Prevalence of diabetes among older adults is rising rapidly. Currently, 1 in 5 adults over age 50 are diagnosed with diabetes, and this number is projected to increase to 1 in 3 by year 2050. Diabetes in the elderly poses serious financial burdens for individuals, for the healthcare system as a whole, and for the Medicare program in particular. Delivering effective, efficient, and affordable diabetes care for older adults is therefore of paramount importance. Yet, evidence is lacking with respect to best strategies and targets of care. A symposium on the burgeoning prevalence of diabetes in the elderly tackled these difficult issues.

Dr. Phillip Levin from Maryland described the many challenges physicians face making treatment decisions in older patients. The recent trials of intensive glucose control (ACCORD, ADVANCE, and VADT), which included many older individuals (mean age 60s), demonstrated that aggressive strategies to lower HbA1c do not improve cardiovascular and all-cause mortality—and may even worsen survival as shown in ACCORD. Therefore, the choice of a glycemic target must be individualized, taking into account the risks and benefits of additional glucose lowering patient by patient. Intensive glucose control has been associated with increased rates of hypoglycemia, which can lead to falls, fractures, possibly cardiac arrhythmias, and cognitive decline. On the other hand, less strict glucose control may lead to peripheral neuropathy and falls, increased susceptibility to infections, and cognitive aberrations due to uncontrolled hyperglycemia. Evidence is lacking as to the exact glycemic “sweet spot” that optimizes the benefits and minimizes the risks—and clinicians lack the evidence to guide them in counseling their patients.

Reflecting this uncertainty, professional societies differ in their recommendations for glycemic targets in older patients. The Veterans Administration/Department of Defense recommend HbA1c between 7% to 9%, depending on individual conditions, the American Geriatrics Society endorses a goal HbA1c <8%, and the American Diabetes Association suggests <7% for most adults, with less strict control in those with comorbidities and frequent hypoglycemia, and emphasizes individual target setting.

A recent retrospective cohort analysis of observational data performed by Elbert Huang (who chaired the session at the ADA) and coworkers (Huang et al., Diabetes Care June 2011) investigated the range of glycemic levels associated with the lowest rates of complications and mortality among older diabetic adults. The analysis involved 71,092 patients with Type 2 diabetes, aged ≥60 years, who were enrolled in Kaiser Permanente Northern California (2004-2008). The cohort (aged 71.0±7.4 years) had an HbA1c of 7.0±1.2%. The mortality curve had a U-shaped relationship between HbA1c; compared with HbA1c <6.0%, mortality risk was lower for HbA1c levels between 6.0 and 9.0% and higher for HbA1c ≥11.0%. Risk of any end point (complication or death) became significantly higher at HbA1c ≥8.0%. These observational relationships between HbA1c and combined end points appear to support the American Geriatrics Society target HbA1c <8.0%, and suggest that HbA1c <6.0% may be associated with increased mortality risk. However, the analysis is based on observational data that do not take into account individual decisions made with respect to glycemic targets and the types of strategies used to achieve these targets. Glucosuria has long been recognized as a consequence of hyperglycemia and is thought to occur at an estimated blood sugar threshold of 180 mg/dl, corresponding to HbA1c of 8% or greater. Dr. Lee from San Francisco and colleagues examined the relationship between glycemia and urinary incontinence in a large diverse cohort of older women with diabetes enrolled in the Northern California Kaiser Permanente (abstract 256-OR). The cohort included 6,026 women who responded to a survey question on urinary incontinence (response rate of 62%). Mean HbA1c preceding the survey was assessed as a predictor of urinary incontinence after adjusting...
Continued from page 1

Hb A1c of 7% to 8%, the analysis predicted that good. If the glycemic target were raised from an older diabetic patients, 63% had an Hb A1c < 7%, among these with diabetes in older individuals is associated with multiple comorbidities, which add to the complexity of management. The nationally representative Health Retirement Study (HRS) study of adults over age 50 showed that diabetes is strongly associated with both prevalent and incident geriatric conditions. Cognitive impairment, falls, urinary incontinence, dizziness, and visual impairment are all more common in those with diabetes. Interestingly, as age increases, the strength of the association of diabetes with new geriatric conditions decreased. For example, for adults age 51-60 years with diabetes, the odds of developing new geriatric conditions is 1.96 times as large as the odds for those without diabetes developing new conditions. In contrast, for adults age 71-80 years with diabetes, the odds of developing new conditions is only 1.25 times greater.

By the time people with and without diabetes reach 80, the overall effects of aging and impact of other diseases reduce the differences between the two groups. Although the mechanisms underlying the development of geriatric conditions in adults with diabetes is not fully understood, it is clear that they contribute substantially to morbidity and functional impairment. These findings suggest that adults with diabetes should be monitored for development of geriatric morbidities at a younger age. If these conditions are recognized and appropriately managed, there could be improvement in symptoms but decreases in disability.

But does diabetes management prevent geriatric conditions and disability (Figure 1)? The direct answer to this question is not known, but observational data provide potential clues. Compared to 1996, older adults with diabetes (70+ years) in 2006 have more comorbid conditions. They also receive a greater number of preventative services—so it is quite likely that the increase in comorbidities results from greater recognition of diagnosis during more frequent contact with providers. However, older adults (ages 71-80) with diabetes have experienced no change in disability rates (defined based on the number of activity of daily living [ADL] dependencies) between 1995 and 2006. In contrast, disability rates among older adults without diabetes are thought to be decreasing overall. The lack of improvement in older diabetic patients suggests that improved glucose management is not necessarily having a beneficial impact on disability rates. Certainly, development and delivery of strategies that improve the quality of life, as well as survival, among older patients with diabetes are needed.

The goals of diabetes care are to prevent complications. This is the rationale for intensive and comprehensive management of the risk factors for these sequelae, such as high glucose levels, lipids, and blood pressure. However, the risk of diabetic complications has to be weighed against the risk of the therapies themselves. Another analysis based on the Kaiser Permanente data found that geriatric syndromes and hypoglycemia affect health-related quality of life as much as, or more so, than diabetes complications in older diabetic patients (Lai et al., Diabetes Care 2011). This suggests that the current goals of diabetes care, particularly in older adults, need to carefully balance the risks and benefits of therapy to arrive at outcomes that are most important to individual patients.

**Figure 1. Pathways Through Which Diabetes May Result in Mobility Disability**

- **Diabetes**
  - Cardiac disease
  - Peripheral vascular disease
  - Peripheral neuropathy
  - Body composition changes
  - Metabolic disorders/inflammation/oxidative stress

- **Decreased aerobic function**
- **Decreased balance**
- **Decreased strength**
- **Mobility disability**

**Diabetes in the Elderly**

for age, race, education, income, BMI, parity, treatment for diabetes, duration of diabetes, and comorbidities. The characteristics of the women with (n=3,916) and without (n=2,110) urinary incontinence were similar with respect to age (mean, 59 years), HbA1c (7.5%), proportion treated with insulin (24%), proportion treated with oral anti-diabetes agents (77%), and proportion with parity ≥3 (50%). Interestingly, there was no association between HbA1c level and the presence of urinary incontinence—67% of women with HbA1c <6% reported incontinence compared to 69% of those with HbA1c 6-7%, 71% of those with HbA1c 7-8%, 69% of those with HbA1c 8-9%, and 70% of those with HbA1c ≥9%. For individuals with incontinence, HbA1c above 9% was associated with more severe limitations, however. The investigators concluded that the presence of urinary incontinence was not associated with HbA1c levels in this observational study. Although glucosuria may be more common as a result of severe hyperglycemia and may lead to urinary frequency, the causal relationship between hyperglycemia and incontinence appears tenuous. Since glycemic targets are not very well defined for older adults and polypharmacy poses serious risks, one might hypothesize that uncontrolled diabetes is rampant in the elderly. On the other hand, the use of HbA1c as a quality measure in clinical practice could potentially result in unnecessary or even harmful over-treatment in this group. To answer the question of what actually happens in clinical practice, Dr. Yeh from Johns Hopkins and colleagues analyzed cross-sectional data from the nationally representative NHANES study (2003-2008) of 876 adults age ≥65 years who self-reported diagnosed diabetes (abstract 255-OR). After excluding individuals with missing HbA1c or creatinine levels, the final sample included 756 individuals with a mean age of 73, HbA1c 6.8%, 46% were men, 12% African American, and 5% Mexican American, and 66% had diabetes for over 10 years. Among these older diabetic patients, 63% had an HbA1c <7%, 24% between 7-7.9%, and 13% ≥8%—actually representing impressive glycemic control. Over 80% of these diabetic elders were treated with medications (39% sulfonylureas, 37% metformin, 19% thiazolidinediones [TZDs], and 17% insulin). One in 5 patients with an HbA1c <7% was taking multiple medications for diabetes—arguably, a practice that could result in more harm than good. If the glycemic target were raised from an HbA1c of 7% to 8%, the analysis predicted that about 50% (corresponding to 3.1 million) of older adults may be able to discontinue or simplify their diabetic regimen. Clearly, it is not possible to say, based on this data, whether such a change would actually result in better outcomes, but it provides provocative food for thought.
There continues to be a lot of interest in optimal management strategies for hyperglycemia in the hospital, as exemplified by the dozens of abstracts at this year’s ADA Scientific Sessions discussing inpatient glucose control.

Shetty and colleagues reported on the updated insulin infusion protocol (IIP) at Yale-New Haven Hospital in Connecticut (abstract 156-OR). Their IIP has been in use since 2003, following the van den Berghe studies, initially targeting a blood glucose (BG) of 100-140 mg/dl, lowered to 90-120 mg/dl in 2005. It has been adopted by many hospitals around the country, because of its validated efficacy and safety with low hypoglycemia rates. However, because of the findings of the multicenter NICE SUGAR study in 2009— which raised the possibility of increased mortality if BG is lowered too aggressively (in contrast to the earlier single-site studies)—the protocol was adjusted to comply with new national guidelines. In response to a changing evidence base, the ADA along with the American Association of Clinical Endocrinologists (AACE) now recommend that glycemia be maintained between 140-180 mg/dl in the critical care unit, whereas previous recommendations suggested absolute euglycemia. The updated Yale IIP targets 120-160 mg/dl, with the intention to keep patients closer to the lower end of the ADA/AACE target range, as suggested in their 2009 consensus statement. Based on their prior experience, Shetty et al. had noted that patients’ BGs tended to cluster in the upper end of the specified range with Yale IIPs. In this study, 115 infusions were tracked. The mean age of the patients was 62±14 years, and 51% were male. The mean BMI was 31.8±9.3 kg/m². Almost two-thirds had preexisting diabetes. Their APACHE II score was very high at 24.4±7.5, which correlates to a mortality risk of at least 30-35%. The most common admission diagnoses were acute respiratory failure, sepsis, pneumonia, and ARDS; 80% required intubation. The patients’ severity of illness was underscored by their mean length of ICU stay of 19.5±24.8 days. The mean ±SD baseline BG was 306±90 mg/dl. Time to target BG was 8.3±5.7 hours; time on infusion was 95±104 hours. Once target BG was achieved, the mean BG was 156±23 mg/dl and the median BG was 150 mg/dl (IQR 127-180) (Figure 2). Hypoglycemia rates were low. Just 0.3% of BGs fell to <70 mg/dl and only 0.02% (1 per 5000) were <40 mg/dl. Dr. Shetty remarked that the ‘per patient’ severe hypoglycemia rate of 1.7% compares favorably to an average of 2.1% in standard treatment groups from published, large intensive insulin therapy trials in the ICU.

Marso and Missouri colleagues presented interesting data from a prospective, open-label, non-randomized study, using IV exenatide, a GLP-1 receptor agonist, in hyperglycemic (BG 140-400 mg/dl) patients admitted to their hospital with a primary cardiac diagnosis (abstract 275-OR). BGs were compared to benchmark data at their institution using two insulin infusion protocols, one targeting 100-140 mg/dl and a second more intensive one, targeting 90-120 mg/dl. Exenatide was administered by infusion to 40 patients (mean age 65 years, 83% male, 63% with acute coronary syndrome, and 75% with Type 2 diabetes). The admission BG was 199±53 mg/dl, as compared to 240±44 mg/dl in the more conservative insulin infusion group (p=0.02). Time to target (<140 mg/dl) was shorter with exenatide (4 vs. 9 hours, p<0.001). Moreover, exenatide patients were maintained more frequently within the target range than with insulin infusion, although this appeared to be predominately driven by the quicker time to target (Figure 3). Hypoglycemia rates were low in both groups and not statistically different. Drug-induced nausea, however, occurred in 20% of patients and 13% needed to discontinue the medication early. BG control was tighter with the more intensive insulin infusion protocol.

The notion of controlling glucose during acute coronary syndrome (ACS) dates back several decades. Although there are many biological theories as to why hyperglycemia should be avoided during acute cardiovascular events, the data in support of tight glycemic control in the ICU is limited. Daoud and Texas colleagues conducted a retrospective study of 1504 consecutively admitted patients undergoing CABG surgery between 2007-2009 (abstract 548-P). Post-operative BG was tracked for 48 hours and patients were divided into quartiles (Q) based on their overall glycemia (means, Q1-Q4: 132, 147, 163, and 199 mg/dl). Glucose levels correlated positively with hours in the ICU, length of total hospital and post-op ventilation time, and overall

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**Figure 2. Performance of the Insulin Infusion Protocol**

**Figure 3. Mean Glucose Over Time Among Cardiac Inpatients Treated with Exenatide vs. Insulin**
Controlling Glucose in the Hospital
Continued from page 3

complication rates. Of course, observational data such as these could be biased by the underlying condition or characteristics of patients, which may be driving the hyperglycemia. Therefore, the conclusions of these investigators, that early hyperglycemia after CABG adversely affects multiple post-operative outcomes, is supported but not proven by their data.

A more mechanistic study was performed by Abdelmoneim et al. from Minnesota (abstract 380-PP) who examined coronary artery flow with contrast echocardiography in 15 healthy individuals (12 female, mean age 46±5 years, BMI 25.2±4.4 kg/m², fasting BG 99±6 mg/dl, HbA1c 5.3±0.3%). The subjects underwent a 2-step pancreatic clamp with somatostatin, glucagon, and growth hormone infusions. Insulin was then infused to mimic postprandial levels, and IV dextrose was administered to maintain euglycemia for 4 hours, followed by a period of hyperglycemia (~230 mg/dl). Myocardial echocardiography was used to assess coronary flow reserve (CFR) during the final 30 minutes of each glucose step. The data are shown in Table 1, which dichotomizes patients based on how much glucose infusion they required to maintain euglycemia (GIR or glucose infusion rate)—i.e., how insulin sensitive vs. resistant they were. CFR was shown to diminish significantly in the setting of hyperglycemia as well as in those with underlying insulin resistance.

The avoidance of hypoglycemia in the hospital is important. Galati and US colleagues theorized that trends in BG monitoring could predict severe hyperglycemia in inpatients. In the AACE/ADA inpatient hyperglycemia consensus statement, reassessment of glucose-lowering therapy once the BG falls <100 mg/dl was advised. So, these investigators decided to examine BG levels in diabetic patients hospitalized on general medical/surgical wards at their hospital over a period of 1 year (abstract 887-P). During this time, 480 patients experienced at least one BG <50 mg/dl (defined as ‘severe hypoglycemia’). Of these, 365 were on insulin injections or a sulfonylurea drug with their event occurring at least 2 days after admission. All BG readings (mean, 8.2) during the antecedent 48 hours were then categorized into 5 ranges: <60, 60-69, 70-79, 80-89, and 90-99 mg/dl. For a control group, Galati chose randomly selected diabetic patients (n=2,387) without severe hypoglycemia (mean BG number, 6.5) and who were contemporaneously hospitalized. By chi-square analysis, the frequency of antecedent mild hypoglycemia was nearly 2-fold higher in those individuals who later experienced a severe episode (21.7% vs. 11.3% of BGs, p<0.0001), with the differences between the patient cohorts widening below the 90 mg/dl mark (Table 2). In addition, a greater proportion of patients with severe hypoglycemia (61.1%) had BG <100 mg/dl in the 48-hours preceding their hypoglycemia event compared to those without (37.6%; p<0.0001). While further analysis is required on this preliminary data set, the investigators concluded that hospitalized patients who experience severe hypoglycemia frequently have low-normal to mildly hypoglycemic BG readings in the 48 hours preceding the event. Accordingly, having a BG value <100 mg/dl may serve as an important trigger to consider adjustment of the glucose lowering regimen, as recommended by AACE and ADA.

As inpatient diabetes specialists further refine their approaches to the management of hyperglycemia in the hospital, we look forward to the development of safer and more effective strategies.

### Table 1. CFR and Other Parameters by GIR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GIR (&lt;5 mg/kg/min) (n=8)</th>
<th>GIR (≥5 mg/kg/min) (n=7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5±4.7</td>
<td>23.7±4.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Waist hip ratio</td>
<td>0.94±0.15</td>
<td>0.90±0.11</td>
<td>0.64</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>139.1±12.9</td>
<td>91.6±13.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglyceride/HDL ratio</td>
<td>2.41±0.25</td>
<td>1.47±0.73</td>
<td>0.02</td>
</tr>
<tr>
<td>CFR at euglycemia</td>
<td>2.77±1.1</td>
<td>3.85±1.69</td>
<td>0.16</td>
</tr>
<tr>
<td>CFR at hyperglycemia</td>
<td>1.80±0.91</td>
<td>2.41±1.55</td>
<td>0.42</td>
</tr>
</tbody>
</table>

CFR=coronary flow reserve, GIR=glucose infusion rate.

### What Role for Insulin Sensitizers?

Several approaches to reducing hyperglycemia in patients with Type 2 diabetes exist. A common one is to improve insulin resistance, a fundamental component of the pathogenesis of this disease. Advantages of using insulin sensitizers (as opposed to drugs that increase insulin supply) include the avoidance of hypoglycemia and the potential for greater durability of effectiveness, as insulin demands from the pancreatic β-cell are reduced. The 2 major sensitizer classes available are the biguanides, which primarily improve insulin response in the liver, and the thiazolidinediones (TZDs), which exert their predominant effects in skeletal muscle and adipocytes. Cardiovascular benefits have been proposed with both of these classes since both modestly improve lipid profiles, hyperinsulinemia, and inflammatory markers; TZDs also reduce blood pressure to some degree.

Data in support of metformin’s cardiovascular benefits come mainly from the UK Prospective Diabetes Study (UKPDS), which demonstrated reduced myocardial infarction rates in a small subgroup of overweight patients randomized to...
What Role for Insulin Sensitizers?  
Continued from page 4

metformin monotherapy versus diet alone. Epidemiological studies have also demonstrated fewer cardiovascular complications with metformin than in patients using sulfonylurea drugs. The TZD story is more complex, with direct vascular effects, which include the suppression of atherosclerosis, proposed from activation of the nuclear transcription factor, PPAR-γ. However, rosiglitazone was removed from the European market last year and is prescribed in the US with great restriction because it has been implicated in increasing myocardial ischemic events. The other TZD, pioglitazone, is either neutral or has a modest benefit on cardiovascular complications, but, with rosiglitazone, increases the risk of heart failure from increased renal sodium retention.

The only trial that has adequately compared the two major glucose-lowering approaches in high-risk patients was BARI-2D. This found no overall cardiovascular benefit in stable coronary artery disease patients randomly assigned to either an insulin sensitizer regimen, involving metformin and, if needed, rosiglitazone, versus an insulin provision regimen, focused on sulfonylureas plus, if needed, insulin (see Diabetes 2009, volume 19, page 29). However, in a prespecified subgroup analysis, those patients who were additionally randomized to urgent revascularization and who underwent coronary artery bypass surgery had a strong trend toward less major adverse cardiovascular events if assigned to insulin sensitizer therapy (18.7% vs. 26.0% with sulfonylurea), the difference was essentially the same at -35% (mean CIMT 0.0054±0.0012 vs. 0.0089±0.0011 mm/year). The investigators concluded that any beneficial effect of pioglitazone on carotid atherosclerosis could not necessarily be explained by improvements in metabolic risk factors, suggesting potential direct vascular effects.

Table 3. Meta-Analysis of Mortality in Patients with Type 2 Diabetes and Heart Failure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Metformin</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inzucchi 2005</td>
<td>93</td>
<td>406</td>
<td>768</td>
<td>2,184</td>
</tr>
<tr>
<td>Masoudi 2005</td>
<td>460</td>
<td>1861</td>
<td>4,345</td>
<td>12,069</td>
</tr>
<tr>
<td>Ehrich 2005</td>
<td>29</td>
<td>208</td>
<td>200</td>
<td>112</td>
</tr>
<tr>
<td>Shah 2010</td>
<td>22</td>
<td>99</td>
<td>112</td>
<td>302</td>
</tr>
<tr>
<td>MacDonald 2010</td>
<td>155</td>
<td>376</td>
<td>733</td>
<td>1,306</td>
</tr>
<tr>
<td>Evans 2010</td>
<td>137</td>
<td>205</td>
<td>183</td>
<td>217</td>
</tr>
<tr>
<td>Aguilar 2010</td>
<td>232</td>
<td>1,437</td>
<td>285</td>
<td>1,437</td>
</tr>
<tr>
<td>Roussel 2010</td>
<td>116</td>
<td>1,220</td>
<td>419</td>
<td>2,790</td>
</tr>
</tbody>
</table>

Total (95% CI) 5.812 2.1078 0.78 (0.70, 0.86)

*Study risk ratios represent published multivariate adjusted risk estimates. The pooled estimate reflects the overall risk estimate of metformin compared to controls after multivariate adjustment for age, sex, comorbidities, drug therapies, ± clinical data as reported in original publications.

Continued on page 6
What Role for Insulin Sensitizers?

Continued from page 5

Metformin is not only the most commonly prescribed anti-hyperglycemic agent for Type 2 diabetes in the US, but it is also gaining in popularity as a drug for diabetes prevention. Its safety and efficacy were confirmed in the Diabetes Prevention Program (DPP). This trial demonstrated a 31% reduction in the incidence of diabetes in a large group of high-risk patients with impaired glucose tolerance assigned to metformin therapy (although such an effect was only half of what occurred in the group randomized to aggressive lifestyle intervention). DPP investigators led by Edelstein this week reported on long-term tolerability and safety of metformin in this trial and its follow-up observational study, DPPOS (abstract 254-OR). The double-blind portion of the DPP lasted on average 3.2 years, with DPPOS adding an additional 6 years in an open-label design. In the DPP, gastrointestinal side effects were nearly 10-fold as common in those participants given metformin (9.5% vs. 1.1%, p < 0.001). Such symptoms decreased over time, however, and in DPPOS, GI complaints were similar between groups. No hypoglycemia or lactic acidosis was reported in either. A slight reduction in hemoglobin/ hematocrit was observed in metformin patients, of uncertain significance. The investigators concluded that metformin is an extremely safe intervention in pre-diabetic patients to prevent the further deterioration of hyperglycemia.

What Role for Insulin Sensitizers?

Metformin-associated lactic acidosis was a topic of study for Frid et al. from Sweden (abstract 364-OR). They studied 5,408 patients in Malmö, Sweden who had three prescription fills for metformin during both 2008 and 2009, assessing their estimated glomerular filtration rate (eGFR) by laboratory testing obtained, and their frequency of hospitalization for lactic acidosis. Individuals were stratified into various age groups (<60, 60-69, 70-79, and 80-89 years). The average eGFR in the three oldest groups were 87, 76, and 66 ml/min/1.73 m² for metformin-treated vs. 77, 66, and 56 ml/min/1.73 m² in controls, respectively (p < 0.001 for all comparisons). (Metformin-treated patients tend to have a higher eGFR than control, non-diabetic patients, likely due to selection bias.) In the oldest group, 38% had a highest eGFR < 60 and 66% had the lowest eGFR of < 60. Three cases of lactic acidosis were identified in patients on metformin, with respective eGFRs of 41, 790, and one unknown. None of these individuals was older than 79 years.

The investigators concluded that metformin associated lactic acidosis is rare, despite many patients with reduced renal function using this agent. Recently, metformin’s relatively strict renal contraindications in the US have been called into question since they may unnecessarily exclude a large number of older individuals from benefiting from this otherwise safe and effective medicine (Lipska et al., Diabetes Care 2011;34:1431).

Smiley et al. from Atlanta were interested in the effect of pioglitazone in young, African American patients with hyperglycemic crisis (abstract 369-OR). Of 90 patients recruited, 35 had DKA (22 men, 13 women, mean age 43 ± 11 years, BMI 40 ± 12 kg/m², admission blood glucose 639 ± 259 mg/dl) and 55 had severe hyperglycemia (31 men, 24 women, age 44 ± 10 years, BMI 38 ± 9 kg/m², BG 645 ± 238 mg/dl). 73% of those with DKA and 59% of those with severe hyperglycemia were able to discontinue insulin within 12 weeks of presentation. 20 of the DKA patients and 24 of those with severe hyperglycemia who had stopped insulin were subsequently randomized to 30 mg/day of pioglitazone vs. placebo and followed for 36 months after their ‘remission’. β-cell function and insulin sensitivity were measured at baseline and within 1 week of stopping insulin, and OGTTs were performed upon the discontinuation of insulin and again at 3 and 6 months during the remission phase. ‘Relapse’ was defined as fasting blood glucose > 130 mg/dl or a random blood glucose > 180 mg/dl x 2 and a HbA1c ≥ 7.0%.

At baseline, the two groups were similar for age, gender, BMI, HbA1c, duration of insulin therapy, and GAD antibody status. Pioglitazone significantly reduced the number of patients with hyperglycemia relapse (32% vs. 68%, p = 0.03). In addition, remission proved to be longer in the pioglitazone group (809 vs. 162 days, p = 0.01). This was associated with better β-cell function and improved insulin sensitivity by OGTT. So, pioglitazone in this small, single-center study appeared to have a significant effect on preventing recurrence of hyperglycemia and in inducing a prolonged, insulin-free interval in overweight African American patients with recent hyperglycemic crisis. These data underscore the importance of insulin resistance in this cohort of patients whose initial severe hyperglycemia belies their actual residual insulin secretory capacity.

Hanefeld and German colleagues tested the combination of both insulin sensitizers, metformin plus pioglitazone, in 121 patients with Type 2 diabetes already taking insulin, with baseline HbA1c 6.5-8.5% (abstract 1156-P). The mean age was 63 ± 7.5 years, BMI 32.2 ± 5.3 kg/m², and HbA1c 7.3 ± 0.5%, and insulin glargine dose 36 ± 21 units. After a run-in phase of glargine monotherapy, patients were randomized to metformin 850 mg BID, pioglitazone 15 mg BID, or 30 mg of pioglitazone and 1.7 g of metformin. A variety of novel cardiovascular risk markers were measured. Hypoglycemia rates were similar, but the pioglitazone patients had more weight gain and edema. Pioglitazone reduced MMP-9 and CRP levels and increased insulin sensitivity and adiponectin levels, independent of glycemic control. However, the triple combination had no further benefit on CVD risk markers.

Several side effects of TZD medications are well known, including weight gain, edema, and in predisposed individuals, heart failure, as well as bone fractures in women. One potential adverse event associated with this drug class is macular edema—to date, an association based mainly on case reports. Idris et al. from the UK assessed 103,368 Type 2 diabetes patients without macular edema at baseline, dividing them into those treated versus not treated with a TZD (abstract 135-OR). At one year the incidence of macular edema was 1.3% among TZD users and 0.2% among non-users (OR 5.78, 95% CI 4.1-7.9%). In Cox models, controlling for potential confounders (HbA1c, age, gender, blood pressure, lipids, and other medications), the OR fell to 3.3, but remained significant (95% CI, 2.2-4.9). The investigators advised avoiding this drug class in those at high risk of sight-threatening macular edema.

Looking toward the future, the insulin sensitizer category of anti-hyperglycemic drugs may also include dual and pan-PPAR agonists, 11-β-hydroxysteroid dehydrogenase (HSD) inhibitors, and the protein tyrosine phosphatase (PTB) 1B inhibitors. The efficacy and side effect profiles of these agents remain to be determined. Very clearly, careful safety assessments will be crucial throughout the developmental stages of these compounds.