The Management of Type 2 Diabetes in 2007—Insights from the 67th Scientific Sessions of the American Diabetes Association

a report by

Zachary T Bloomgarden, MD

Clinical Professor, Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York

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Rosiglitazone—Association with Adverse Outcome?

On May 21, 2007, a meta-analysis of 42 trials comparing rosiglitazone with placebo or other agents appeared on the *New England Journal of Medicine* website. The results suggested a significant (43%) increase in myocardial ischemia episodes and a 64% increase in cardiovascular mortality, which is almost statistically significant.[1] There were a number of flaws in the meta-analysis that led to a great deal of controversy. The analysis omitted a study hypothesis, which is considered 'data snooping.' One might argue that the study hypothesis was that myocardial infarction was increased by rosiglitazone, based on one of the author's earlier observations[2] pertaining to the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial.[3] If this were the case, the inclusion of those data in the meta-analysis would be flawed, since it would, in essence, mean using the same information twice. Furthermore, many of the studies in the meta-analysis included only one, and in some cases no, event; also, the events were not end-points in the standard sense, but rather were based on non-adjudicated investigator reports lacking documentation.

The authors used a fixed-effect rather than a random-effect method in the meta-analysis. A fixed-effect calculation does not consider variability among studies, while random-effect analysis makes the assumption that individual studies estimate different treatment effects, and is considered the more conservative approach.[4] If one re-analyzes the data in the study with both fixed- and random-effect approaches, the fixed-effect analysis relative risk (RR) is 1.42 with 95% confidence limits of 1.03–1.96 (p=0.033) as published, while the random-effect RR is 1.30 with 95% confidence limits of 0.94–1.79, a non-significant difference (p=0.110).[5] The meta-analysis used the number of events rather than time to first event. This approach is biased against longer trials and weighted toward smaller and, perhaps, less reliable short-term studies. Furthermore, it appears that rosiglitazone, as a particularly effective glycemic treatment, is associated with greater adherence. This would lead to shorter length of follow-up among persons taking comparators, who would nevertheless be included in study results using the 'last observation carried forward' approach, allowing clinical trials to use all enrolled persons in analyzing efficacy of various treatments. Such an approach, while being conservative in comparing only those persons responding to treatment, leads to a shorter period of observation for persons taking the less effective treatment.

The subsequently reported Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) study[6] was designed primarily as a cardiovascular safety study and further calls into question the results of the meta-analysis. Its primary end-point was a composite of cardiac and vascular events, and the study was designed with an active comparator group, with rosiglitazone used in combination therapy and assessed for non-inferiority. The RECORD study compared 2,220 type 2 diabetic patients receiving rosiglitazone in combination with either metformin or a sulfonylurea (SU), with 2,227 receiving metformin and an SU in combination. Baseline age was 59 years, 51% were males, diabetes duration was seven years, and initial glycated hemoglobin (A1c) averaged 7.9%. Interim analysis of adjudicated events at 3.75 years showed cardiovascular death in 29 versus 35 persons and total mortality rates in 74 versus 80, with the combined end-point of cardiovascular death, myocardial infarction, and stroke—a standard approach used in many trials—in 93 versus 96 persons, and 43 versus 37 myocardial infarctions. None of these differences was significant. The one significant adverse association with rosiglitazone was of more frequent heart failure in 38 versus 17 persons, a previously recognized adverse effect of thiazolidinediones, leading the US Food and Drug Administration (FDA) to require a 'black box warning' to this effect for both rosiglitazone and pioglitazone. The strengths of RECORD are its specific design for ascertainment of cardiovascular outcomes and the fact that it is a long-term trial in a large cohort using active comparators.

Approaches to Treatment of Type 2 Diabetes—Metformin, Sulfonylureas, Thiazolidinediones, and Insulin

Achieving and maintaining optimal glycemic control is essential to decreasing complications; however, progressively worsening hyperglycemia caused by declining beta-cell function appears to be characteristic of type 2 diabetes, posing a major challenge. The majority of type 2 diabetic

Zachary T Bloomgarden, MD, is a Clinical Professor in the Division of Endocrinology, Department of Medicine at the Mount Sinai School of Medicine in New York City. He has a national reputation for writing and lecturing on diabetes and has published several hundred reviews pertaining to insulin resistance syndrome and the treatment of type 2 diabetes, which have appeared in numerous professional publications. Dr Bloomgarden's *Perspectives on the News* series is a widely read and respected analysis of the latest research and developments in the treatment and management of diabetes. The series has appeared in the American Diabetes Association's (ADA) clinical journal, *Diabetes Care*, each month for more than 12 years. With the constant influx of new information and the ever-increasing numbers of adults and children being diagnosed with type 2 diabetes, *Perspectives* keeps physicians informed on a regular and timely basis about the most effective disease treatment and management strategies available. Other activities that have gained Dr Bloomgarden prominence include his work as a reviewer for the *Archives of Internal Medicine* and the *Journal of Clinical Endocrinology and Metabolism*, his status as a founding member of the Metropolitan Diabetes Society of New York, and his service on the Editorial Board of *Practical Diabetology*, the Board of the American Association of Clinical Endocrinologists (AACE), and the Journals Managing Subcommittee of the Endocrine Society.

E: zbloomgard@aol.com

persons do appear to require insulin over time, although it is noteworthy that initial insulin treatment in the United Kingdom Prospective Diabetes Study (UKPDS) was not more successful than oral agents.[7]

A Diabetes Outcome Progression Trial (ADOPT) compared the durability of glycemic control in 4,360 persons with newly diagnosed diabetes with fasting glucose between 126 and 180mg/dl followed for a median of four years. Patients were treated with the thiazolidinedione rosiglitazone at a maximal dose of 8mg/day, metformin at a maximal dose of 2,000mg/day, or the SU glyburide at a maximal dose of 15mg/day.[8] A1c was 7.3% at baseline and initially showed the most rapid and greatest decrease with glyburide, but subsequently had the greatest rate of increase with this agent—approximately twice that of metformin and three times that of rosiglitazone. The time to two consecutive fasting glucose levels >180mg/dl—a standard that would currently not be considered adequate—was shortest with glyburide. Metformin was intermediate and rosiglitazone was associated with the longest duration of glycemic control.

The most meaningful clinical translation of ADOPT may be in the development of appropriate treatment combinations.[9] Most organizations have suggested glycemic guidelines aiming for A1c levels below 6.5–7% and fasting glucose below 110mg/dl. The traditional approach of initiating and then intensifying oral agents, giving further oral agents in combination, adding basal insulin, and finally moving to multiple insulin injections may be less appropriate than one with more rapidly intensifying treatment.[10] Combination therapy allows complementary mechanisms to be employed to achieve greater benefit, perhaps with lowering of side effects by reducing dosages of individual drugs, with glucose-lowering also potentially preserving and improving the function of beta-cells. A comparison of the addition of glyburide versus rosiglitazone to metformin showed A1c decreasing from 8.4 to 6.9 versus 7.3%, but with hypoglycemia frequency of 38 versus 1%.[11] The combination of rosiglitazone with metformin in mean doses of 7 and 1,800mg daily, respectively, led to a 2.3% fall in A1c, while rosiglitazone 8mg daily led to a 1.6% fall, and metformin 1,847mg daily to a 1.8% fall in A1c from baseline levels of 8.8%.[12] In a study of initial therapy with glyburide, metformin, or both, glyburide 5mg decreased A1c by 1.2% and metformin 1,317mg decreased A1c by 1%; however, the combination in lower component doses reduced A1c by 1.5%.[13] In a two-year study of glyburide versus nateglinide in combination with metformin, A1c similarly fell from 8.3 to 6.8% versus 6.9%, with a hypoglycemia prevalence of 18 versus 8%.[14] In a study of glimepiride with rosiglitazone, at 28 weeks A1c fell from baseline levels of 9–9.2% by 1.7% with glimepiride 4mg alone, by 1.8% with rosiglitazone 8mg alone, and with the combination by -2.5%.[15] Thus, a variety of combinations can effectively reduce A1c, with more than half of persons starting at a baseline A1c of 8–9% able to attain the glycemic goal of A1c <7% with these approaches, although it must be recognized that the four-year findings of ADOPT suggest that studies showing excellent initial response to an SU should not be taken to suggest that these agents will result in ongoing benefit.

Insulin for Treatment of Type 2 Diabetes

Although acknowledging that no single agent can be recommended over the others in all cases, many current practitioners suggest that at diagnosis of diabetes metformin be given along with lifestyle treatment, bearing in mind that many persons are unable to tolerate metformin, particularly in full dose. Relatively early use of insulin may be appropriate. In a study comparing two combinations—insulin plus metformin versus an SU plus metformin plus a thiazolidinedione—both groups attained a mean A1c of 7.6% from a baseline of 9.6%. Insulin with metformin reduced triglyceride and cholesterol levels to a greater extent, and the combination of some insulin preparations with metformin is less costly than the triple oral hypoglycemic agent approach.[16] A further, more costly, approach is of a thiazolidinedione and metformin with insulin. A particularly useful combination is of insulin with metformin. Compared with administration of neutral protamine Hagedorn (NPH) insulin twice daily, with administration of insulin with glyburide, and with administration of insulin with both glyburide and metformin, bedtime NPH insulin added to metformin alone provides similar glycemic benefit to the other approaches, with a lesser degree of weight gain.[17] In type 2 diabetic persons failing to achieve goal with two oral hypoglycemic agents, both insulin glargine and NPH show convincing benefit,[18] although the former causes less hypoglycemia.[19]

Typically, insulin is used late in diabetes therapy. This may reduce the potential for benefit. Indeed, some experimental data suggest that intensive insulin treatment early in the course of type 2 diabetes may lead to remission.[20] An implanted pump study in patients with type 2 diabetes showed partial restoration of the acute insulin secretory response to glucose,[21] suggesting the potential for a particular benefit of insulin when used to attain euglycemia. Such an approach may, however, require large doses of insulin. In a Veterans' Administration co-operative study of 153 men with type 2 diabetes comparing standard with intensive insulin treatment, the former began on approximately 20 units daily, increasing to approximately 50 units daily, while the latter began with approximately 30 and increased to approximately 80 units daily, with A1c remaining around 9.5 in the former group and decreasing to <7% in the intensive group.[22] Similarly, a study with aggressive administration of NPH insulin at bedtime reduced A1c from 9.5 to 7.2% at a mean daily dose of 85 units.[23] Such studies do suggest that A1c levels around 7% are achievable, typically with insulin doses near one unit/kg bodyweight daily.

The most meaningful clinical translation of ADOPT may be in the development of appropriate treatment combinations.

Difficulties Treating Type 2 Diabetic Persons with Insulin

Barriers to insulin include patient resistance and fear of injections, as well as limited time for treatment adjustment, therapeutic inertia, and inadequate resources for teaching and care intervention, leading to failure to use adequate doses and to adjust doses in a sufficiently timely fashion.[24] Insulin is considered to require increased self-care efforts and to be associated with more frequent adverse effects such as hypoglycemia. Many diabetic persons feel there is a stigma associated with its use. Certainly, the addition of insulin may increase the overall complexity of treatment for a given patient.

Some 27–28% of diabetic persons in the US take insulin, with the percentage remaining stable from 1988 to 2003, although many more use it now in combination with oral agents.[25] Approximately one-third of patients experience anxiety about injections, with at least half of those declining to initiate insulin treatment.[26] It is not widely recognized that, presumably for these reasons, more than one-quarter of the 496 persons in the UKPDS randomized to insulin refused this treatment.[27] Furthermore, physicians are resistant to initiation of insulin treatment, and many are not familiar with its use. In the UKPDS there was no clear proof of greater efficacy of insulin over other treatment approaches.[7]

> Concepts of the relationships between type 2 diabetes and incretins have developed new complexity with recognition of the importance of polymorphisms of the TCF7L2 gene.

Compared with the Diabetes Control and Complications Trial (DCCT), the risk of severe hypoglycemia is considerably lower in type 2 than in type 1 diabetes.[28] This does, however, remain an issue for both patients and physicians. In the UKPDS, total and severe hypoglycemia occurred in approximately 35 and 2.5% of persons receiving insulin, respectively. In both the overall population and the overweight subgroup, both figures were considerably greater than with sulphonylurea (SU) and metformin.[7,29] Similarly, in the study comparing glargine or NPH insulin added to treatment of persons failing oral agents with weekly forced titration for 24 weeks, severe hypoglycemia occurred five to six times per 100 person-years with both agents, although there was more nocturnal hypoglycemia with bedtime NPH than with glargine.[18] With both type 2 and type 1 diabetes, the frequency of hypoglycemia appears to be decreasing,[30] suggesting that this may become a less important issue.

Another problem with intensive insulin treatment is weight gain. In the UKPDS, patients gained 4–5kg after 10 years with insulin treatment, and in the DCCT similar weight gain was reported in the intensive treatment group. In a study of intensive insulin treatment in type 2 diabetes in which patients required approximately 100 units daily, there was an 8.7kg one-year weight gain, although A1c decreased to nearly 6%.[31] A study of glyburide-treated type 2 diabetic patients randomized to addition of metformin, NPH at bedtime, or insulin lispro before meals showed similar glycemic control with the two insulin approaches, but greater weight gain with the single long-acting insulin dose,[32] although metformin may reduce the weight gain seen in such regimens.[17,33] Other approaches should, however, be considered in such settings, such as the use of exenatide, which, in comparison with glargine insulin, led to weight loss rather than weight gain, with similar improvement in glycemia.[34]

Incretin Mimetics and Dipeptidyl Peptidase 4 Inhibitors for Type 2 Diabetes

There is increasing evidence of the important glucose-lowering effect of gut peptides. The term 'incretin' refers to molecules found in the gut that have an insulin-stimulating effect that is greater than that achieved when nutrients are given intravenously to attain the same degree of glycemia.[35] Abnormal secretion of incretins is a major cause of the hyperglucagonemia of type 2 diabetes. The most important incretins are glucagon-like peptide (GLP)-1, secreted by the L-cells of the distal small bowel, and glucose-dependent insulinotropic peptide (GIP), secreted by the K-cells of the proximal gut. Both are secreted in response to neural input rather than in direct response to nutrients in the gut lumen. Both have short half-lives and are degraded by dipeptidyl peptidase 4 (DPP-4). There is a progressive decline in the GLP-1 response to an oral glucose load as glucose tolerance worsens, from persons with normal glucose tolerance, to impaired glucose tolerance, to type 2 diabetes. There is, however, a paradoxically high GIP level in type 2 diabetes, suggesting resistance to its effect. Comparison of the insulin-secretory responses to infusion of GLP-1 and GIP in type 2 diabetes shows considerably greater response to the former. However, intensive insulin treatment to normalize glucose levels appears to improve the insulin secretory response to both incretins, so that what has been considered an abnormality of beta-cell responsiveness caused by type 2 diabetes may in part be a reversible feature of poor glycemic control.

Concepts of the relationships between type 2 diabetes and incretins have developed new complexity with recognition of the importance of polymorphisms of the transcription factor 7-like 2 (TCF7L2) gene. TCF7L2 was discovered as a diabetes-related gene in 2003,[36] with a polymorphism associated with type 2 diabetes in a number of populations.[37,38] TCF7L2 acts in a signal transduction pathway, leading to decreased phosphorylation of the cytoplasmic adhesion and nuclear signaling protein beta-catenin. Mice not expressing TCF7L2 have a defect in gastrointestinal tract endocrine cells,[39] which may reduce GLP-1 transcription.[40] Human studies have confirmed an association between TCF7L2 and reduction in insulin secretion.[41,42] Diabetes Prevention Program participants showed risk of conversion from impaired glucose tolerance to be associated with a TCF7L2 genotype at rs79702, with carriers of the genotype having decreased insulin secretion and showing particular benefit from lifestyle intervention.[43] If GLP-1-induced insulin secretion is decreased by the at-risk genotype, measures to increase circulating GLP-1 or to increase GLP-1 receptor activation may be particularly important in this subset of type 2 diabetic patients.

The GLP-1 receptor agonist exenatide shows a dose–response effect in stimulating insulin and inhibiting glucagon to improve glucose homeostasis in type 2 diabetic persons. Exenatide reverses the abnormality in first-phase insulin secretion in type 2 diabetes, suggesting that it is a physiological approach to insulin replacement and not associated with hypoglycemia, as its insulin secretory effect is attenuated as glucose levels fall toward normal. In a study of 336 metformin-treated type 2 diabetic persons with a baseline A1c of 8.2% treated with placebo or exenatide 5 or 10mcg twice daily for 28 weeks, there was a 1–1.2% decrease in A1c at the higher dose, with dose-dependent weight loss averaging eight pounds.[44] Another GLP-1 receptor agonist, liraglutide, gives placebo-subtracted improvement in A1c by 1.2–1.6% (with placebo increases of 0.3%, so the absolute fall was approximately 0.9%).[45] This agent is given once daily rather than twice daily with exenatide, and may cause greater reductions in fasting glucose than are seen with exenatide. A long-acting form of exenatide given weekly is in

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development, with 15-week falls in A1c of 1.4–1.7% compared with a rise in A1c of 0.4% in the placebo group, suggesting that this drug would also potentially be highly effective as an agent in type 2 diabetes treatment.[46] The use of these agents, therefore, reduces A1c, promotes weight loss, stimulates insulin, and suppresses glucagon. In animal models, GLP-1 receptor agonists increase islet cell replication with neogenesis from pancreatic ductal cells and with decreased apoptosis.

GLP-1 and GIP both have the amino acid alanine in the second N-terminal position, allowing inactivation by DPP-4. More than 50% of secreted GLP-1 is degraded by local DPP-4 prior to absorption into plasma, so the glucose-lowering effect of endogenous GLP-1 is limited by its short half-life. Most long-term clinical studies of DPP-4 inhibitors have used two agents: sitagliptin and vildagliptin. Both are given once daily, reach their maximal effect after two to three hours, and can be taken with or without meals. Sitagliptin shows a >1,000-fold greater specificity for DPP-4 than for other proline-specific peptidases. In animal studies with sitagliptin, beta-cell apoptosis decreased with increased islet neogenesis, suggesting potential structural benefit.[47] In a 28-day study with vildagliptin, both GLP-1 and GIP levels were increased throughout the day. Glucagon levels decreased by half, insulin secretion was increased, and glucose response to a standard meal decreased. In monotherapy, both vildagliptin and sitagliptin decreased A1c by approximately 0.8% from a baseline of 8%, due to both improvement in fasting and, to a greater extent, post-prandial glucose.[48] In a comparative study of rosiglitazone with vildagliptin, both led to similar reductions in A1c, showing greater A1c-lowering at higher baseline levels.[49] The combination of pioglitazone with vildagliptin has also been studied, with pioglitazone 30mg daily reducing A1c from 8.7% by 1.4%, vildagliptin 100mg daily from 8.6% by 1.1%, and the combination decreasing A1c from 8.8% by 1.9% at 24 weeks.[50] In a 104-week trial comparing vildagliptin with metformin, both had sustained glucose-lowering effects, metformin showing somewhat greater effect at 52 weeks but not at the end of the two-year study. Sitagliptin has been studied in combination with metformin[51] and with pioglitazone,[52] showing additive effect. Similarly, in a 24-week study sitagliptin 100mg daily decreased A1c from 8.9% by 0.7%, metformin 1,000 and 2,000mg daily decreased A1c from 8.9% by 1% and from 8.7% by 1.3%, respectively, and the combination of sitagliptin 100mg with metformin 1,000 and 2,000mg daily decreased A1c from 8.8% by 1.6% and 2.1%, respectively.[53] Furthermore, a comparison of adding glipizide and sitagliptin to metformin showed identical glucose-lowering effects, with similar effects at increasing baseline glucose levels, although with greater hypoglycemia frequency and weight gain in patients treated with the SU.[54] In insulin-treated type 2 diabetic patients, addition of vildagliptin led to a greater fall in A1c with less hypoglycemia, suggesting an additional potential for this agent.[55] Both GLP-1 receptor agonists and DPP-4 inhibitors, then, appear to be useful agents for the treatment of type 2 diabetes, and potentially have specific benefit for acquired or inherited abnormalities in incretin response in the condition. The DPP-4 inhibitors have additional effect on GIP, which may increase glucose-lowering, although their effect is limited by endogenous secretion. The requirement for parenteral administration, however, may limit use of GLP-1 receptor agonists. ■

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