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STRATEGIC BRIEFINGS

Recent Clinical Developments in Type 2 Diabetes

Preventing Diabetes and Preventing Cardiovascular Events in Diabetics

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The market for a diabetes-prevention drug is potentially $15 billion per year, according to a recent report in *The Wall Street Journal*. There are an estimated 54 million people in the US with prediabetes, the American Diabetes Association says. Prescribing an approved antidiabetic drug to prediabetic individuals is thus an option being examined for the prevention of diabetes and its corollaries.

In this Strategic Briefing, we report on the results of recent trials that studied the ability of marketed antidiabetic drugs to 1) prevent diabetes, and 2) prevent cardiovascular (CV) events in those patients already diagnosed. The decision to prescribe an antidiabetic drug to a prediabetic individual must take into account the differential between successful reduction in progression to full-blown diabetes, and the adverse side effects of some antidiabetic drugs. The chasm is further widened when one considers the proven efficacy and safety that intensive lifestyle modifications related to diet and exercise can have on reducing disease incidence. Nevertheless, the following paragraphs highlight the urgent need to curb the ever-increasing incidence of diabetes—whether by using drugs or via lifestyle interventions.

Diabetes is a public health crisis… Development of new means of prevention of diabetes, and of prevention of CV events in diabetics, is critical for the United States , and for much of the world. The latest WHO (World Health Organization) estimate for the number of people with diabetes, worldwide, in 2000, was 177 million. By 2025 WHO predicts that number will increase to at least 300 million people.

In 2005, 5.62% of Americans had been diagnosed with diabetes. The Centers for Disease Control and Prevention (CDC) predicts the prevalence of diabetes will double by 2050, driven by the alarming rise in obesity in the United States . Obesity carries with it a decidedly higher risk of developing diabetes. At the same time, this increase in obesity is also occurring in much of the rest of the world, especially in India and China . Diabetes itself greatly increases the risk of CV disease (CVD), which is the major cause of death in type 2 diabetics.

…and it poses an economic burden. According to the American Diabetes Association, the total annual economic cost of diabetes in 2002 was estimated at $132 billion, or one out of every 10 health care dollars spent in the United States .

The market for oral antidiabetic drugs is lucrative. According to one recent report, in 2004 the global diabetes drugs treatment market reached a value of over $13 billion. Of this value, oral antidiabetics took a 54% market share and had a growth rate of 9% (Visiongain, "The World Diabetes Market, 2005–2011," March 2006). Clearly, companies with marketed antidiabetic drugs would like to expand their labels to include preventive use.

At last month's 42nd Meeting of the European Association for the Study of Diabetes (EASD) (Copenhagen, Denmark and Malmo, Sweden; September 14–17, 2006), several presentations were made on prevention of type 2 diabetes and prevention of CV complications in type 2 diabetics. These presentations were based on current results from two large, double-blind randomized placebo-controlled clinical trials: DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone) and PROactive (PROspective PioglitAzone Clinical Trial in MacroVascular Events). Most of the results of these clinical trials were also published in leading medical journals (see reference list at end of article).

DREAM was designed to study prevention of progression to diabetes in prediabetic individuals by administration of either ramipril (Sanofi-Aventis/Wyeth/King Pharmaceuticals' Altace) or rosiglitazone (GlaxoSmithKline's Avandia). PROactive was designed to study prevention of CV events in type 2 diabetics who already had macrovascular disease by administration of pioglitazone (Lilly/Takeda's Actos). Information on these drugs and the goals of these trials are summarized in Table 1.

For companies that are the developers of drugs tested in these trials, definitive success in preventing diabetes in prediabetics or CVD in diabetics may result in a major expansion of the market for their drugs. As it stands, pioglitazone and rosiglitazone achieved combined 2004 global sales of US $3.96 billion shared between Takeda and Eli Lilly (52%) and GlaxoSmithKline (48%), according to La Merie Business Intelligence. In 2005, Avandia achieved worldwide sales of $2.45 billion.

Table 1: Drugs tested in the DREAM and PROactive trials

Drug	**Drug Class**	**Approved indications**	**Potential new indication tested in DREAM or PROactive trial**
Ramipril (Sanofi-Aventis/Wyeth/King Pharmaceuticals' Altace)	ACE inhibitor	Hypertension; prevention of CV events in patients over 55 with a high risk of developing a major CV event.	Prevention of diabetes in prediabetic individuals. (DREAM)
Rosiglitazone (GlaxoSmithKline's Avandia)	PPARγ agonist (insulin sensitizer)	To improve glycemic control in type 2 diabetics, either as a monotherapy or in combination	Prevention of diabetes in prediabetic individuals. (DREAM)

		with other standard antidiabetic agents, and together with diet and exercise.	
Pioglitazone (Lilly/Takeda's Actos)	PPARγ agonist (insulin sensitizer)	To improve glycemic control in type 2 diabetics, either as a monotherapy or in combination with other standard antidiabetic agents, and together with diet and exercise.	Secondary prevention of CV events in type 2 diabetics with macrovascular disease. (PROactive)

Source: Haberman Associates

Background: Preventing progression to type 2 diabetes in prediabetic individuals by diet/exercise or metformin.

The metabolic syndrome, which is present in large numbers of people in the United States and increasingly in the rest of the world, is a risk factor for development of type 2 diabetes, as well as for CVD. The metabolic syndrome is a cluster of risk factors that include abdominal obesity, dyslipidemia, hypertension, insulin resistance (with or without impaired glucose tolerance), and elevated fasting blood glucose. People with three or more of these risk factors are deemed to have the metabolic syndrome. Those with abnormalities in glucose levels are considered to be prediabetic.

Specifically, those with fasting blood glucose levels between 100 milligrams per deciliter (mg/dL) and 126 mg/dL are considered to have elevated fasting blood glucose and to be prediabetic; those with levels over 126 mg/dL are diagnosed with diabetes. Individuals with impaired glucose tolerance (140–199 mg/dL after a 75-gram oral glucose challenge) are also prediabetic. Approximately one-third of prediabetics progress to diabetes.

Current treatment for prediabetics consists of recommendations for diet, exercise, and weight loss from their primary care physicians. Results of a study by the Diabetes Prevention Program (DPP) showed that a more intensive program of diet/exercise intervention can be effective in preventing diabetes over the short term, as can treatment with the well-established oral antidiabetic metformin (Merck KgaA/Bristol-Myers Squibb's Glucophage; also available in generic form). In this large randomized trial in 3,234 prediabetic subjects over a mean period of 2.8 years, an intensive program of lifestyle intervention (diet, exercise, and weight-loss recommendations, including individualized one-on-one instruction over a 24-week period) reduced the incidence of diabetes by 58%; metformin treatment reduced the incidence of diabetes by 31% as compared with placebo (DPP Research Group 2002). Thus, a more intensive version of the lifestyle modification that is the mainstay of current treatment of prediabetics proved significantly more effective than metformin over the short term.

Because of the significant benefit of both interventions in the DPP, the trial was terminated prematurely. This prevented the trial from assessing the long-term effects of intensive diet/exercise interventions and metformin. However, a long-term outcomes study (over a five-year period) of participants in the trial has been in progress, with the results not yet determined (Ratner; The Diabetes Prevention Program Research Group 2006). Nevertheless, unpublished results of a smaller clinical trial in Finland indicate that the benefits of intensive lifestyle intervention in preventing diabetes are sustained for many years (Tuomilehto and Wareham 2006; Tuomilehto, Lindstrom, Erickson et al. 2001).

Most prediabetic individuals do not receive intensive lifestyle intervention, which is usually difficult to administer in the primary care setting, and is often difficult for many patients to fit into their schedules. Especially under these "field conditions," long-term maintenance of weight loss sufficient to reduce the risk of developing diabetes (5–10% of body weight) is difficult for most overweight or obese people, including prediabetics. [However, the Finnish study indicates that meeting the exercise goals of an intensive lifestyle intervention program significantly reduces the risk of developing diabetes even in prediabetic individuals who do not meet the weight-loss goals of the program (Tuomilehto, Lindstrom, Erickson et al. 2001).] Because of this, researchers are interested in developing other means to prevent diabetes in this population. The DREAM trial represents studies aimed at determining whether ramipril or rosiglitazone treatment may constitute such preventive therapies.

Can ramipril prevent progression to type 2 diabetes in prediabetic individuals?

The DREAM trial consisted of two arms: one comparing ramipril and placebo, and the other rosiglitazone and placebo. Ramipril is an angiotensin-converting enzyme inhibitor (ACEI) approved for the treatment of hypertension and for prevention of CV events in patients older than 55 with a high risk of developing a major CV event. Rosiglitazone is an oral antidiabetic agent. It is an insulin sensitizer of the thaizaolidinedione (TZD) class of drugs. Studies with the other marketed TZD, pioglitazone, are discussed later in this article. TZDs are peroxisome proliferator-activated receptor (PPAR) agonists that target PPARγ, which controls glucose metabolism and adipocyte differentiation.

The results of the rampiril arm were simultaneously reported at the EASD meeting and published in the online edition of the *New England Journal of Medicine* (The DREAM Team Investigators 2006). In this arm of the trial, 5,269 prediabetic patients (without CVD, uncontrolled hypertension, or heart failure, and with fasting blood glucose between 110-126 mg/dL or blood glucose between 140–200 mg/dL in an oral glucose tolerance test) were randomized to receive ramipril or placebo. The patients were followed for a median of three years. The primary outcome was the incidence of diabetes or death, and secondary outcomes included regression to normoglycemia. There was no significant difference between the ramipril group (18.1%) and the placebo group (19.5%) in the incidence of the primary outcome. Among the secondary outcomes, at the end of the study 42.5% of subjects in the ramipril group had fasting blood glucose levels below 110 mg/dL and normal glucose tolerance tests, as compared to 38.2% of subjects in the placebo group. This difference was statistically significant.

Based on these results, the researchers concluded that ramipril was ineffective in preventing diabetes in this population over the study period, but that it had a modest positive effect on glucose metabolism. The difference between the ramipril group and the placebo group in the primary outcome diverged during the third year, however, with the rampiril groups showing a lower incidence. This suggests the possibility that a

longer follow-up period might have shown a significant benefit of ramipril in the prevention of diabetes.

The results of the ramipril arm of the DREAM study appear to contradict the results of earlier studies that suggested that ramipril might have a positive effect in preventing diabetes in some populations. These trials were not, however, specifically designed to determine whether ramipril prevents diabetes. Moreover, subjects in these earlier studies had uncontrolled hypertension, CVD, and/or heart failure, and were older by an average of 10 years than participants in the DREAM study. Therefore, it is possible that ramipril may be beneficial in preventing diabetes in these other populations. For example, in the Heart Outcomes Prevention Evaluation (HOPE) trial, researchers showed that patients older than 55 with vascular disease or diabetes plus one other CVD risk factor, but without heart failure, who were treated with ramipril were 34% less likely than placebo-treated patients to report a new diagnosis of diabetes over the mean five-year period of the trial (The HOPE Investigators 2000).

Despite the lack of evidence for the efficacy of ramipril in preventing diabetes in the DREAM study, ramipril or other ACEIs may still represent good choices in treating hypertension and/or various other conditions in populations of patients with metabolic syndrome, impaired fasting glucose or glucose tolerance, or diabetes. For example, in the HOPE trial rampiril significantly reduced the rate of death from CV causes, myocardial infarction (MI), and stroke (as compared to placebo) in the patients at high risk for CVD (most of whom had diabetes or metabolic syndrome) who were the subjects in this trial. Moreover, among commonly prescribed classes of antihypertensives, thaizide diuretics and beta-blockers may exacerbate the metabolic syndrome and increase the risk of developing diabetes (Taylor, Hu, and Curhan 2006). Therefore, other classes of antihypertensives, including ACEIs and calcium-channel blockers (both of which include drugs available as generics), may be better choices for many patients with hypertension and other aspects of the metabolic syndrome.

Can rosiglitazone prevent progression to type 2 diabetes in prediabetic individuals?

The methodology, types of patients studied, and clinical endpoints for the rosiglitazone arm of the DREAM trial were the same as for the ramipril arm. 5,269 patients were randomized to receive either rosiglitazone or placebo, and followed for a median of three years. The results of the trial were presented at the EASD meeting, and simultaneously published in *The Lancet* (DREAM Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. 2006). In this study, 11.6% of subjects treated with rosiglitazone and 26.0% of subjects treated with placebo developed the composite primary outcome (diabetes or death). Rosiglitazone gave a statistically significant reduction in the risk of developing the primary outcome of 60%, and a 62% reduction in the risk of developing diabetes as compared to placebo.

Because of the three-year duration of the DREAM trial, the results of longer-term treatment with rosiglitazone, or whether the results seen with rosiglitazone persist after termination of treatment, remain unknown. The DREAM investigators plan to present the results of such “washout data” (i.e., results after termination of treatment) at a later meeting. As a note, the results with earlier studies with the TZD troglitazone (Warner-Lambert’s Rezulin, which was discontinued for safety reasons) suggested that the risk of diabetes returned to untreated levels after termination of drug treatment.

The DREAM study showed that rosiglitazone is effective in reducing the risk of diabetes in prediabetic individuals over the short term. Despite this, the long-term effects of

treating prediabetic individuals with rosiglitazone, both in terms of efficacy and safety, are unknown. As discussed in a previous *Pharma DD* article, TZD treatment is associated with weight gain, and more rarely peripheral edema and congestive heart failure (CHF) (Haberman 2006). The DREAM investigators did report significant weight gain in rosiglitazone-treated patients in their study, as well as a significant sevenfold increase in the incidence of heart failure (0.5% of rosiglitazone-treated patients, as compared to 0.1% in the placebo group) over the three-year period of the trial. Moreover, rosiglitazone treatment also gave a 37% increase in a composite of CV events (2.9% of rosiglitazone-treated patients versus 2.1% in the placebo group), which was not statistically significant. However, this increase, together with the significant increase in heart failure, troubled Steven Nissen (Cleveland Clinic), who was also the lead author of a safety analysis of the discontinued dual PPAR agonist muraglitazar (Bristol-Myers Squibb's Pargluva) discussed in the earlier *Pharma DD* article (Herper and Kang 2006). This is of special concern to Nissen because otherwise healthy prediabetic patients such as those studied in the DREAM trial have a low risk of CV events, and because of the short-term nature of the trial. It is possible that in longer-term studies, the risk of CV events would reach statistical significance.

The unknown long-term effects of rosiglitazone treatments in prediabetic patients, as well as the high cost of treatment and the increased risk of heart failure, may well limit third-party payers' willingness to fund treatment in this population. Moreover, intensive lifestyle intervention gives comparable results to rosiglitazone, without the adverse effects of the drugs and with the potential for long-term benefits (Tuomilehto and Wareham 2006). As discussed earlier, however, the great majority of patients do not receive intensive lifestyle interventions. Moreover, otherwise healthy prediabetic patients are treated by primary care physicians, who are likely to be hesitant to prescribe rosiglitazone for these patients because of the same factors, and who tend to be conservative about prescribing novel treatments before they are well proven. Factors that militate against the use of rosiglitazone in diabetes prevention, despite the results of the DREAM trial, are summarized in Table 2.

Table 2: Factors that militate against the use of rosiglitazone in prevention of diabetes in prediabetic individuals

- Risk reduction with rosiglitazone is comparable to that with intensive lifestyle (diet and exercise) intervention, a safe, cost-effective, and proven alternative
- Rosiglitazone treatment is associated with weight gain, which counters the central role of weight loss in treatment of metabolic syndrome
- Risk of heart failure
- Lack of data on long-term efficacy and safety of treatment
- High cost of treatment

Source: Haberman Associates

Can pioglitazone prevent CV events in type 2 diabetics?

The results of the PROactive study on the effects of pioglitazone treatment in

secondary prevention of CV events in type 2 diabetics with macrovascular disease were presented at the September 2005 EASD meeting (Athens, Greece), and a month later published in *The Lancet* (Dormandy, Charbonnel, Eckland, et al. 2005). Updates on this study were presented at the 2006 EASD meeting.

PROactive was a double-blind randomized placebo-controlled study in 5,238 patients with type 2 diabetes and evidence of macrovascular disease (e.g., previous MI, stroke, coronary revascularization, or peripheral arterial disease, etc.). These patients were randomized to receive either pioglitazone or placebo; they were concurrently treated with standard medications for type 2 diabetes, dyslipidemia, hypertension, and with antiplatelet drugs such as aspirin. Mean follow-up was 2.8 years. The investigators found a nonsignificant 10% reduction by pioglitazone as compared to placebo in the study's primary endpoint (a composite of all-cause mortality, nonfatal MI, stroke, major leg amputation, acute coronary syndrome, and cardiac or leg revascularization). They also found a significant 16% reduction by pioglitazone as compared to placebo in the prespecified secondary endpoint (all-cause mortality, nonfatal MI, and stroke). The investigators concluded that the results with the primary endpoint were influenced by the lack of effect of pioglitazone treatment on cardiac and leg revascularization. This might be because the decision to perform these procedures is influenced by local medical practice.

In terms of safety, there was a significant increase in reported cases of heart failure with pioglitazone as compared to placebo (11% versus 8%), as well as pioglitazone-related weight gain and edema. Heart failure was not a centrally adjudicated event in this trial, however, and reports of heart failure may have been affected by the increased cases of edema (a symptom of heart failure) owing to the drug treatment. Patients are nevertheless faced with a trade-off between increased vascular health and the potential for heart failure. Weight gain is also a factor that runs counter to weight-reduction goals for the treatment of diabetes and CVD.

The update to the PROactive study presented at the 2006 EASD meeting was a prespecified subgroup analysis of the previously published trial results. In this analysis, the researchers found that pioglitazone treatment reduced the recurrence of stroke in patients who had a prior history of stroke by a statistically significant 47% as compared to placebo. There was no significant reduction in the rate of new cases of stroke in patients who had no prior history of stroke, however.

Despite the positive findings of the PROactive trial, it is not likely to change medical practice because of questions about the tradeoff between CV benefits of pioglitazone versus its adverse effects. Pioglitazone (and rosiglitazone) are important components of the armamentarium of oral agents to treat the hyperglycemia associated with diabetes, as well as other components of the metabolic syndrome seen in type 2 diabetics. However, it is not likely that physicians will want to prescribe pioglitazone specifically to prevent CV events in type 2 diabetics who are not already receiving the drug.

Outlook

As discussed previously, it is unlikely that the results of either the DREAM or PROactive trials will change medical practice, or result in market expansions for any of the drugs tested in the trials. The trade-off between the adverse effects of TZDs and their benefits as demonstrated in the trials is a major factor that militates against their expanded use. In the case of prevention of diabetes in prediabetic individuals, this has led some industry commentators to propose that other non-TZD oral antidiabetics be tested for diabetes prevention in this population. In particular, two novel late-stage

drugs that work via a mechanism different from TZDs and other current drugs, sitagliptin (Merck's Januvia, approved by the FDA in October 2006) and vildagliptin (Novartis' Galvus, which may be approved before the end of 2006), have been suggested as candidates (Herper and Kang 2006). However, although the approval of sitagliptin opens the door to clinical trials on diabetes prevention, any results are speculative and are years away. Therefore, intensive lifestyle intervention remains the best therapy for diabetes prevention in prediabetic individuals.

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References

Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393–403.

Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): A randomized controlled trial. *Lancet*. 2005;366:1279–1289.

The Dream Team Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med.* Sept. 15, 2006 [Epublished ahead of print].

Gerstein HC, Yusuf S, Bosch J et al. DREAM (Diabetes Reduction Assessment With Ramipril And Rosiglitazone) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: A randomized controlled trial. *Lancet.* 2006;368:1096–1105.

Haberman AB. Safety issues hamper dual PPAR agonists. Is partial antagonism the solution? *Pharma DD*. September 22, 2006.

The Heart Outcomes Prevention Evaluation Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145–153.

Herper M, Kang P. Glaxo's Faustian pill. *Forbes.* September 15, 2006. Available online at: http://www.forbes.com/2006/09/15/glaxo-avandia-heart-bizhealth-cx_pk_mh_0915avandia_print.html.

Ratner RE. The Diabetes Prevention Program Research Group. An update on the Diabetes Prevention Program. *Endocrinology Practice.* 2006;12(Suppl 1):20–24.

Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care.* 2006;29:1065–1070.

Tuomiletho J, Lindstrom J, Erickson JG et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.

Tuomilehto J, Wareham N. Glucose lowering and diabetes prevention: Are they the same? *Lancet*. September 15, 2006 [Epublished].