

## Rosiglitazone Reduced Risk of Progression to Type 2 From Prediabetes

In the largest completed diabetes prevention trial to date, rosiglitazone (Avandia; GlaxoSmithKline, Philadelphia) reduced the risk of developing type 2 diabetes by 62% compared with placebo among patients with prediabetes. The results of the landmark study were reported in Copenhagen at the 42nd annual meeting of the European Association for the Study of Diabetes (EASD) and in the *Lancet*.

### NEWS FROM THE EASD MEETING

This 62% reduction was highly statistically significant ( $P < .0001$ ) and additive to standard counseling with regard to healthy eating and exercise, which was provided to all participants in the trial, according to a news release. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial evaluated the likelihood of progression to type 2 diabetes over a 3-year median follow-up among 5,269 patients with prediabetes.

Patients were randomized to rosiglitazone (8 mg/day) or placebo and ramipril (15 mg/day) or placebo and were assessed every 6 months for 3 to 5 years. The study was not designed as a direct comparison between rosiglitazone and ramipril. Results from the ramipril arm of the study were reported and published separately.

In this study, 10.6% of patients receiving rosiglitazone progressed to type 2 diabetes versus 25% of patients assigned to the placebo group. In the composite primary endpoint of the development of diabetes or death from any cause, rosiglitazone demonstrated a 60% risk reduc-

tion versus placebo ( $P < .0001$ ).

"The DREAM findings are particularly significant as we are in the midst of an epidemic of type 2 diabetes with global implications. It is also noteworthy that the damaging complications of type 2 diabetes can often precede the diagnosis of this condition by several years," said Bernard Zinman, MD, a member of the DREAM Steering Committee and director of the Diabetes Centre at Mount Sinai Hospital and professor of medicine at the University of Toronto. "By demonstrating that rosiglitazone significantly reduced the risk of developing type 2 diabetes, these data provide important evidence that it may be possible to alter the course of rising blood sugar levels and its consequences." Dr. Zinman is also a member of the DIABETIC MICROVASCULAR COMPLICATIONS TODAY editorial board.

Over the median 3-year follow-up, 51% of the patients assigned to rosiglitazone achieved normal blood sugar levels versus 30% of those assigned placebo. In other words, patients assigned rosiglitazone were 70% more likely ( $P < .0001$ ) than those assigned placebo to achieve normoglycemia. Patients in the placebo group who had a higher body mass index (BMI) were more likely than those with a lower BMI to progress to type 2 diabetes. The risk of developing diabetes, however, did not increase with BMI in the group randomized to rosiglitazone, the investigators found. These findings suggest that rosiglitazone may reduce the risk of developing diabetes that is attributable to obesity.

## Pioglitazone Associated With Cardiovascular Improvements Among High-Risk Type 2 Diabetes Patients

Several abstracts presented at the EASD indicated that pioglitazone (Actos; Takeda, Lincolnshire, Ill) reduced the risk of myocardial infarction (MI) and/or stroke and acute coronary syndrome (ACS) in patients with type 2 diabetes.

"We are continuing to see the benefits of [pioglitazone] beyond glycemic control," said Erland Erdmann, MD, chairman of the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) Executive Committee and director of the Clinic III for Internal Medicine, University of Cologne, Germany. "We know that patients with diabetes are two to four times more likely to develop heart disease or have a stroke than people without diabetes. The data presented at EASD showed that [pioglitazone] can have a positive effect on several measures of cardiovascular disease (CVD) out-

comes in high-risk patients with type 2 diabetes.”

Results from one of the studies showed that pioglitazone significantly reduced the occurrence of major adverse cardiovascular events, such as MI, nonfatal stroke, ACS and cardiovascular death in high-risk patients with type 2 diabetes. Compared with placebo, patients treated with pioglitazone demonstrated statistically significant risk reductions of MI (23%,  $P=.046$ ), the combined risk of cardiovascular death, nonfatal MI or nonfatal stroke (18%,  $P=.020$ ) and the combined risk of all-cause mortality, nonfatal MI, nonfatal stroke or ACS (17%,  $P=.010$ ). These results were part of the landmark PROACTIVE study.

In patients who had experienced a previous MI, pioglitazone, combined with standard-of-care treatment, reduced the recurrence of fatal or nonfatal (excluding silent) MI by 28% ( $P=.045$ ).

Additional data presented at the meeting showed that pioglitazone improved components of diabetic dyslipidemia. The data indicated that pioglitazone decreased triglycerides and increased HDL cholesterol.

## Inhaled Insulin Analyses Presented

Adult patients with diabetes who used Exubera (insulin human [rDNA origin]; Pfizer, New York, NY) inhalation powder safely maintained blood sugar control even if they developed a respiratory infection or were exposed to passive cigarette smoke.

Exubera is a product of a developmental collaboration between Pfizer and Nektar Therapeutics (San Carlos, Calif), according to a news release. In a retrospective analysis of 14 phase 2 and 3 clinical studies, the inhalable insulin was well tolerated and efficacious, even during respiratory illness in adults with type 1 or type 2 diabetes.

Another study found that while passive smoke exposure could result in decreased absorption, inhalable insulin could be used by patients who were exposed to a smoky environment. “This information is important for health care providers who have prescribed or are considering prescribing [inhalable insulin] to their patients,” said Professor Philippe Camus, lead investigator from the University Medical Center, Dijon, France, in a news release. “It shows that the efficacy and tolerability of [inhalable insulin] remain unchanged even if patients develop a cold or the flu. Also, studies showed patients taking [inhalable insulin] are no more likely to

develop a respiratory infection than patients using injectable insulin.”

Inhalable insulin, however, should not be used by people who smoke or have smoked in the past 6 months, or by people who have underlying lung diseases such as asthma or chronic obstructive pulmonary disease, according to the manufacturer.

An analysis of a previously reported study showed that inhalable insulin may encourage twice as many people with uncontrolled type 2 diabetes to use insulin therapy (ie, 44% choosing inhalable insulin vs 17% choosing without the availability of inhalable insulin). This held true even in countries where insulin pens are commonly used to administer insulin, according to a news release. Previous reports have shown that people avoid or delay starting insulin therapy due to the fear and pain of injection, even when suffering from complications.

“This finding contradicts the perception that insulin pens can overcome people’s resistance to using insulin. If [inhalable insulin] can get more people to accept insulin at all and to accept it earlier than they ordinarily might, we would expect that more people could get their blood sugars under control,” said Nick Freemantle, PhD, professor of clinical epidemiology and biostatistics from the University of Birmingham, UK. “This is incredibly important in helping people to reduce their chances of suffering from the serious complications of uncontrolled diabetes such as blindness and amputations as well as for health care systems responsible for reducing diabetes-related morbidity and mortality.”

Another analysis of five clinical trials showed that people with either type 1 or type 2 diabetes who used inhalable insulin gained less weight than those using injectable insulin. Type 2 patients gained less than half with inhalable insulin (0.7 kg vs 1.6 kg), while the difference was even greater for type 1 patients (0.2 kg with inhalable insulin vs 1.1 kg with injected insulin).

“Many of my patients worry about weight gain with insulin,” said Priscilla Hollander, MD, lead investigator from Baylor University Medical Center. “This analysis reassures me that people who need insulin will not gain as much weight if they use [inhalable insulin]. This may be another reason for physicians and their patients to consider [inhalable insulin] to control blood sugar levels.”

Exubera is the first inhaled form of insulin and the first insulin option in the European Union, United States, Brazil and Mexico in more than 80 years that does not need to be administered by injection. It is currently available in the United States, United

Kingdom, Ireland and Germany. In the European Union, inhalable insulin is approved for the treatment of adult patients with type 2 diabetes who require insulin therapy and are not adequately controlled with oral therapy. In patients with type 1 diabetes, inhalable insulin should be used in combination with long- or intermediate-acting insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns.

In the United States, inhalable insulin is approved for the treatment of adults with type 1 or type 2 diabetes for the control of high blood sugar levels. In patients with type 2 diabetes, Exubera can be used alone or in combination with oral agents or longer-acting insulin. In patients with type 1 diabetes, inhalable insulin should be used in combination with a longer-acting insulin.

## ADA Calculated Economic Cost of Diabetes

In 2002, direct and indirect medical expenditures attributable to diabetes were estimated at \$132 billion in the United States, according to a report from the American Diabetes Association, published in *Diabetes Care*.

That figure is >50% of what spending would be without diabetes and does not include intangibles like pain and suffering, the cost of care provided by informal caregivers and administrative costs of insurers. The report, prepared by members of the Lewin Group, Falls Church, Va, including Paul Hogan, senior vice president; Timothy Dall, vice president; and Plamen Nikolov, stated that direct medical expenses for people with diabetes totaled \$91.8 billion; including \$23.2 billion for diabetes care, \$24.6 billion for chronic complications attributable to diabetes and \$44.1 billion for excess prevalence of general medical conditions. Lost productivity due to diabetes (ie, lost workdays, lost home services, permanent disability and premature mortality) was estimated at \$39.8 billion.

According to the study, US health expenditures for health care components included in the study totaled \$865 billion, and of that, people with diabetes incurred \$160 billion. Per capita, medical expenditures totaled \$13,243 for people with diabetes versus \$2,560 for nondiabetic people.

The study found that if diabetes prevalence rates remained constant over time, controlling for age, sex, race and ethnicity, the number of people diagnosed with

diabetes could increase to 14.5 million by 2010. This suggests that the annual cost could rise to an estimated \$156 billion by 2010 and to \$192 billion by 2020.

The investigators said reducing problems caused by diabetes through better preventive care, widespread diagnosis, more intensive disease management and the advent of new technologies could significantly improve the quality of life for people with diabetes while potentially reducing national expenditures and increasing productivity.

## Poorer Diabetes Control in Blacks

An analysis combining 11 research studies found that black patients with diabetes have poorer glucose control compared with white diabetes patients, according to researchers.

Julienne Kirk, PharmD, and colleagues from Wake Forest School of Medicine analyzed studies conducted between 1993 and 2005, creating the first metaanalysis of racial and ethnic differences in blood glucose control among patients with diabetes. The metaanalysis included 42,273 white and 14,670 black patients aged >50 years with type 2 diabetes.

The researchers analyzed studies that measured glucose control among blacks and whites using HbA1c and found that whites had values approximately 0.65% lower than blacks. Previous research has shown that for every 1% reduction in HbA1c, there is a 21% reduction in the risk of developing complications. In this study, white patients had a 15% lower risk of complications versus black patients.

"This lower level of control may partly explain why blacks have disproportionately higher rates of death and complications from diabetes," said Dr. Kirk, lead author of the study published in *Diabetes Care*. Still, HbA1c levels only account for a portion of the disparity, she added. "We need to understand more fully why this disparity exists and to eliminate factors that may be changeable, such as improving access to care."

## Kidney Patients Fall Into Donut Hole

Medicare beneficiaries with end-stage renal disease (ESRD) are at high risk for increased medication costs related to a gap in coverage, as reported in the *Journal of the American Society of Nephrology*.

Uptal D. Patel, MD, and colleagues at Duke University, analyzed survey data on prescription drug use and cost for approximately 42,000 Medicare beneficiaries. An estimated 70% of ESRD beneficiaries fell into the *donut hole* — a lack of available benefits between \$2,251 and \$5,100 in medication expenses under Medicare's Part D prescription drug benefit — compared with 43% of non-ESRD patients. Once in the donut hole, patients received no help with prescription costs until they reached the catastrophic threshold (n=\$5,100). Patients with ESRD were three times more likely to reach that threshold and had higher estimated drug costs overall (\$6,500 vs \$2,700).

According to the study results, ESRD beneficiaries would reach the coverage gap earlier than other patients and could experience high monthly variations in out-of-pocket drug costs.

“Based on these findings, we suggest that policy makers who are considering modifications in the Part D program may benefit from further research to monitor patterns and gaps in coverage, medication use and spending and hospitalizations and survival trends,” said Dr. Patel in a news release.

## Insulin Resistance in Teens May Predict Diabetes, Heart Disease Later

Decreased insulin response, beginning as early as 13 years of age, may mean increased CVD risk by age 19, according to research reported in *Hypertension*.

The results indicated that the prevalence of atherosclerotic CVD risk factors and type 2 diabetes were related to insulin resistance independent of obesity, said Alan R. Sinaiko, MD, professor of pediatrics, University of Minnesota Medical School.

“This is the first study to show insulin resistance by itself is a significant predictor of [CVD], beginning in childhood,” said Dr. Sinaiko, in a news release.

In the study, 224 participants (58% male and 83% white) were categorized by sexual development and underwent a complete physical examination (ie, blood pressure, height, weight, percentage body fat, HDL, triglycerides and fasting insulin levels). Insulin resistance was measured with insulin clamp studies at ages 13, 15 and 19 years.

Insulin resistance at ages 13 and 19 years predicted high systolic blood pressure. Researchers concluded that

for every unit increase in insulin resistance, a 0.412 mm Hg increase in systolic blood pressure and 1.91 mg/dL in triglycerides occurred.

## Drop in Kidney Function, Increased Mortality Linked

Even a small reduction in kidney function after radiocontrast dye injection for x-ray procedures may lead to an increased risk of death, researchers reported in the *Journal of the American Society of Nephrology*.

Steven D. Weisbord, MD, and colleagues at the University of Pittsburgh School of Medicine, analyzed data from nearly 11,500 patients who underwent coronary angiography to evaluate possible heart disease. Changes in serum creatinine — an indicator of kidney function — were evaluated pre- and postoperatively.

After adjustment for other factors, patients with a 25% to 50% increase in serum creatinine level after dye injection had a >39% mortality risk. An absolute increase of 0.25 mg/dL to 0.5 mg/dL serum creatinine was associated with >83% risk of death, while a  $\geq 1.0$  mg/dL increase raised mortality by >200%. Patients with raised serum creatinine levels also spent more time in the hospital.

“Although it is difficult to establish a definition of radiocontrast nephropathy in a single study, our results identify the levels of change in kidney function that predicts adverse events, including death,” said Dr. Weisbord.

## Diabetes, Colon Cancer Linked

Patients with type 2 diabetes have an increased risk of developing colorectal cancer (CRC) when compared with nondiabetic persons, according to a study in the *American Journal of Gastroenterology*.

Physicians from Mayo Clinic Cancer Center, University of Cincinnati and the H. Lee Moffitt Cancer Center, highlighted the need for CRC screening exams among diabetes patients. Risk was increased in males and in patients who smoked.

“The need for all adults to follow a healthy diet, lifestyle and regular medical visits becomes even more important when considering that about one-third of persons with type 2 diabetes may not be aware of their diagnosis,” wrote Paul Limburg, MD, MPH, at Minnesota's Mayo Clinic Cancer Center.

Further research is needed to clarify the increased risk of developing all cancer types in diabetic patients. ■