivery of glucose through a nasally inserted feeding tube. This supports the hypothesis that glucose stimulation of the jejunum in a bypassed gastric system promotes an overly aggressive increase in the incretin-insulin axis, with a resulting abnormal decrease in plasma glucose.

For prevention and treatment of hypoglycemia in post-bypass patients, Dr. Hanaire recommended the consumption of six small meals per day, limiting carbohydrate intake to no more than 30 grams per meal, and specifically avoiding high glycemic index carbohydrates. She also suggested separating food from fluid intake by 30 minutes in order to slow gastric emptying. Increasing food viscosity with pectin or guar gum and avoiding stress while eating also appears to slow gastric emptying. If hypoglycemia is persistent despite diet therapy, then acarbose is recommended as an initial medication with each meal. This rarely used antihyperglycemic drug impairs the breakdown of complex sugars in the intestine, slowing the absorption of monosaccharides. It is a safe medication but does increase intestinal gas, a phenomenon that requires careful discussion with the patient. Reducing insulin secretion with calcium channel blockers (verapamil), somatostatin analogs Continued on page 2
Incretin-based therapies, including both glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors, have gained popularity since their initial introduction in the mid 2000s. There are now multiple molecular entities and formulations within each class, prompting a large amount research and clinical investigation. Multiple symposia, oral sessions, and posters addressed their evolving role, impact in combination therapy, long-term efficacy, and several additional clinical outcomes.

Dr. Clifford Bailey, Aston University, UK began a Thursday morning symposium addressing the GLP-1 receptor agonists, in particular, providing an overview of their metabolic effects, summarizing recent studies, and identifying lingering questions and possible future roles. He reviewed several meta-analyses that compare the outcomes of the individual agents. Bailey commented that due to the subtle differences in the various clinical trials, it is difficult to compare the individual drugs directly. Yet, despite this, results have been strikingly consistent relative to their impact on HbA1c lowering (generally, -1.0 to -1.5%) and body weight (-2 to -3 kg). Lingering questions include variability of responses, with substantial percentages of patients experiencing little glucose lowering effect, and durability over time. There is yet no clear answer relative to their impact on β-cell function. Data regarding the role of GLP-1 receptor agonists in Type 1 diabetes are promising, demonstrating modest decreases in HbA1c, but with lower basal insulin doses and decreased glycemic variability when used in combination with basal insulin. Future prospects for the compounds include the potential for chimeric peptides that are part glucagon, GLP-1, and GIP. There are also investigations with non-peptide GLP-1 receptor agonists permitting oral administration as well as inhaled, transdermal, and osmotic pump delivery systems. Finally, early studies suggest some pleiotropic effects on cardiac and neural tissues. For example, a small study raised a potential role in decreasing myocardial infarct size.

The following presentations made this week affirm several of the properties identified by Professor Bailey. Additionally, several investigations evaluated combination therapy with insulin—a increasingly popular use—while others directly compared GLP-1 agonists against insulin regimens. Jendle and international colleagues tested the weekly investigational dulaglutide versus bedtime insulin therapy, each combined with pre-meal lispro in a 52-week parallel, open-label study in Type 2 diabetes patients inadequately managed on conventional insulin therapy (abstract 42). Patients (n=884, mean age 59.4 years, HbA1c 8.5%, BMI 32.5 kg/m², total daily insulin dose 56 units) were randomized 1:1:1 to once-weekly dulaglutide 1.5 mg or 0.75 mg, or bedtime insulin glargine titrated to target. Each dose of dulaglutide was statistically superior to insulin at weeks 26 and 52 with respect to change in HbA1c (p<0.025) as well as percent of patients achieving HbA1c <7.0% (p<0.05). Mean prandial insulin doses at 26 weeks were 93 units, 97 units, and 68 units for patients receiving dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine, respectively, but equalized by 52 weeks. The insulin glargine dose required was 65 units. Body weight decreased with the 1.5 mg dose of dulaglutide (-0.87 kg at 26 weeks, -0.35 kg at 52 weeks) and increased in both the 0.75 mg dose group (+0.18 kg at 26 weeks, +0.86 kg at 52 weeks) and insulin glargine group (+2.33 kg at 26 weeks, +2.89 kg at 52 weeks) (p<0.05, glargine vs. each GLP-1 dose group). Event rates of hypoglycemia, both symptomatic and severe events, were lower, and gastrointestinal-related side effects were more common in the groups receiving GLP-1 therapy versus insulin (statistical analysis not provided).

In another comparative trial with basal insulin, the daily-dosed GLP-1 agonist, lixisenatide, was compared with placebo when added to patients receiving pre-existing basal insulin (≥20 units/day) with or without metformin (≥1500 mg/day). In this 26-week, double-blind trial, Lahtela and multi-national investigators randomized patients with Type 2 diabetes (BMI 32 kg/m²; HbA1c 8.2%, diabetes duration 12.1 years) to lixisenatide 1.8 mg (n=226) or placebo (n=225) with change in Hba1c as the primary outcome.
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(abstract 37). In addition to significantly greater changes from baseline HbA1c, the patients in the liraglutide group were also significantly more likely to achieve HbA1c <7.0% and <6.5%, and experience greater weight loss, lower FPG values and improvements in systolic blood pressure and select lipid parameters (Table 1). Similar to other investigations of this type, risk of hypoglycemia was low, with no severe hypoglycemic events documented. GI-related side effects, however, were higher with liraglutide (nausea 22.2% vs. 3.1% with placebo; vomiting 8.9% vs. 0.9% with placebo).

Weissman and researchers from the US and UK evaluated efficacy and safety of the recently-approved albiglutide 30 mg once weekly compared with insulin glargine in a 3-year, randomized, open-label trial of Type 2 diabetes patients poorly controlled on metformin with or without a sulfonylurea (abstract 837). Patients in both groups (n=745) were treated to target (HbA1c ≤7.0% and FPG ≤100 mg/dl) and, where required, could increase the albiglutide dose to 50 mg or up titrate the glargine dose per pre-specified criteria. At week 52, albiglutide was deemed non-inferior to glargine with respect to HbA1c, with a treatment difference of 0.11% (95% CI: -0.04%, 0.27%). At the 3-year mark, both groups achieved a durable reduction in HbA1c and similar proportion of patients required hyperglycemic rescue in each group (albiglutide 56.2%, glargine 48.0%, p=0.1515). From these data, it appears that GLP-1 receptor agonists may provide an alternative to basal insulin, providing comparable glycemic control with less hypoglycemia. They may also be paired with insulin therapy.

In this light, fixed-dose combinations of a GLP-1 receptor agonist and basal insulin are another interesting area of investigation. Rosenstock et al. from the US, Netherlands, and France randomized 323 insulin naïve Type 2 patients currently on metformin (mean baseline HbA1c 8.0%, BMI 32.1 kg/m², diabetes duration 6.7 years) to a single formulation combination of the investigational GLP-1 receptor agonist, lixisenatide (1 μg) plus insulin glargine (2 units) or to glargine alone (abstract 241). At week 24, mean HbA1c was reduced to 6.3% with the combination and 6.5% with glargine alone (LS mean difference -0.17% (95% CI: -0.31%, -0.03%); p=0.0130). Additionally, body weight was significantly reduced in the lixisenatide/glargine group (p<0.0001), with no increase in hypoglycemic events and no severe hypoglycemia. Those receiving combination therapy did, however, experience higher rates of nausea and vomiting (7.5% vs. 2.5% with glargine).

Within the incretin mimetic group, it is reasonably established that GLP-1 receptor agonists provide a more robust lowering of HbA1c with the added benefit of weight loss than DPP-4 inhibitors, which are weight neutral. Madani and co-researchers from France investigated the potential improvement in glycemic control and weight management in patients who converted to a GLP-1 receptor agonist after treatment with a DPP-4 inhibitor (abstract 832). Utilizing data from the EVIDENCE study, a multicenter, observational surveillance of glycemic durability during long-term (2-years) therapy with liraglutide, 1,002 (of 3,152, 32%) who were converted from a DPP-4 inhibitor were evaluated. A total of 624 subjects (mean age 58±10 years, BMI 34±6 kg/m²; HbA1c 8.4±1.4%) continued liraglutide for 2 years demonstrating significant (all p<0.0001) reductions in mean HbA1c (-0.85%), FPG (-28 mg/dl), and weight (-3.6 kg). Additionally, a greater percentage of patients achieved HbA1c <7% after converting to liraglutide (31.7% vs. 9.7% receiving a DPP-4 inhibitor at baseline, p<0.0001). The researchers noted that previously conducted controlled clinical trials have not produced such improvements upon switching incretin modality as their observational data demonstrates, and may be reflective of different baseline characteristics.

The role of liraglutide in the prevention of pre-diabetes and delaying onset of Type 2 diabetes is also of some interest. Pi-Sunyer et al., in the SCALE obesity and pre-diabetes trial (abstract 73), overweight/obese patients (BMI ≥27 kg/m²) with at least one co-morbidity or obese patients (≥30 kg/m²) were educated regarding a 500 kcal/day deficit diet and exercise program and randomized 2:1 to receive once-daily liraglutide 3.0 mg or placebo for 56 weeks. At baseline, 61% of patients were considered to have pre-diabetes (ADA 2010). At 56 weeks, those receiving liraglutide achieved significantly greater weight loss (8.0% vs. 2.6% for placebo; p<0.0001). Of those patients defined as having pre-diabetes at baseline, 69.7% vs. 32.1% reverted to normoglycemia on liraglutide and placebo, respectively (estimated OR 4.9, p<0.0001). Similarly, more normoglycemic patients at baseline progressed to pre-diabetes in the placebo group (19.9% vs. 6.9% liraglutide 6.9%; estimated OR=3.34, p<0.0001). While few patients progressed to Type 2 diabetes, this also occurred at a greater frequency in the placebo arm than in the liraglutide arm (1.3 vs. 0.2 events/100 patient years exposure, respectively; p=0.0003). In a follow-up cessation study, at week 56, patients on liraglutide and without pre-diabetes were re-randomized to liraglutide or placebo for an additional 12 weeks. At week 68, patients re-randomized to placebo regained more weight than those maintained on liraglutide (estimated treatment difference 2.2%, p<0.0001) and progressed to pre-diabetes (8.0% to 22.4% for placebo and from 9.1% to 8.6% for liraglutide; p<0.0001).

On behalf of the DURATION-1 investigators Dr. E. Klein presented long-term efficacy and safety from an open-label extension study of once-weekly exenatide in Type 2 diabetes (abstract 77). 127 patients completed 6 years of therapy, the longest assessment of GLP-1 therapy to date. Significant improvements in HbA1c, FPG, and weight were achieved between baseline and year 6: HbA1c (LS mean -1.6% [95% CI: -1.9, -1.4]; FPG (-28.4 mg/dl [-38.3, -18.5]); and weight (-4.3 kg [-6.0, -2.6]). 45% and 32% of patients achieved HbA1c <7.0% and ≤6.5%, respectively. Patients generally experienced improvements in parameters at week 30 and maintained them throughout the six years. Nausea (mostly mild) was the most common adverse event and decreased over time (events/year of patient exposure: 0.85 from baseline to week 30 and 0.08 from week 30 to year 6). Injection site reactions also decreased over time. Over the six-year study period, 2 pancreatitis, 1 pancreatic carcinoma, and 3 acute renal failure cases were reported.

Table 1. Liraglutide vs. Placebo Added to Pre-Existing Insulin Regimens: Results at Week 26

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (n=225)</th>
<th>Placebo (n=225)</th>
<th>Estimated Treatment Difference (95% CI)</th>
<th>Estimated OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>-1.30</td>
<td>-0.11</td>
<td>-1.19 (-1.39, -0.99)</td>
<td></td>
</tr>
<tr>
<td>Patients achieving HbA1c &lt;7% by week 26 (%)</td>
<td>59.2</td>
<td>14.0</td>
<td>8.91 (5.45, 14.59)</td>
<td></td>
</tr>
<tr>
<td>Patients achieving HbA1c ≤6.5% by week 26 (%)</td>
<td>42.9</td>
<td>3.6</td>
<td>20.12 (9.92, 40.84)</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>25.9</td>
<td>2.9</td>
<td>-23.04 (-30.6, -15.48)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-3.5</td>
<td>-0.4</td>
<td>-3.11 (-3.85, -2.37)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>-5.8</td>
<td>-0.8</td>
<td>-5.02 (-7.45, -2.59)</td>
<td></td>
</tr>
</tbody>
</table>

Note: All p<0.0001. OR=odds ratio

Continued on page 4
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There were no major cases of hypoglycemia. From these long-standing data, the investigators concluded that treatment with GLP-1 receptor agonists, specifically weekly exenatide, provides glycemic durability and maintained improvements in weight, with no unexpected safety findings. We would point out that open-label extensions of randomized clinical trials are limited in what they can teach us about durability of a drug’s effectiveness, since non-responding patients tend not to continue in these studies. So, the patients sticking with the therapeutic option are usually a selected group of ‘responders.’

The second session of the symposium, presented by Dr. David Nathan, Harvard, US, addressed the question, “Do we need GLP-1 based therapies?” Dr. Nathan mentioned that the primary rationale for therapy, at this point, is the need to decrease microvascular complications. Based on data from the UKPDS for Type 2 disease and DCCT for Type 1 disease, we know that HbA1c lowering is proportional to decreased microvascular complications (about 30% for every 1% reduction in HbA1c). Accordingly, an HbA1c goal of <7.0% remains a reasonable target. He reminded the audience that although the benefits of sulfonylureas, metformin, and insulin therapy in this regard have been demonstrated, there are no data yet with either the GLP-1 receptor agonists or the DPP-4 inhibitors. Nonetheless, using HbA1c as a surrogate marker for a presumed effect on microvascular complications is reasonable. Whether the same can be said for macrovascular complications is far less clear. The primary question, according to Dr. Nathan, is how to choose wisely from a growing list of Type 2 diabetes therapeutic options in the absence of comparative effectiveness data—i.e., how to balance between the risks and benefits of selected agents. Data previously described weighing the pros and cons of incretin-based therapies relative to other medication therapies were reviewed. Reverting back to his original question, Dr. Nathan stated that it is not whether we need the incretin-based therapies, but when to use them and in whom. Drug selection, calibrating the ‘value added’ as well as the ‘value subtracted’ of each drug can be a challenge. He concluded his remarks by stating that the GRADE (Glycemia Reduction Approaches in Diabetes: a comparative Effectiveness study) trial has been enrolling subjects in the US since January 2013. This trial is prospectively comparing four commonly used entities after metformin (sulfonylurea, DPP-4 inhibitor, GLP-1 receptor agonist, and basal insulin) and may provide further clarification regarding medication selection for patients with Type 2 diabetes.

Finally, the morning session concluded with an evaluation of the adverse effects attributed to GLP-1-based therapies. Dr. Baptist Gallwitz of Tubingen University, Germany posed the question, “Should There Be Concern?” He focused on data regarding pancreatic safety, thyroid cancer, and cardiovascular (CV) effects. He reminded the audience of the joint statement of the FDA and European Medicines Agency (EMA) (N Engl J Med, 2014: 370;794-7); there are inconsistent data and no final conclusion regarding a causal relationship between the incretin-based drugs and pancreatic disease. It should be considered a possible risk until more definitive data become available.

Gallwitz also detailed the data from the SAVOR-TIMI 53 trial (Diabetes Care 2014;37(9): 2435-41) that demonstrated a small (HR 1.09, 95% CI: 0.66, 1.79; p=0.80), but insignificant increase in the event rate of confirmed pancreatitis cases for saxagliptin versus placebo. Further investigation of this data revealed an uneven distribution of pre-existing risk factors, such as ethanol consumption and previous pancreatitis history, in the saxagliptin group. He also shared the results of a recent meta-analysis (Li, et al. BMJ 2014, 348:g2366) of randomized (n>350,000) and observational (n>320,000) studies that concluded that the frequency of pancreatitis is very low with no imbalance between patients treated with or without incretin-based drugs. Lastly, earlier data identifying morphologic changes in pancreatic histology have been challenged based on methodologic deficiencies.

With respect to thyroid cancer, although animal studies demonstrate that GLP-1 receptor agonists bind to C-cells, leading to calcitonin release, C-cell abnormalities, and tumor production, there is no coupling of GLP-1 agonists to receptors in humans or systemic changes in calcitonin levels. No single case report of medullary thyroid cancer in humans treated with these drugs has been reported to date.

Finally, CV outcomes remain a question for incretin-based therapies. The SAVOR-TIMI 53 and EXAMINE trials (Scirica, N Engl J Med 2013; 369:1317-26; White, N Engl J Med, 2013:369:1327-35) demonstrated no increased risk of overall CV outcomes, with saxagliptin and alogliptin, respectively, when compared with placebo. However, neither was protective—despite preclinical data suggesting a possible beneficial vascular effect and some improvement in surrogate markers of CV disease in humans. Saxagliptin also resulted in a small, but statistically significant increase in heart failure hospitalization (HR 1.27, 95% CI: 1.07, 1.51; p=0.007). An explanation for this remains elusive. Another CV concern is the increase in pulse rate (2-4 beats) associated with the GLP-1 receptor agonists, particularly the more long-acting formulations. Gallwitz shared that the ongoing CV outcomes trials will provide much more data relative to CV safety. He concluded his presentation with the answer to his original question, “No” we should not be concerned—that the benefits of the incretin-based therapies appear to far outweigh their potential risk. However, more data are needed both from randomized clinical trials and observational studies.

In summary, incretin-based therapies, have inculcated themselves into common treatment regimens for our patients with Type 2 diabetes. The DPP-4 inhibitors, while generally somewhat less efficacious than other antihyperglycemic agents, are extremely well tolerated and are frequently used in conjunction with metformin. The GLP-1 receptor agonists have tolerability issues and require injection for administration. However, they too, appear to be experiencing an expanding role either in place of or in combination with insulin to improve control, with less hypoglycemia and weight gain.

Statins & Diabetes Risk: Taking the Good with the Bad?

Recent controversy regarding the influence of statin therapy on risk for diabetes has stimulated a number of investigations to further elucidate the nature of this risk and its biological underpinnings. Over the past two decades, various studies have suggested an increased risk of diabetes in statin users, but the data were not consistent. It wasn’t until the results of the JUPITER study were published in 2008 that the diabetes community became concerned ( Ridker et al., N Engl J Med 2008;359:2195-207). In this randomized clinical trial involving rosuvastatin 20 mg QD, the relative risk of developing diabetes in the active therapy group was increased by 26% (95% CI: 4%-51%). In post-hoc analysis, risk factors for diabetes development on statin therapy were metabolic syndrome, impaired fasting glucose, HbA1c >6%, and BMI >30 kg/m².

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Several presentations this week explored this controversial area. Cai and Chinese colleagues conducted a meta-analysis of published statin trials between 1966 and 2012, focusing on larger and longer duration studies with more than 1,000 participants followed for at least 2 years (abstract 666). The investigators calculated risk estimates using a random-effect model and meta-regression in order to identify the potential risk factors of ‘statin-induced diabetes.’

There was a total of 95,102 non-diabetic patients among 14 trials. When the LDL-C target was <70 mg/dl (<1.8 mmol/l) the odds ratio (OR) for diabetes was 1.33 (95% CI: 1.14-1.56), but only 1.16 (95% CI: 1.06-1.28) when the LDL-C target was 70-100 mg/dl (1.8-2.59 mmol/l). Moreover, there was no increase in diabetes risk when the LDL-C target was >100 mg/dl (>2.59 mmol/l). Further adjustments for age, female, and baseline lipid levels through meta-regression demonstrated that there were three major determinants of diabetes risk: baseline LDL-C, target LDL-C, and relative LDL-C reduction. The investigators concluded that the intensification of lipid-lowering therapy appeared to be the main driver of diabetes risk. One limitation of this study is that the investigators appeared not to have controlled for the specific statin drug used. Prior work has suggested that more potent statins (atorvastatin, rosuvastatin, simvastatin) may have a larger effect on glucose metabolism than pravastatin. Of course, since the trials with lower targets tended to use drugs with greater LDL-C lowering efficacy, the results of this meta-analysis could be confounded.

Related directly to the question of different effects on diabetes risk based on specific statin type, Shiba et al from Japan presented their findings from the J-PREDICT study, a prospective randomized, open-label trial evaluating the effects of the newer pitavastatin on the incidence of diabetes in patients with impaired glucose tolerance (IGT) (abstract 272). A total of 1,269 patients were randomized to 1-2 mg of pitavastatin (n=634) vs. lifestyle modification alone (n=635). The primary outcome was incident diabetes defined as fasting plasma glucose of ≥126 mg/dl or a 2-hour plasma glucose of ≥200 mg/dl after a 75g oral glucose tolerance test (OGTT), the latter performed twice annually. The full analysis set consisted of 1,090 individuals, about 40% of whom were female. Both genders had similar baseline glycemic- and insulin-related measures, the latter a reflection of their insulin sensitivity. And pitavastatin, not unexpectedly, significantly reduced LDL-C compared with the control group.

The incidence of diabetes in women was actually reduced by 32% (HR 0.68, 95% CI: 0.49-0.93; p=0.02) in the pitavastatin vs. control group (Figure 1). In men there was no difference (HR, 0.97, 95% CI: 0.78-1.21; p=0.78). The analyses using stratified log-rank tests and Cox proportional hazard models also indicated a beneficial effect in women only. However, while in the overall cohort, there was no influence in males, a trend towards higher incidence of diabetes was observed in men below age 55. It was concluded that pitavastatin does not increase the risk of diabetes overall, with seemingly protective effects in women. The reasons for these gender differences are not known.

To provide more insights into the pathophysiology of this association, Professor Markku Laakso from Kuopio University, Finland presented, "Mechanisms for the Diabetogenic Action of Statins" at a lipid symposium on Thursday. Prior data have been conflicting as to whether statins might affect β-cell function or insulin action—two methods by which a drug could increase the risk of diabetes. In recent studies from his group, Dr. Laakso studied the effects simvastatin and pravastatin in two in vitro systems—the first, an insulinoma cell line from mice, known as MIN6, to study possible effects on insulin secretion, and, the second, a rat skeletal muscle myotube system to assess effects on insulin responsiveness in target tissues. In the MIN6 cells, his group has demonstrated potent effects of simvastatin (but not pravastatin) to dampen the stimulatory effects of several insulin secretagogues, including sulfonylureas, acetylcholine, GLP-1 receptor agonists, GPR-40 receptor agonists (free fatty acid receptor agonists), and calcium channel activation. In addition, simvastatin (but also not pravastatin) decreased insulin signaling in the myotubes via Akt (a protein kinase), the expression of the important glucose transporter GLUT-4, and glycolytic flux. As a result, Dr. Laakso suggests that simvastatin may influence both insulin secretion and action through multiple mechanisms. How many and which of these are actually relevant in the human situation remain unclear, but further work in this area could potentially lead to safer lipid-lowering drugs in the future.

We would also point out that despite the risk of diabetes, statins remain a potent tool to reduce CV risk in both patients with diabetes and those at risk for diabetes. For example, the JUPITER investigators have reported that in those trial participants with diabetes risk factors, allocation to rosuvastatin was associated with a 39% relative risk reduction in the primary composite CV endpoint (p=0.0001) and a 28% increase in the risk of diabetes (p=0.01) (Ridker et al., Lancet 2012;380:565). In this group, 134 vascular events or deaths were avoided with rosuvastatin for every 54 new cases of diabetes diagnosed. In participants with no major diabetes risk factors, statin therapy was associated with a 52% reduction in the primary endpoint (p=0.0001), and no increase in diabetes (hazard ratio (HR) 0.99; p=0.99). In these individuals, 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed. Moreover, when they focused upon the 486 trial participants who did develop diabetes during follow-up (270 on rosuvastatin vs. 216 on placebo, p=0.01), the point estimate of CV risk reduction with the statin (HR 0.63) was similar to that observed in the trial as a whole (HR 0.56).
Several presentations this week focused on emerging clinical trial data on the newest insulin formulations—primarily of the basal variety. The challenge for these novel products is to demonstrate specific advantages as compared to established insulin analogues which are already quite good in terms of their smooth pharmacokinetic profile and low risk of hypoglycemia. That is, incremental benefits can be difficult to prove, particularly when using primary trial endpoints such as the relatively crude marker of glycemic control, HbA1c, or when focusing on relatively uncommon adverse events like hypoglycemia. The majority of clinical trials assessing the new insulins are designed as so-called ‘non-inferiority’ studies for changes in HbA1c, for registration purposes. They typically involve large numbers of patients, in order to ascertain any differences in hypoglycemic events. Newer diagnostic modalities such as continuous glucose monitoring (CGM) allow for a more detailed examination of hypoglycemia risk, as well as the potential to be associated with reduced glycemic variability. The former is of particular interest in Type 1 diabetic patients, because they are more frequently afflicted with this complication of insulin therapy than are those with Type 2 diabetes.

Nakamura et al. (abstract 952) reported on 32 patients with Type 1 diabetes, mean age 57.4±13.9 years and HbA1c 7.4±0.8%, who received either insulin degludec (IDeg) a new ultra-long acting basal insulin available in Europe or glargine (IGlar) for 4 weeks in a randomized, cross-over trial. While HbA1c levels were similarly lowered during the trial period, the mean fasting glucose was lower during IDeg use than IGlar (139.5±31.8 vs. 154.2±37.2 mg/dl; p=0.03) and IDeg achieved this benefit with a lower total daily insulin dose than IGlar (1.11 vs. 1.34 U/kg; p<0.05). Hypoglycemia rates were numerically lower with IDeg, but did not achieve statistical significance.

Dzygalo and colleagues (abstract 977) examined hypoglycemia rates with improved power through a meta-analysis of 4 studies comprising 1,846 patients with Type 1 diabetes treated with IDeg, IGlar, or detemir (IDet). The investigators found a significant decrease in nocturnal hypoglycemia events with use of IDeg, as compared to IGlar or IDet (RR 0.70, 95% CI: 0.62 to 0.79; p=0.000). However, they found no differences between the groups in terms of control of HbA1c or fasting glucose.

Glargine has a 300 U/ml concentrated formulation undergoing clinical testing versus its commonly used original 100 U/ml version. This allows not only for reduced injection volume (particularly important in those patients requiring high doses of insulin), but a smoother pharmacokinetic profile than traditional glargine, resulting from unique physicochemical properties once injected subcutaneously. Riddle and colleagues (abstract 980) studied 1,807 people with Type 2 diabetes randomized to either IGlar-300 or IGlar-100 once daily for 6 months. Both groups showed improvements in HbA1c and fasting glucose levels, with IGlar-300 having a slightly larger reduction from baseline for both HbA1c (-0.86±0.05% vs. -0.69±0.05%) and fasting glucose (-1.7±0.1 vs. -1.4±0.1 mg/dl). Rates of hypoglycemia were similar between the groups, however.

The value-added of these newer formulations remains uncertain, given their anticipated higher cost, particularly with a biosimilar version of glargine 100 U/ml now under FDA review. This should provide a more cost effective alternative to branded glargine, whose price has increased dramatically in recent years.

**New Insulins**

**So Many Posters, So Little Time…**

**Novel Notions on Metformin’s Mechanism of Action**

Metformin delayed release (DR) is formulated to deliver metformin directly to the lower bowel where absorption is poor, resulting in low systemic exposure. Previously conducted studies have shown the same dose of metformin DR and metformin immediate release (IR) similarly lower fasting (FPG) and postprandial plasma glucose and augment the gut-derived peptides GLP-1 and PYY, with plasma metformin levels reduced by approximately 50% with the DR compared to IR formulation. How much of a role this mechanism plays in metformin’s multiplicity of actions to lower glucose is not clear.

In a double-blind study, Fineman et al. from the US randomized patients with Type 2 diabetes to 1 of 3 doses of metformin DR (600 mg, 800 mg, or 1000 mg) or to placebo for 12 weeks (abstract 793). Two open-label groups of metformin extended release (XR) (1000, 2000 mg) were also included as reference. The study population was comprised of 240 patients (mean age 52 years, mean BMI 33 kg/m², mean FPG at screening 144 mg/dl, and HbA1c 7.4%) who were on diet and exercise (12%) or washed off previous metformin (88%, median dose 1500 mg) and/or DPP-4 inhibitor for 2 weeks prior to randomization.

Median FPG decreased from baseline to Week 4 (Figure 2; p=0.006 for metformin DR 800 mg vs. placebo) and from Week 4 to Week 12 in each of the metformin DR groups (all p<0.05 vs. placebo). FPG decrease for metformin XR 1000 mg was similar to that observed with metformin DR 600 mg and 800 mg, despite 4-9 fold higher fasting metformin plasma concentrations (515 vs. 56 and 119 ng/mL, respectively). The similar glucose-lowering effect of metformin DR 600 mg and metformin XR 1000 mg represented an approximately 40% shift in the dose response for the former, consistent with the gut being the primary site of metformin action.

At Week 12, mean HbA1C increased by 0.45% for placebo, reflecting withdrawal of oral agents, remained unchanged for the metformin DR and 1000 mg metformin XR groups, and was reduced (-0.21%) for the 2000 mg metformin XR group. GI tolerability was similar among the metformin treatment groups.

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