Type 2 Diabetes

Uses of thiazolidinediones and insulin

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This is the first of a series of articles based on presentations at the American Diabetes Association (ADA) 70th Scientific Sessions held on 25–29 June 2010 in Orlando, Florida, pertaining to thiazolidinedione(s) (TZD) and to approaches to insulin treatment for type 2 diabetes. At a symposium on the role of TZD, Thomas Buchanan (Los Angeles, CA) discussed the β-cell benefits of TZD and their action to slow the progression of diabetes. Clinically, the agents increase body fat, acting to increase appetite, but making fat "behave better" and leading to a reduction in insulin resistance and improved glycemia. TZDs alter circulating lipids, lower blood pressure, reduce coronary artery restenosis after percutaneous intervention, and decrease ultrasonographic progression of carotid and coronary artery disease but increase the risk of distal extremity (and perhaps other skeletal) fracture and of congestive heart failure. They may alter the risk of acute occlusive events.

To set the stage for understanding the TZD effect on β-cell function, Buchanan reviewed the hyperbolic relationship between insulin sensitivity and insulin secretion. The product of the two parameters, the disposition index, decreases as diabetes develops. Cross-sectional data suggest that, as the fasting glucose increases from under 100 to 100–140 and again from 140 to 180 mg/dL, there is particularly great deterioration in β-cell function, with lesser deterioration as glucose levels increase further (1).

Buchanan reviewed his studies, comparing those who had developed diabetes with those who had not after having had gestational diabetes. There was a nonlinear relationship between reduction in β-cell function and elevations in glucose levels, with greater reduction leading to the development of diabetes (2). Although he pointed out that higher blood glucose, lesser β-cell function, and worse degrees of insulin resistance "doesn't actually tell you why they develop diabetes," Buchanan reviewed further analysis showing weight gain to be the strongest predictor of diabetes, mediated by reductions in insulin sensitivity on euglycemic clamp studies and, perhaps more importantly, by changes in cytokines, including decreases in adiponectin and increases in C-reactive protein (3). Individuals with impaired fasting glucose and, even more so, with diabetes have exhibited a reduction in β-cell mass at autopsy (4), and there is a direct relationship between β-cell mass and function in islets of individuals with type 2 diabetes (5). Type 2 diabetes then develops in the setting of β-cell failure to compensate for decreased insulin sensitivity, leading to slowly accelerating elevations in blood glucose.

In this context, one can suggest a model of the effects of TZD. In diabetes prevention trials, the continuous process of worsening glycemia is arbitrarily dichotomized. Buchanan suggested that prevention of diabetes could conceptually involve either *1*) a reduced rate of progression/slope of the increase in glucose levels or 2) a change at the starting point, which could be regarded as masking progression. In the first option, there are progressively fewer cases with intervention, but if the treatment is stopped, the intervention and control groups will develop diabetes in parallel. In the second option, the two groups develop diabetes in a parallel fashion but with a lag in the intervention group and with relatively rapid return to control diabetes prevalence after withdrawal of intervention. He suggested that TZD seem to reduce the rate of disease progression and that, after withdrawal of these agents, diabetes rates do not converge in intervention and control groups. "You can actually," he said, "arrest the decline in β-cell function," with the level of insulin secretion the strongest predictor of those who will develop diabetes. In the Troglitazone in Prevention of Diabetes (TRIPOD) study (6), pioglitazone (PGZ) was given after withdrawal of troglitazone (7), the overall effect of the agents appearing to be "β-cell unloading."

In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) and Actos Now for Prevention of Diabetes (ACT NOW) studies, diabetes development rates gradually diverged. The lifestyle intervention in the Diabetes Prevention Program (DPP) showed a similar effect, whereas the use of metformin (MET) in the DPP and that of acarbose in the Study TO Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial seemed to prevent diabetes by directly reducing glycemia, with both trials showing relatively rapid development of diabetes after withdrawal of treatment. In studies of patients with existing diabetes, Buchanan suggested that rosiglitazone (RGZ), given as monotherapy in A Diabetes Outcome Progression Trial (ADOPT), or in combination with MET or a sulfonylurea (SU) in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, delayed rates of progression of hyperglycemia. Buchanan interpreted these studies to show that TZD may slow the loss of β-cells and stabilize β-cell function. Elaborating on the notion of disease stability, he suggested that this is particularly probable early in the course of the disease when lifestyle intervention fails; however, he raised the caveats that approximately one-third of treated patients are nonresponders and that "they are not heavier… [and] not more insulin resistant." One should then, perhaps, carefully assess the TZD response after 3 months. In prediabetes and early-onset diabetes, Buchanan suggested that their action can be ascertained from a reduction in the fasting insulin; however, this has not been assessed in all racial/ethnic groups.

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Furthermore, the long-term microvascular outcomes of diabetes prevention with TZD are not known and there remain questions pertaining to side effects.

Andrew Gray (Auckland, New Zealand) discussed the effects of TZD on bone (8). Between 5 and 10% of the skeleton is remodeled actively at any given time; in osteoporosis, either osteoclast function is increased or osteoblast function is decreased. Osteoblasts are derived from mesynchymal precursors, with peroxisome proliferator–activated receptor γ (PPARγ) increasing precursor maturation as adipocytes. Bone resorption is increased by the TZD in vitro (9). TZD-induced reduction in bone mass involves decreased bone formation in younger animals and increased resorption in older animals. Furthermore, Gray stated that mice with heterozygous deletion of PPARγ have increased bone formation and increased bone mass. Specific homozygous deletion of PPARγ in the osteoclast lineage leads to osteopetrosis (10).

In a 14-week study, RGZ decreased the bone formation marker procollagen type I NH_2-terminal propeptide in healthy postmenopausal women, without accompanying decline in serum β-COOH-terminal telopeptide of type I collagen, a marker of bone resorption, and hip and spine bone mineral density decreased by 1–2% (11); a number of other authors have reported similar findings (12), with evidence of change in bone biomarkers in ADOPT (13) and of increased fracture risk in the RECORD trial (14). The increased fracture risk particularly affects the distal skeleton (15), but recent studies suggest increased hip fracture with these agents as well (16,17). Furthermore, there may be increasing fracture risk in hip and spine over time in both men and in women (18). In a study presented at the ADA Scientific Sessions, Bilezikian et al. (abstract 394) showed that comparison of MET vs. MET plus RGZ showed reduction in hip dual-energy X-ray absorptiometry (DEXA) bone mineral density in the latter group. Colhoun et al. (abstract 74) reported a "self-controlled case series" of individuals treated with TZD, suggesting significant doubling of hip fracture risk, in both men and women, in a study with 4,730 and 2,503 individuals and years of observation before and during TZD treatment.

"The drugs are toxic to the skeleton," Gray concluded, recommending that DEXA bone density measurement as well as the use of clinical risk factor assessment such as FRAX be conducted. "My own feeling," he said, "is that if estimated fracture risk exceeds 10%, you should think about not using the drugs or. . . [giving agents to] protect bone." In the Womens' Health Initiative, he stated that postmenopausal hormone replacement treatment somewhat reduced fracture risk among women receiving TZD, but he considered bisphosphonates to be "the most attractive option." The development of selective PPAR modulators not inducing bone loss would be desirable.

Phillip Home (Newcastle, U.K.) addressed the question of PPARγ agonist cardiovascular (CV) effects by asking, "Has the dust settled? What is the effect of the TZD on CV risk after all?" "The story goes back quite a long way," he continued. There was evidence of CV toxicity with the PPARα agonist clofibrate. The PPARγ agonist ciglitazone was found to cause cardiac hypertrophy and fluid retention, combined PPARαγ agonists were found to cause bladder tumors in rodents and possibly in humans, PPARα and PPARγ agonists seemed to cause colon and lung tumors, and the PPARαγ agonist muriglitazar was reported to cause cardiac toxicity.

RGZ and PGZ were licensed in Europe with the condition that CV studies be conducted. The secondary prevention PROspective pioglitazone Clinical Trial in macrovascular Events (PROactive) enrolled individuals with extensive evidence of CV disease, and RECORD recruited a more typical diabetic population, both starting in 2001. The results of PROactive were reported in 2005, with the primary end point showing a nonsignificant 10% reduction, which was caused by an increase in peripheral vascular disease events, whereas virtually all other CV end points were reduced by 15–20%, with the principal secondary end point of mortality, myocardial infarction, and stroke significantly reduced by 16% ($P = 0.027$). "For RGZ, the situation was a little different," Home stated. A meta-analysis conducted by GlaxoSmithKline (Research Triangle Park, NC) in 2006 suggested an increase in myocardial infarction, confirmed by a publication in 2007 (19), although Home stated that both studies "just reached statistical significance" and that an update with an additional 10 studies just released showed a nonsignificant 10% increase in events. Home observed that there may be an issue with "instability of the data within these meta-analyses." A meta-analysis of low-quality studies of magnesium supplementation in 1993, for example, showed a benefit in acute myocardial infarction; however, the 1995 International Study of Infarct Survival (ISIS-4) showed absolutely no benefit (20). "The randomized controlled trial trumped meta-analysis," Home observed, noting that a recent meta-analysis reporting increased rates of malignancy with angiotensin receptor blockers similarly should be considered highly speculative.

Home stated that the RECORD study has then become the hypothesis test of the RGZ meta-analyses. RECORD studied 4,458 individuals with type 2 diabetes, comparing RGZ with either MET or SU to the combination of MET+SU (14). The primary end point was CV death or CV hospitalization. Full follow-up is available for more than 80% of patients at 7 years. Changes after randomization did occur in treatment, and they increased over time, but for 88% CV follow-up, those allocated to the RGZ arm received the agent. The likelihood ratio of the primary outcome was 0.99 (95% CI 0.85–1.16), and "unlike PROactive," Home noted, "in RECORD, heart failure is included." With inclusion of atherosclerotic events only, the likelihood ratio was 0.970, and with separate comparisons of MET with RGZ vs. SU, the likelihood ratio was 1.01, whereas with background SU, the ratio for RGZ vs. MET was 0.98. "These sensitivity analyses lead you to have great confidence," Home continued, "that there is no difference in CV events." For all-cause and CV mortality, the respective likelihood ratios were 0.86 and 0.84, so that, although not statistically significant, "the probability is overwhelmingly in favor of benefit rather than harm as it pertains to death." The trial was not powered for other end points, but the likelihood ratios were 1.14 for myocardial infarction; 0.72 for stroke; 0.93 for CV death, myocardial infarction, or stroke; 1.05 for acute coronary syndrome (ACS); 0.96 for ACS or angina; and 0.99 for ACS, angina, or revascularization. "It's very difficult to suggest," Home concluded, "that there is any increase in acute coronary events." In contrast, there was the recognized increase in likelihood of heart failure, with a likelihood ratio of 2.1.

Because of the progression of diabetes, therapies change over time, so one "can only make sense of these for about 5 years," Home stated, but he noted that there was very good mortality ascertainment and that very strict definitions of myocardial infarction were applied. Event rates in

diabetes studies are not high, but he stated that, in RECORD, the number of events was sufficient to confidently state that noninferiority was shown. Acute coronary events were indistinguishable with RGZ from those in patients treated with MET/SU; recurrent events among the 64 patients receiving RGZ and the 56 patients treated with MET/SU, upon suffering their first myocardial infarction, were indistinguishable, with four deaths in each group. Home pointed out the similarities of RECORD to the findings of the BARI 2D study in individuals with proven coronary disease, who had been receiving insulin or SU-based vs. MET and RGZ-based treatment, and similarities to the findings of the APPROACH intravascular ultrasound study of patients receiving RGZ vs. glipizide, with event rates of 11.7 vs. 11.2% (21). Likewise, in both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and in Veterans Affairs Diabetes Trial (VADT), RGZ has been noted not to have increased risk. It is noteworthy that stroke reduction was found in RECORD with a likelihood ratio of 0.72, in ADOPT with a ratio of 0.77, in early RGZ studies with a ratio of 0.48, and in PROactive with a ratio of 0.81. Home showed a meta-analysis demonstrating a significant 25% reduction in the likelihood of a stroke. He concluded that TZD are not associated with increased CV risk or myocardial infarction risk. Furthermore, Home said, TZD may have benefit, as opposed to harm, for death and for stroke compared with the combination of MET and SU.

Ian Blumer (Toronto, ON, Canada) discussed clinical use and monitoring of TZD, focusing on selected aspects of the U. S. guidelines on prescribing information or product monographs. "In the interests of making the session meaningful," he said, he would discuss both RGZ and PGZ as a class. The adverse effects of both TZD may include macular edema in the eye, active liver disease (with transaminase levels more than 2.5- to 3.0-fold above the upper normal), and increased fracture rates as previously discussed. Finally, there is RGZ's increased rate in myocardial infarction according to the meta-analysis (19). Blumer stated that "we talk about heart disease perpetually," use of nitrates is not recommended in class 3 and class 4 heart failure, and combined use of insulin with RGZ is also not recommended.

Despite >14 million patients and years of use, he said, "we still ask ourselves if and when we should be using drugs from this class." There are certainly studies showing that TZD prevent diabetes, but he raised "concerns, including unproven long-term efficacy, adverse effects, [and] costs." The current ADA standards state that "metformin should be the only drug considered for use in diabetes prevention," and Blumer recommended that TZD not be used for this purpose. He noted that TZD are not recommended as monotherapy in the ADA/European Association for the Study of Diabetes consensus statement, but stated that, in considering add-on therapy for glycemic control, "it's not a matter of if, it's a matter of when" to use a TZD. The factors influencing his choices of add-on therapy include efficacy, durability, other auxiliary benefits, adverse effects, long-term safety, label vs. off-label use, clinical practice guidelines, expert opinion, cost/coverage, and, perhaps most tellingly, what he termed as "hassles,...the response my patients have to medication." Noting that guidelines are not infallible, he stated that TZD are considered "suitable, [if] not necessarily ideal," by guidelines of the ADA, American Association of Clinical Endocrinologists, National Institute for Health and Clinical Excellence, and various agencies in Europe, Italy, Germany, Scotland, Australia, Singapore, and the United Arab Emirates. None of the guidelines suggests that TZD use be abandoned. He "anticipate[d] ongoing concerns about TZD safety and the possibility that these concerns will never be resolved." Given the medicolegal issues raised by these concerns, the development of new drugs, and the inevitable lack of promotion as patents expire, he predicted that the drugs "will gradually fade away."

Add-ons to Insulin

Candis M. Morello (San Diego, CA) discussed choices in adding oral agents for individuals with type 2 diabetes already receiving insulin (22). Insulin resistance is a major feature of the pathogenesis of type 2 diabetes, with MET and TZD acting at this level. The dipeptidyl peptidase (DPP)-4 inhibitors reduce hepatic glucose production; the DPP-4 inhibitors and SUs act to increase insulin secretion, and the bile acid sequestrants and α-glucosidase inhibitors (AGIs) act in the gut. A number of studies have assessed the addition of MET to treatment of patients with type 2 diabetes receiving insulin (23,24), showing reduction in A1C and body weight, with lipid benefit as well. In a Turkish study on insulin alone or in comparison with acarbose, MET, or RGZ, the latter two agents were particularly effective in lowering levels of glucose and A1C, whereas all agents reduced the insulin dose requirement (25). A number of studies have analyzed the addition of TZD in insulin-treated patients (26); there seems to be particular benefit in patients with greater degrees of insulin resistance, although weight gain, hypoglycemia, peripheral edema, and heart failure are adverse occurrences. The use of DPP-4 inhibitors in conjunction with insulin is another potential approach, with a study of 641 patients receiving insulin randomized to 100 mg sitagliptin daily vs. placebo showing a 0.6% reduction in A1C and 15 mg/dL and 20 mg/dL reductions in fasting and 2-h postprandial glucose levels (with evidence of increased endogenous insulin secretion in response to increase in blood glucose, no change in body weight but greater frequency of hypoglycemia) (27); a similar study has been reported with vildagliptin, a DPP-4 inhibitor that is not available in the U.S. (28). A study of 287 insulin-treated patients showed that bile acid sequestrant colesevelam reduced fasting glucose and A1C, as well as LDL cholesterol, but increased triglyceride levels (29). Morello concluded that MET and TZD particularly reduce fasting glucose, whereas postprandial glucose is better reduced with DPP-4 and AGI, that weight gain and hypoglycemia particularly seem to complicate the addition of insulin to TZD treatment, and that there is some degree of favorable CV effect with the addition of MET, whereas all of the agents should be considered to have potential adverse effects, such as MET causing gastrointestinal effects and vitamin B_{12} deficiency and having renal contraindications, osteoporosis and fluid retention issues with TZD, and potential gastrointestinal side effects with AGI and bile acid sequestrants, so appropriate patient screening and follow-up are essential.

In a study presented at the ADA Scientific Sessions, Schwartz et al. (abstract 564) administered the sodium-glucose transporter (SGLT) 2 inhibitor canagliflozin vs. placebo to 19 insulin-treated diabetic patients, showing a 0.2 vs. 0.7% reduction in A1C from baseline levels of 0.3%, with a 38 mg/dL decrease vs. 9 mg/dL increase in fasting glucose. Wilding et al. (abstract 021-LB) and Parikh et al. (abstract 563) reported a much larger study of 808 insulin-treated type 2 diabetic patients with baseline A1C 8.5% randomized to the SGLT2 inhibitor

dapagliflozin at daily doses of 2.5, 5, and 10 mg, or placebo, showing that no insulin dose increase was required with active treatment, with A1C decreasing 0.3% with placebo but 0.9% with 10 mg dapagliflozin and with a weight loss of 1.7 kg in the latter group, suggesting the potential of this treatment to be effectively added to insulin.

Wendy S. Lane (Asheville, NC) discussed the use of U-500 insulin therapy. U-500 insulin is intermediate in onset of action between regular and NPH insulin (30), and in a study presented at the conference, Jackson et al. (abstract 014-LB) confirmed the prolonged time to peak effect and longer duration of action of U-500 vs. human regular U-100 insulin. Its use should be considered in patients requiring high doses of insulin, as suggested by Lane, particularly in those requiring >100 units (and hence more than one injection) per dose. Advantages include improved insulin absorption, fewer (and lower volume) injections to enhance comfort and compliance, and, importantly, cost savings, with U-500 insulin costing approximately $0.02/unit, less than one fifth the cost of insulin analogs. Potential candidates include obese type 2 diabetic patients receiving multiple daily doses of insulin, particularly after transplant, or steroid treatment. Patients with systemic infection or gestational diabetes causing severe insulin resistance or patients with genetic and autoimmune defects of insulin action also may benefit from such treatment (31).

Lane noted that there are relatively few studies on this method of insulin treatment, none randomized or controlled. In a retrospective analysis of 20 patients whose treatment was changed to U-500, A1C decreased from 9.6 to 8.5% (32). In a study of nine patients followed for 6 months, all gained weight (mean 4.7 kg), but A1C decreased from 10.3 to 7.9%, without significant change in total insulin dose (33). Lane discussed the "off-label" use of U-500 administration by insulin infusion pump, suggesting that it be considered when the basal insulin requirement exceeds 3 units/h. A report of U-500 insulin administered by pump to four patients noted reduction in A1C from 10.8 to 7.6%. Two patients required reduction in total daily dose from 446 to 201 units, whereas the other two had little change in dose (but improved glycemia). Estimated cost savings per patient were $2,600 for insulin and $3,400 for pump supplies (34); such costs might be twice as great today. A similar study of six patients on insulin pumps reported a decrease in daily insulin requirement from 391 to 296 units per day, in A1C from 9.1 to 6.9% and a weight loss of 6.1 pounds at 6 months, without clinically significant hypoglycemia (35). In Lane's study of nine patients receiving U-500 insulin by infusion pump, A1C decreased from 8.8 to 7.7% at 3 months without increase in hypoglycemia (36); she showed follow-up evidence of sustained A1C reduction at 1 year. She recently reported that, in a cohort of 21 patients receiving U-100 by infusion pump when changed to U-500 in 12 months, A1C decreased by 1.2% from 8.9% with 71% increase in time spent in euglycemia on continuous glucose monitoring (37). A suggestion for frequency of U-500 administration is to convert patients receiving 200–300 units/day to U-500 twice daily, 300–750 units/day to three times daily, 750–2,000 units/day to four times daily, at doses exceeding 2,000 units/day to consider insulin pump treatment (38). Lane emphasized the potential for administration error and suggested that, when used in hospital, U-500 should be stored, dispensed, and administered separately from U-100 insulin, with its use highlighted in the medication record.

Matthew C. Riddle (Portland, OR) discussed the use of GLP-1 agonists and pramlintide with insulin, reviewing the effectiveness and also limitation of prandial and basal insulin and the potential benefits of basal insulin with an amylin agonist or with a GLP-1 agonist. In the Treating To Target in Type 2 Diabetes (4-T) Study, three different approaches to adding insulin to oral agents were compared in 708 persons receiving MET plus SUs (39). A1C decreased with all approaches, with basal-bolus approaches reducing A1C from ~8.5 to 7%. Riddle pointed out that all approaches using prandial insulin are limited by the need for frequent glucose testing and dose adjustment to address the complications of weight gain and hypoglycemia, which were least with an initial basal insulin approach. A1C can readily be reduced from 8.6 to 6.9% with either glargine or NPH insulin at bedtime (40); however, Riddle noted that the proportion of patients achieving goal decreases with higher starting levels, and even when A1C levels are below 7%, there is quite a bit of postmeal hyperglycemia (41), which Riddle referred to as the "prandial problem," leading to a large subset of patients being unable to achieve excellent control, with titration of basal insulin limited by hypoglycemia.

He reminded the audience that amylin and GLP-1 are secreted and that glucagon and ghrelin are suppressed postprandially (42,43), so that consideration of use of agents mimicking and affecting these systems may be relevant to prandial glycemic control. He pointed out that such treatment is currently "off-label." Amylin treatment with pramlintide is currently approved in use with prandial insulin. In a 24-week study of 113 obese patients with baseline A1C 8.4% on oral agents and basal insulin, the latter titrated to ~45 units/day, those randomized to prandial rapid-acting insulin received ~12 units before each meal and were compared with a group given pramlintide before meals. A1C decreased by 1.1 and 0.9%, the 90-min postprandial glucose increment was similar, and weight increased 4.2 kg vs. decreasing 0.3 kg, respectively (44). Exenatide is approved for use as monotherapy or in combination with MET, SU, or TZD as a twice daily injection. Riddle presented results of a 24-week study of 34 patients not easily controlled with oral agents with or without basal insulin, treated with insulin glargine plus MET, and randomized to exenatide vs. placebo twice daily (Riddle et al., abstract 18-LB). The baseline BMI was 34 kg/m^2, both groups were titrated to 0.5 units/kg glargine, and fasting glucose fell similarly from ~165 to 120 mg/dL; however, there was a nearly significant difference in A1C decrease from 8.0 to 7.3% with placebo and from 7.9 to 6.5% with exenatide, with similar frequency of hypoglycemia and with weight increasing by 4 kg with placebo but no weight change with exenatide. Continuous glucose monitoring at the end of the study showed that glycemic excursions after breakfast and dinner were considerably less with exenatide, although levels increased similarly after lunch, suggesting that if exenatide was to be administered three times daily, a greater glycemic effect would be observed. Riddle also reviewed a 259-patient study presented at the meeting that compared the addition of exenatide vs. placebo with insulin glargine treatment in type 2 diabetic patients with a baseline BMI of 33. Insulin was titrated from 50 to 62 units/day vs. from 47 to 69 units/day, whereas fasting glucose decreased from 142 to 116 vs. 149 to 118 mg/dL. There was, however, greater

reduction in A1C with exenatide, from 8.3 to 6.7 vs. 8.5 to 7.4%, greater improvement in a seven-point glucose profile, and a weight loss of 1.8 kg vs. weight gain of 1 kg, respectively (Buse et al., LB-10). Riddle concluded that gastrointestinal peptide-related treatments offer mechanisms beyond insulin for control of prandial glycemia, in a fashion that reduces the likelihood of hypoglycemia and weight gain. Whether other amylin and incretin agonists will have similar effects, whether there is heterogeneity in patient responsiveness to such regimens, and whether these approaches will improve medical outcome are not known.

A number of studies presented at the ADA conference also addressed combination treatment with insulin. Ellis et al. (abstract 9-LB) reported an effect of sitagliptin on glucose control in patients with type 1 diabetes, with 0.3% reduction in A1C, and 11 mg/dL decrease in mean glucose on continuous monitoring. Zinman et al. (abstract 40) treated 182 patients with type 2 diabetes with MET plus insulin glargine or with insulin degludec three times weekly or daily for 16 weeks, titrating to fasting glucose 113–116 mg/dL, with insulin doses of 0.45–0.49 units/kg/day given at bedtime; A1C decreased from 8.7 to 7.2, 8.8 to 7.3, and 8.7 to 7.4%, respectively. Gallwitz et al. (abstract 557) randomized 354 MET-treated patients to the addition of exenatide vs. insulin as part of a finding similar to 0.9 vs. 1.0% A1C reduction from baseline 7.9%, but with 8 vs. 21% developing hypoglycemia and weight loss of 4.1 kg vs. gain of 1.0 kg; adverse gastrointestinal effects occurred more commonly with exenatide.

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