Important data on diabetes presented at the 70th Annual Scientific Sessions of the American Diabetes Association come to you in Diabetes 2010, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of Diabetes 2010 will be followed by a Diabetes 2010 booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2010 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Supported in part through educational grants from Amylin Pharmaceuticals, Inc. and Lilly USA, LLC, Bayer HealthCare Diabetes Care, Boehringer Ingelheim Pharmaceuticals, Inc., Medtronic MiniMed, Inc. dba Medtronic Diabetes, Merck & Co., Inc., Novo Nordisk Inc., and Takeda Pharmaceuticals of North America, Inc. It is understood that supporters will in no way control the content of this program.

The evidence establishing an association between Type 2 diabetes and cancer is building in both the epidemiological and basic science literature (Figure 1). The American Diabetes Association and American Cancer Society recently published online Diabetes and Cancer: A Consensus Report (J Clin Endocrinol Metab 2010; 95: 710), reviewing this data and providing a united front on the collection and dissemination of information on this topic. Meanwhile, last years’ four publications of observational studies regarding exogenous insulin use and cancer risk have undergone appropriate scrutiny. In a packed symposium, experts presented the latest thinking about topics relating cancer with diabetes and its therapy.

From a scientific standpoint, insulin has clear mitogenic (growth-promoting) activities, which may actually be enhanced in the setting of insulin resistance with its resultant hyperinsulinemia— as seen in patients with obesity and Type 2 diabetes. Clinically, two common skin findings in obese and diabetic patients, namely acanthosis nigricans (‘skin tags’), are likely a direct manifestation of these properties. Certain tumors like breast cancer are known to have increased levels of insulin receptor (IR)-type A (IR-A), which is thought to have greater mitogenic potential than its isomer cousin, IR-B, upon activation by insulin. A further concern is that exogenous insulin analogues may also activate the insulin-like growth factor 1 (IGF-1) receptor to a greater degree than human insulin. IGF-1 translates many of the mitogenic effects of growth hormone itself.

Jeffrey Johnson, PhD, an epidemiologist from Alberta, Canada, launched the forum by stating that cancer is a close contender to cardiovascular disease as the leading cause of death in Type 2 diabetes (29% vs. 31% in a population study by the US Centers for Disease Control (CDC)), and may indeed overtake it. He reviewed many observational studies highlighting two strong and consistent findings. First, people with Type 2 diabetes have an increased risk of certain cancers, predominantly those of the endometrium (OR 2.10), liver (OR 2.50), breast (OR 1.20), and pancreas (OR 1.82). Second, people with Type 2 diabetes have a higher mortality rate from cancer as compared to the general population.

For example, diabetic women were found to have a -40% increased risk of mortality in a large retrospective study of over 6,100 women with breast cancer aged 55-79 years old from Ontario, Canada (HR 1.39, 95% CI 1.22-1.59). Although they can be difficult to tease apart in observational cohort studies, many factors such as obesity, hyperinsulinemia, hyperglycemia, or delayed screening may contribute to this increased mortality rate. For example, women with Type 2 diabetes require more complex medical care, and physicians may simply miss opportunities for general cancer screening. In support of this notion, Dr. Johnson quoted Maruthur et al. who demonstrated that women with obesity have a reduced likelihood of receiving a Papanicolaou smear (Obesity 2009:17, 375-81).

Dr. Johnson also addressed the use of exogenous insulin and cancer. He referred to a soon-to-be published retrospective study of a cohort of 10,309 individuals with Type 2 diabetes followed for a mean of 5.4 years. The mortality risk increased for those with a higher number of
Diabetes & Cancer: Making the Link
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prescriptions for insulin when compared to those who had never taken insulin. For less than 3 prescriptions a year, the hazard ratio (HR) for any cancer was 2.22; 3-11 prescriptions, HR 3.33; and ≥12 prescriptions, HR 6.40. Of note, metformin use attenuated the mortality rates, with HR of 0.80 when used as a single agent. While these associations are of interest, they do not necessarily imply any causality. The need for insulin therapy may simply be serving as a marker of a group of patients (e.g., longer diabetes duration) that may be predisposed to the development of malignancy. Or, perhaps, the ability to take and be controlled with oral agents may identify a healthier group of individuals.

Dr. Derek LeRoith from Mt. Sinai in New York provided murine evidence that hyperinsulinemia may be the main driver behind the increased growth of breast cancer in women with Type 2 diabetes. He demonstrated that non-obese, hyperinsulinemic mice have an increased tumor volume and more aggressive metastatic spread than occurs in wild-type mice with normal insulin levels. Also, blocking the insulin receptor in these mice prevents this excess tumor growth. He pointed out that his model mimics the endogenous hyperinsulinemia that occurs in people for years prior to their diagnosis of Type 2 diabetes, but excludes the confounding variable of obesity.

John Lachin, ScD from George Washington University in Washington, D.C. critiqued the statistics used in the controversial retrospective German study that reported an association between insulin glargine and cancer (Hemkens, et al. Diabetologia 2009; 52:1732-44). The article was published alongside other observational studies that did not find a consistent signal between this insulin analogue and cancer incidence. Dr. Lachin emphasized that observational studies are for the purpose of hypothesis generation, and only randomized control trials can determine a causal association. The Hemkens study was retrospective from an insurance company database, including 127,031 patients exposed for an average of 1.63 years to glargine. Important covariates such as type of diabetes, duration of diabetes, degree of glucose control, and body mass index were not available. In fact, the patients requiring glargine were different in their baseline characteristics than the patients using NPH, and it is statistically difficult, if not impossible, to adjust for these differences. Also, the researchers computed an average insulin dose for each subject over the entire follow-up period, which introduced bias in the results interpretation. When the analysis was repeated and not adjusted for dose, the study did not demonstrate any increased risk for cancer.

In the final presentation, Jay S. Skyler, MD from the University of Miami reiterated the weaknesses of the Hemkens study. He remarked on the disconnect between the cautiously worded articles and editorials in Diabetologia, and the ensuing press releases that intimated a clear relationship between glargine and cancer. He argued for a more measured and scientific approach to such issues.

To date, there is no clear-cut evidence that glargine is associated with an increased risk of cancer. However, there is a strong association between Type 2 diabetes itself and an increased risk of certain malignancies as well as higher cancer-related mortality. Long-standing elevation in endogenous insulin levels are a possible culprit. It remains to be seen whether high dose exogenous insulin, often required in today’s very obese diabetic population, affects malignancy rates and/or growth.

TZDs: New Insights, Continued Controversies

In the late 1990’s, the thiazolidinediones (TZDs) were touted as the edge of the new frontier of anti-hyperglycemic therapy, focusing on insulin resistance. The opening session of the ADA, provocatively entitled “The Good, The Bad, and The Ugly,” addressed the impact of these drugs on diabetes care since then, with a focus on both their purported benefits and an increasing array of concerns. Although these PPAR-γ agonists decrease insulin resistance and likely preserve beta-cell function, they also increase the risk for heart failure and bone fractures, the latter at least in women. One member of the class, rosiglitazone, may also increase cardiovascular events, although the data here are conflicting. Four speakers discussed old and emerging issues with this drug class.

Dr. Tom Buchanan from the University of Southern California highlighted the benefits of TZDs on beta-cell preservation with resultant slowing of disease progression. Metabolically normal individuals compensate for changes in insulin sensitivity by increasing insulin secretion and thus maintain glucose concentrations in the normal range. Type 2 diabetes results from the combination of defects in both insulin sensitivity and insulin secretion—which are, notably, present long before hyperglycemia ensues. Several studies have shown that TZDs decrease diabetes incidence in individuals at high risk. Importantly, Dr. Buchanan argued, they do so not by merely decreasing glucose and delaying the onset of the disease, but by actually modifying the progression of the disease. Support for this comes from multiple trials, including TRIPOD (Troglitazone in the Prevention of Diabetes), PIPOD (Pioglitazone in the Prevention of Diabetes), DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), and most recently Act Now (Actos Now for the Prevention of Diabetes). Diabetes incidence over time for individuals treated with TZDs is not only lower than for controls, but, when plotted, the incidence lines appear to diverge and never meet, even after pharmacological intervention is ceased. Furthermore, the early trials with troglitazone (since then removed from the market) in Hispanic women with a history of gestational diabetes (TRIPOD) showed that these beneficial beta-cell effects also extend to those with already established Type 2 diabetes. TheADOPT (A Diabetes Outcome Progression Trial) trial compared metformin, glyburide, and rosiglitazone treatment in patients with diabetes. Although sulfonylureas achieved the most rapid reduction in fasting glucose and HbA1c levels, TZDs were associated with the most durable effect over time. The recent RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial similarly showed stability of HbA1c over time in patients treated with rosiglitazone as compared to those on sulfonylureas and metformin. Therefore, Dr. Buchanan argued, TZDs are highly attractive agents early in the disease process once lifestyle interventions fail. However, he cautioned, not everyone responds to these drugs (in his studies, ~1/3 of patients don’t respond and have no change in fasting insulin levels even after 3 months). Also, data for TZD use is not available for all ethnic groups, information on long-term effects on microvascular disease is lacking, and other factors (such as weight gain, risk of fractures, edema) need to be considered carefully.

Much recent attention has been focused on the deleterious effects of TZDs on bone health. Dr. Andrew Grey from the University of Auckland reminded the audience that bone loss results...
from an imbalance in the normal process of bone remodeling, during which osteoclast recruitment/activation are tightly coupled to bone formation by osteoblasts. PPAR-γ activation appears to disrupt this delicate balance by inhibiting the differentiation of mesenchymal cells into osteoblasts and, instead, diverting these progenitor cells to adipocyte lineage (Figure 2). In addition, PPAR-γ activation may also stimulate the development of osteoclasts.

Multiple preclinical studies confirm that PPAR-γ agonists promote adipogenesis and inhibit osteoblastogenesis with resultant decreases in bone formation and increases in bone resorption. In animal studies, the mechanism by which these agents affect bones appears to differ based on age. In younger animals, PPAR-γ activation primarily decreases bone formation while in older animals, it primarily increases bone resorption. Whether similar age-related differences apply to humans remains unclear.

To elucidate the mechanisms of PPAR-γ in human studies, markers of bone formation and resorption were examined by Grey’s lab in 50 postmenopausal women randomized to rosiglitazone or placebo for 14 weeks. The osteoblast markers (procollagen type I N-terminal propeptide and osteocalcin) declined in the rosiglitazone group, but there was no change in a bone resorption marker (C-terminal telopeptide of type I collagen) in this short-term study. Bone mineral density was significantly reduced at the hip in the rosiglitazone group compared to placebo (spine bone density fell but was not significantly different between the groups). More recently, analysis of the ADAPT trial comparing longer-term therapy with rosiglitazone, metformin, or glyburide showed that a marker of osteoblast activity (C-terminal telopeptide) was increased in women (but not men) on rosiglitazone, while it decreased on the other two agents. In this study, markers of osteoblast activity were reduced for both men and women in almost all treatment groups (greatest in metformin, intermediate in rosiglitazone, and smallest in the glyburide group). Therefore, both bone formation and bone resorption may be influenced by TZD therapy.

Although biomarkers and bone density help elucidate the mechanisms of TZD’s effects on bone health, it is the rate of fractures that is the most relevant patient outcome. In the 2008 analysis of the ADAPT trial, rosiglitazone therapy for 4 years resulted in fractures in 60 (9.3%) women, compared to 30 (5.1%) on metformin, and 21 (3.5%) on glyburide. Fractures were seen predominantly in the lower and upper limbs, but this may not be surprising since these fractures are more common in general. Subsequent meta-analyses of 10 randomized trials and 2 observational studies by Loke et al. showed that pioglitazone and rosiglitazone doubled the risk for fractures among women, but not among men.

The next question raised was whether classical osteoporotic fractures occur more commonly in TZD users and whether the risk is really only increased in women. Based on the analysis of a large UK primary care database, hip and femur fractures were more common in users of TZDs, suggesting that the risk may not be limited to distal fractures. In addition, a recent large prospective cohort study in British Columbia comparing treatment with a TZD or a sulfonylurea reported that the risk of fractures may be indeed increased in both men and women. Finally, the Scottish Diabetes Research Network group examined national data and showed that TZD exposure was associated with hip fractures in both men (age-adjusted incidence rate-ratio 2.23, 95% CI 1.16-4.28) and women (1.90, 95% CI 1.29-2.81) (74-OR).

The totality of evidence suggests that TZDs are, in fact, detrimental to skeletal health. Dr. Grey recommended a careful assessment of the risk for fractures for patients considering treatment with TZDs and felt that if the estimated risk exceeds 10%, TZDs should be avoided or used with caution in concert with therapies aimed at protecting bone. He conceded, however, that the efficacy of bone protective therapies (e.g., bisphosphonates) has not been evaluated for patients treated with TZDs.

Next, Dr. Phillip Home took the podium to talk about cardiovascular effects of these agents. Rosiglitazone and pioglitazone were approved by the FDA in 1999, when both fluid retention and probable heart failure were recognized as potential adverse side effects. However, early on, TZDs appeared to have a beneficial effect on cardiovascular events. In 2005, PROActive, a secondary prevention trial of pioglitazone, showed a 10% relative risk reduction in the primary endpoint (a composite of cardiovascular events and procedures), which did not achieve statistical significance, but a 16% relative risk reduction in the secondary, more conventional, endpoint of all-cause mortality, MI, and stroke was significant.

The tide began to turn in 2006 when the sponsor of rosiglitazone, GSK, performed a meta-analysis suggesting increased risk of MI with an odds ratio of 1.31 (95% CI 1.01-1.70). In 2007, Nissen and Wolski published their meta-analysis again showing increased risk signal for rosiglitzone (OR 1.43, 95% CI 1.03-1.98). Dr. Home reported that recently GSK performed an additional meta-analysis (including RECORD and ADAPT studies) that actually showed a lower OR of 1.10, which was not statistically significant (95% CI 0.89-1.35). These meta-analyses are partly based on studies with small numbers of events, not designed for assessment of cardiovascular outcomes. He concluded that meta-analyses are generally less convincing than a large prospective controlled trial specifically designed to assess the outcome of interest. Meta-analyses can only be hypothesis-generating.

To that point, he turned our attention to the RECORD trial, for which he served as principal investigator. In this large (n=4,447) randomized controlled study, with an average follow-up of 5.5 years, addition of rosiglitazone to metformin or sulfonylurea was compared to the combination of the latter two agents with the primary outcome of cardiovascular death or hospitalization for cardiovascular events. The hazard ratio for this primary endpoint was 0.99 (95% CI 0.85-1.16), meeting the criterion of ‘non-inferiority’ and, Dr. Home argued, gave no suggestion at all for cardiovascular harm. Dr. Home showed various analyses performed (per protocol, for each secondary outcome, for atherosclerotic events only, for cardiovascular deaths only, subgroup analyses of background metformin and background sulfonylurea) as well as a variety of individual secondary endpoints (MI, acute coronary syndrome [ACS], angina, revascularization, etc.), none of which showed any increased cardiovascular risk with rosiglitzone therapy, except for the known risk of heart failure (HR 2.10, 95% CI 1.35-3.27).

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Diabetes and Depression: Chicken or Egg?

Diabetes and depression are highly prevalent in US adults, and their coexistence has been reported by many (Anderson RJ, Diabetes Care 2001). Pan et al. from Massachusetts and the United Kingdom evaluated the diabetes-depression association using data from the Nurses’ Health Study (n=52,745 women, aged 50-75 years in 1996 who were followed until 2006) (abstract 1985-P). Clinical depression was defined as having diagnosed depression or using antidepressants; depressed mood was defined as clinical depression or severe depressive symptoms based on Mental Health Index (MHI-5) score ≤52. During a 10-year follow-up (473,233 person-years), 2,521 incident cases of Type 2 diabetes were documented. After adjustment for BMI, physical activity, and other covariates, there was a 16% increased risk of developing Type 2 diabetes among individuals with depressed mood (RR, 1.16; 95% CI, 1.04-1.30). In a parallel analysis, 5,327 incident cases of clinical depression were documented over the 10-year follow-up (407,746 person-years). Compared to subjects without diabetes, the risk of developing clinical depression was substantially increased among patients with diabetes: multivariate-adjusted RR=1.32 (95% CI, 1.20-1.46) for all diabetes patients, 1.24 (95% CI, 1.06-1.43) for those not treated with medication, 1.37 (95% CI, 1.18-1.59) for those treated with oral antihyperglycemic agents, and 1.45 (95% CI, 1.14-1.84) for those treated with insulin. These associations remained significant after adjustment for comorbidities. These results support the bi-directional association between diabetes and depression and underscore the importance of simultaneous prevention and management of both conditions.

The connection from diabetes to depression is not difficult to understand, as any chronic condition may unmask an underlying predisposition to affective symptoms. That from depression to diabetes is more difficult to comprehend, however. If it is indeed cause-and-effect, perhaps activation of counter-regulatory factors, such as catecholamines and/or cortisol may be to blame. Another fascinating consideration is a link through inflammation. Doyle et al. from the US and Italy studied the possibility that inflammatory factors may mediate the relationship between diabetes and depression (123-LB). The hypothesis for their study was formed on the basis of up-regulated levels of interleukin-6 (IL-6), TNF-α (TNF), and C-reactive protein (CRP) being common to both Type 2 diabetes and depression. The study cohort included 3,014 adults, aged 70-79 years, who participated in the Health ABC Study. Presence of Type 2 diabetes was assessed per self-report, medication use, fasting glucose, and/or glucose tolerance test results. Depressed mood was categorized using the Center for Epidemiologic Studies Depression scale. IL-6 (pg/ml) was significantly higher (p<0.05) among patients with Type 2 diabetes and depression compared to the other groups analyzed (4.4 versus 2.7 for diabetes only, 2.6 for depression only, and 2.3 for healthy controls). Similarly, CRP (mg/l) was significantly higher among those with Type 2 diabetes and depression (5.3) compared to depression only (2.9, p<0.05) or healthy controls (2.8, p<0.05), and approached the level of statistical significance for diabetes only (3.6, p=0.07). After adjustments for potential confounding factors, the interaction between Type 2 diabetes and depressed mood status with levels of IL-6 and CRP was significant. A graded relationship was not observed for TNF after adjustment for covariates. These findings support the hypothetical model that links inflammation, Type 2 diabetes, and depressed mood. Further study of these relationships will enhance our understanding of the biological pathways driving the relationship between these two common conditions.

The RECORD trial has been heavily criticized for several methodological flaws. It was an open-label trial and, due to the concurrent TZD controversy, many patients stopped taking the study drug. There was greater use of statins in the rosiglitazone arm, likely driven by the increase in LDL associated with this medication. Finally, the number of cardiovascular events was ~1/3 of that expected based on other contemporary trials, with similar patient populations, raising questions about assessment of events.

Dr. Home cited other trials, such as BARI-2D (Bypass Angioplasty Revascularization Investigation) and VA DT (Veterans Affairs Diabetes Trial), which showed no association of rosiglitazone with increased mortality or MIs. In contrast, several studies (RECORD, ADOPT, PROactive, and some of the early rosiglitazone studies) suggest that TZDs may markedly lower the risk of stroke—this needs to be confirmed in larger trials. He noted that TZDs: New Insights, Continued Controversies

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Adding to the data presented by Home, a just-published study in JAMA (June 28, 2010) examined whether cardiovascular outcomes associated with the use of the two TZDs, rosiglitazone and pioglitazone, are different. Graham et al. analyzed a large observational database of 227,571 Medicare beneficiaries over the age of 65 who started rosiglitazone or pioglitazone through Medicare Part D coverage during 2006-2009 and had at least 3 years of follow-up. Because this was not a randomized trial, and thus subject to confounding, the investigators took great care to collect data on multiple variables known or suspected to be associated with clinical outcomes under study, as well as variables related to general health of the participants. In adjusted Cox proportional hazard models, rosiglitazone was associated with increased risk of stroke (HR 1.27, 95% CI 1.12-1.45), heart failure (HR 1.25, 95% CI 1.16-1.34), death (HR 1.14, 95% CI 1.05-1.24), and the composite of acute myocardial infarction, stroke, heart failure, and death (HR 1.18, 95% CI 1.12-1.23), compared to pioglitazone use, but was not significantly associated with acute myocardial infarction (HR 1.06, 95% CI 0.96-1.18). The authors postulated that in an older population of patients with diabetes, in which the cause of death is cardiovascular in 70% of cases, the increased risk of death in the rosiglitazone group is most likely due to cardiovascular disease. Finally, they concluded that with a number needed to harm (NNH) of 60 persons treated for 1 year to produce one excess event of the composite endpoint attributable to the use of rosiglitazone, rather than pioglitazone, the effect on the population may have been quite considerable. Surely, these findings will fuel further debate on the safety of rosiglitazone.

Finally, Dr. Ian Blumer from the University of Toronto summarized the selected aspects of prescribing TZDs in the US. Based on available data and recommendations from expert groups, he concluded that TZDs should not be used for prevention of diabetes due to their unproven long-term effects, cost, and side effect profile. They should not generally be used as monotherapy for the treatment of diabetes, but are suitable as add-on therapy. Clearly, and as with any pharmacological agent, the prescribing clinician must weigh both the potential risks and potential benefits when using TZDs.
**SGLT-2 Inhibitors**

Sodium-glucose cotransporter (SGLT)-2 inhibitors block glucose reuptake in the proximal nephron, allowing hyperglycemia to be corrected by glycosuria, particularly in the postprandial period. While modest efficacy and some weight loss have been shown in early clinical trials of SGLT-2 inhibitors, concerns has been raised about their potential for increasing urinary tract infections and candidal vaginitis/balanitis.

Rosenstock *et al.* from Texas and New Jersey conducted a double-blind, dose-ranging study in which they randomized 451 Type 2 diabetes patients who were suboptimally controlled on metformin (mean age 53 yrs, weight 87 kg, Hba1c 7.7%, fasting plasma glucose 162 mg/dl) to the SGLT-2 inhibitor, canagliflozin 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, or 300 mg bid, to the DPP-4 inhibitor, sitagliptin 100 mg qd, or to placebo (abstract 77-OR). Statistically significant improvements from baseline in fasting plasma glucose and Hba1c, relative to placebo, were observed at week 12 for all active treatment groups, with maximum and similar decreases for each in the canagliflozin 300 mg qd and 300 mg bid groups. Dose-related weight reduction was seen with canagliflozin, compared to a small mean increase with sitagliptin (Table 1). Treatment-emergent adverse events were generally similar in type and incidence across the treatment groups, with the exception of slightly higher rates of symptomatic genital infections with canagliflozin (3.8% vs. 2% with both placebo and sitagliptin). Of note, the incidence of urinary tract infections ranged from 3.9% across the canagliflozin dose groups, with the rate not related to dose, was 6% for placebo, and 2% for sitagliptin. The incidence of hypoglycemia with canagliflozin (0-6%) was not related to dose, and compared to rates of 2% and 5% for placebo and sitagliptin, respectively.

Wilding *et al.* from North America and Europe reported the results of a 48-week study of another SGLT-2 inhibitor, dapagliflozin 2.5 mg, 5 mg, or 10 mg daily, compared to placebo, in 808 Type 2 diabetes patients (mean Hba1c 8.5%) poorly controlled with insulin (mean 77 units/day ± oral antihyperglycemic agents [abstract 21-LB]). Insulin was up-titrated if Hba1c was >8% or fasting plasma glucose was >178 mg/dl from weeks 24-48. Reduction in Hba1c at week 24 (primary endpoint) was maintained at week 48 (-0.43% for placebo; -0.74%, -0.94%, and -0.93% for 2.5 mg, 5 mg, and 10 mg dapagliflozin, respectively), as was weight reduction, even when including data after insulin up-titration (+0.9 kg for placebo vs. -1.5 kg for dapagliflozin 10 mg). Insulin dose increased over the study period in the placebo group and was stable for patients treated with dapagliflozin. Consistent with the findings from the Rosenstock study, urinary tract infections (7.9-10.8% vs. 5.1% with placebo) and genital infections (6.4-10.7% vs. 2.5% with placebo) were reported more commonly with dapagliflozin, with most events reported during the first 24 weeks and responsive to treatment.

The SGLT-2 inhibitors appear to be modestly effective antihyperglycemic agents with an unusual mechanism of action. More information is needed on their safety profiles, particularly involving the urogenital tracts.

**SPPARMs**

While PPAR-γ activation leads to improvements in insulin resistance, hyperglycemia, endothelial function, and markers of inflammation, it is also associated with unwanted side effects such as weight gain, fluid retention, and increased risks of heart failure and bone fractures. Research is underway to determine if actions through the PPAR-γ receptor can be selectively modulated to separate insulin-sensitizing actions from the less desirable effects. Early evidence from clinical studies suggests favorable metabolic effects and potentially fewer adverse effects with the SPPARM, INT131.

DePaoli and American coworkers reported the results of a 24-week, double-blind study of INT131 (0.5, 1, 2, or 3 mg qd), pioglitazone 45 mg qd, or placebo in 366 patients with Type 2 diabetes who were on a stable dose of sulfonylurea with or without metformin (mean age 55.9 ± 9.5 yrs, duration of diabetes 8.4 ± 6.1 years, 47% women, BMI 32.0 ± 5.5 kg/m², Hba1c 8.3 ± 0.72%) (315-OR). Improvement in Hba1c at endpoint was directly related to INT131 dose, and comparable to TZD at the higher doses studied. Incidence of edema (feet, ankles, mid-pretilial) with INT131 was not different from baseline or placebo, and was less than that with pioglitazone (Figure 3). These findings suggest the potential for fewer edema-related adverse effects with this SPPARM than with currently available PPAR-γ agonists, although trials of longer duration are clearly needed. More information will be needed regarding weight and bone changes.

**PPT-1B Antisense Inhibitor**

Protein tyrosine phosphatase 1B (PPT-1B) is a negative regulator of insulin action. In preclinical models, reduction of PPT-1B activity enhances insulin sensitivity. Brandt *et al.* of California conducted a multicenter, double-blind study of patients with Type 2 diabetes (duration ≤12 yrs, Hba1c ~8.7%, fasting plasma glucose ~190 mg/dl), poorly controlled by maximal doses of sulfonylureas, who they randomized to 100 mg or 200 mg (N=26) weekly injections of ISIS 113715, a novel PPT-1B antisense inhibitor, or placebo (n=26) for 13 weeks (316-OR).

**Table 1. Placebo-Adjusted Mean Change from Baseline: Canagliflozin vs. Sitagliptin**

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<th>Canagliflozin</th>
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<td>50 mg qd</td>
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<td>Hba1c, %</td>
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<td>Baseline</td>
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<td>Δ A1C (%)</td>
<td>-0.45*</td>
<td>-0.51*</td>
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<tr>
<td>Δ Fasting plasma</td>
<td>-16.2*</td>
<td>-25.2*</td>
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<td>glucose (mg/dl)</td>
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<tr>
<td>Δ Weight (%)</td>
<td>-1.3†</td>
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P-value vs. placebo: *p<0.001, †p<0.01.
The 200 mg dose was superior to placebo based on improvements in fasting plasma glucose and self-monitored plasma glucose (<25 mg/dl, p=0.026), fructosamine (<25 µmol/l, p=0.009), glycated albumin (p=0.03), LDL-cholesterol (<11 mg/dl, p=0.005), apoB, and HDL-cholesterol, indicating favorable effects on glycemia and metabolic dyslipidemia. Consistent, but less robust, glycemic effects were seen with the 100 mg dose. Additionally, placebo-subtracted weight loss of >0.5 kg was recorded after 13 weeks in the 200 mg group, preceded by an improvement in adiponectin (an adipokine that increases with insulin sensitization), which increased by 65% by the end of the study (p=0.023). Injection site erythema was the most common adverse event. PTP-1B inhibition may be promising as a novel target for treating Type 2 diabetes patients.

**GPR-119 Agonist**

GPR-119 is a G-protein coupled receptor that regulates glucose by enhancing glucose-sensitive insulin secretion while simultaneously stimulating incretin hormone release from the intestines. Suppressive effects on food intake and GI motility have also been described. Roberts et al. from California conducted a phase 1, dose-ranging pharmacokinetic/pharmaco-dynamic study of MBX-2982, an oral GPR-119 agonist, at once daily doses of 25 mg, 100 mg, 300 mg, and 600 mg (n = 8 per dose) vs. placebo (n = 12), in subjects who fulfilled impaired fasting glucose or impaired glucose tolerance criteria, or had an HbA1c ≥5.8% (abstract 603-P). A significant reduction in glucose was observed with all doses of active study drug during a mixed meal tolerance test performed on Day 4; there was a pooled 48% reduction in glucose AUC (p <0.001 vs. placebo). Glucose lowering was best in subjects with the greatest derangements in glucose tolerance: -76% in subjects with postprandial glucose >180 mg/dl (n = 3), -61% in those with both postprandial glucose >160 mg/dl (n = 6), and -49% in those with postprandial glucose >140 mg/dl (n = 13).

In an increasingly crowded anti-hyperglycemic drug space, it remains unclear which of these agents, if any, will eventually be approved by the FDA and be available for clinical use. Safety is a key focus of the agency these days, and new agents must now demonstrate convincing cardiovascular safety before approval.

As mentioned in our review of the cardiovascular symposium in yesterday’s edition (Getting to the Heart of Diabetes, pg 3), although intensive glucose lowering strategies did not improve cardiovascular outcomes in patients in the VADT trial, they did appear to lower the risk for patients with lower coronary calcium (by EBCT) at baseline. Saremi et al. from the US examined 197 subjects participating in a sub-study of VADT to examine whether intensive glucose therapy reduced the progression of coronary and abdominal aortic artery calcium (CAC and AAC, respectively) (405-PP). Baseline and follow-up scans (average 4.6 years) were performed and CAC and AAC were categorized into none, low (≤100 for CAC; ≤1,000 for AAC), and high (>100 for CAC; >1,000 for AAC). Treatment assignment to intensive or standard therapy was not associated with annual changes in calcium or in progression of atherosclerosis, irrespective of baseline CAC and AAC category in these patients with long-standing Type 2 diabetes. These data support the current notion that once substantial atherosclerosis has become manifest, glucose control may have little impact on its further evolution.

Patients with diabetes not only have a higher rate of coronary disease, but also of heart failure. In another abstract presentation, Eurich et al. from Canada and the United Kingdom performed a nested case control study using the United Kingdom General Practice Research Database to determine the effects of various treatments on mortality in patients with co-existent Type 2 diabetes and heart failure (731-PP). There were 1,633 cases (≥35 years of age, newly diagnosed with diabetes and heart failure after January 1988 who had died before October 2007) and 1633 controls matched on age, sex, site, year, and duration of follow-up. The mean age was 78 years, 53% were male, and one-fifth had a HbA1c >8%.

In multivariate analyses, as may be expected, the use of beta blockers, ACE inhibitors, and angiotensin receptor blockers was associated with reduced mortality. The use of metformin was also associated with lower mortality compared to patients who were diet- or lifestyle- controlled for their diabetes (OR 0.66, 95% CI 0.49-0.89), but should obviously still be avoided in those with unstable status, acute decompensation, or superimposed renal disease. Prospective studies will be needed to demonstrate whether this biguanide medication may actually improve outcomes in the growing population of patients with both diabetes and ventricular dysfunction.

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