

We Bring You the Best of the ADA, 71st Scientific Sessions, 2011

[Diabetes in control](#)

ADA: Scientists Getting Closer to Artificial Pancreas.....	2
ADA: Preventive Efforts in Type 2 Diabetes Are Cost Effective	4
ADA: Liraglutide Shows Potential as Treatment for Weight Loss.....	5
ADA: ACTID Results Emphasize Diet Alone Over Diet and Exercise.....	7
ADA: Insulin Pump Suspend Feature Halts Hypoglycemia	9
ADA: Diabetes Patients Lead Peers to Healthier Status.....	11
ADA: Vascular Status Predicts Hypoglycemia	13
ADA: Even Diet Soda Induces Weight Gain in the Elderly	15
ADA: Intensive Therapy Yields Negligible Benefits in Type 2 Diabetes.....	16
ADA: Higher Vitamin D Levels Linked to Lower Diabetes Risk	18
ADA: TAK-875 a Novel Agent in the Treatment of Type 2 Diabetes.....	20
ADA: Restoring Visual Acuity in Diabetes with VEGF Inhibitor.....	21
ADA: Vascular Status Predicts Hypoglycemia	22
ADA: Tiny Pump Helps Improve Glycemic Control.....	23
ADA: Public Knows about Diabetes, Yet Takes No Action.....	24
NC-stat – DPNCheck.....	25
Worst Cocktails for Blood Sugar	26
Safety and Efficacy of Once-Monthly Exenatide over 20 Weeks in Patients with Type 2 Diabetes	27
ADA: Exenatide/Diet vs. Diet Alone for Treatment of Prediabetes.....	28
ADA: Linagliptin Has Similar Efficacy to Glimepiride but Improved Cardiovascular Safety over 2 Years in Patients with Type 2 Diabetes Inadequately Controlled on Metformin	29
ADA: Efficacy and Safety of Lixisenatide Once-Daily vs. Exenatide Twice-Daily in Type 2 DM Inadequately Controlled on Metformin (GetGoal-X).....	30
ADA: CV Risk with Linagliptin in Patients with Type 2 Diabetes: A Pre-Specified, Prospective, and Adjudicated Meta-Analysis from a Large Phase III Program	32

ADA: Scientists Getting Closer to Artificial Pancreas

[Diabetes in control](#)

With lawmakers and diabetes advocates ramping up the pressure, U.S. officials this week outlined a regulatory path for a preliminary version of the device....

While a seamless device that tracks blood sugar and automatically administers the right dose of insulin is still years away from commercial use, results of several studies being presented this week at the American Diabetes Association meeting in San Diego show real promise.

In one, researchers from Boston University and Massachusetts General Hospital tested a system using Abbott Laboratories' FreeStyle Navigator continuous glucose monitor and two insulin pumps made by Insulet Corp, all controlled by a laptop.

The system, which is designed to better mimic the body's natural mechanism of controlling both high and low blood sugar, was portable enough to allow adults with type 1 diabetes to roam around a hospital and use an exercise bike.

At the end of the 51-hour study, which involved daily exercise, two nights and six meals, six patients had an average blood glucose in the high 140s, equivalent to an A1c reading of about 7.

"It is very good. This is what we would call near normal blood glucose," said Dr. Steven Russell of Massachusetts General Hospital in Boston who is developing the system with Edward Damiano, a biomedical engineer at Boston University.

In another study, a team at Mayo Clinic hooked patients to accelerometers to track their movements and found that even moderate exercise plays a role in glucose. The team, led by Yogish Kudva, will incorporate this data into a sophisticated software program that acts as the "brain" of an artificial pancreas system, analyzing blood sugar and calculating when diabetes patients need a dose of insulin. The team plans to start a clinical trial with the system this year or early next year, Kudva says.

So-called closed-loop systems -- in which a computer calculates a person's insulin dose and delivers insulin automatically through a pump -- are a far cry from the earliest version of an artificial pancreas developed in the late 1970s, says Dr. Aaron Kowalski of the Juvenile Diabetes Research Foundation or JDRF.

"It was the size of a refrigerator," said Dr. Kowalski, who oversees the group's Artificial Pancreas Project, a multimillion-dollar initiative aimed at accelerating progress toward a closed-loop automated insulin-delivery system. With that device, patients were hooked up to an IV and could not leave their hospital bed.

The JDRF is working with Johnson & Johnson's Animas unit, which makes insulin pumps, and DexCom Inc, which makes continuous glucose monitoring devices.

Dr. Kowalski said, nearly five years into the project researchers are showing promising results, but he is frustrated with the pace of progress. "People need better tools. Despite insulin pumps and continuous glucose monitors, there are still big challenges in diabetes management."

On Wednesday, the group urged Senators at a hearing to call on the FDA to stop delaying the study and approval of an artificial pancreas. They cited a study published in the British Medical Journal that found that, if an artificial pancreas were available, Medicare would save nearly \$2 billion over 25 years in costs related to diabetes complications.

The group is pushing to move beyond studies in academic settings and begin studies of the devices outside of the hospital setting. "It's great that we can do this in academic centers, and we're learning a ton, but we need to get these projects to reach people with diabetes," Dr. Kowalski said.

"The FDA wants the artificial pancreas on the market as much as anyone else does. We just have to operate within U.S. laws to make sure it is safe and effective," Chip Zimlik, PhD, chair of the FDA's critical path initiative on the closed-loop device said. Last week, the agency released guidance for how to develop a low glucose suspend system, an automatic shut-off mechanism used with an insulin pump. Medtronic already sells pumps with this feature in Europe. It safeguards against a dangerous drop in glucose levels by temporarily halting insulin delivery.

By year-end, FDA plans to release detailed guidance on more complicated closed-loop systems, Zimlik said. "We think of this system, the artificial pancreas, as one unit. There is going to have to be agreement among various companies to determine who is the reporting party for submitting it," he said.

"That is a relatively new idea with respect to these systems." Zimlik, who is a type 1 diabetic, thinks the first approved devices will be ones that deliver insulin only, but he is very encouraged by the system being developed by the team at Boston University and Massachusetts General. "They have what I call the Cadillac of closed-loop systems," he said. In addition to delivering insulin, the device also delivers an infusion of glucagon. "They are showing some very promising results," he said.

Presented at the ADA 71st Scientific Sessions 2011

ADA: Preventive Efforts in Type 2 Diabetes Are Cost Effective

[Diabetes in control](#)

Preventive treatment with metformin or lifestyle intervention in patients with type 2 diabetes reduced the cost of medical care, including costs for inpatient and outpatient care and prescriptions, compared with placebo....

William H. Herman, MD, MPH, professor of medicine and epidemiology at the University of Michigan, Ann Arbor, and coinvestigator of the Diabetes Prevention Program Research Group, and colleagues presented the findings in the late-breaking session here at the American Diabetes Association (ADA) 71st Scientific Sessions.

In the DPP, overweight and obese participants with impaired glucose tolerance were randomly assigned to lifestyle intervention, metformin, or placebo. Previous results, reported in 2002, indicated that lifestyle intervention led to a 58% reduction in the development of diabetes, from about 11% per year to about 5% per year. By comparison, metformin resulted in a 31% reduction in the development of diabetes.

These findings indicate that treatment with metformin or lifestyle intervention reduced the cost of medical care by \$1700 and \$2600 per person, respectively, over 10 years, compared with placebo. However, lifestyle intervention cost more to administer than metformin or placebo, so when the reductions in the cost of medical care were balanced against the cost of the interventions, metformin saved \$30 per person, whereas the lifestyle intervention cost \$1500 per person over the 10-year period.

The lifestyle intervention aimed for a 7% reduction in body weight and the goal of 150 minutes per week of moderate-intensity activity. The lifestyle intervention was found to halve the number of people who progressed to diabetes, compared with the metformin intervention.

The lifestyle intervention also improved quality of life, compared with metformin or placebo. When cost of care and measures of health and quality of life were considered simultaneously, both interventions were found to be highly cost effective.

These study findings put “diabetes prevention in the category of prenatal care or pediatric immunizations,” noted Dr. Herman in an ADA release. “It’s dramatic when an intervention can improve the health of the population and potentially save money at the same time,” he added.

“The DPP has shown that lifestyle intervention and metformin can decrease the epidemic of diabetes that is currently affecting the United States and much of the world and, in doing so, may save money,” noted David M. Nathan, MD, DPP chair and professor of medicine at Harvard Medical School, Boston, Massachusetts. “The cost savings may seem modest now, but any decrease in medical costs is welcome, and the savings may very well increase in the future.”

According to the researchers, healthcare and societal policies should support the use of lifestyle intervention and metformin to prevent or delay diabetes.

American Diabetes Association (ADA) 71st Scientific Sessions: Abstract 0136-LBOR. Presented June 28, 2011.

ADA: Liraglutide Shows Potential as Treatment for Weight Loss

[Diabetes in control](#)

Liraglutide, recently approved in the United States for the treatment of type 2 diabetes, has demonstrated its potential as a weight-loss drug for nondiabetic, obese patients....

At the American Diabetes Association 71st Scientific Sessions, investigators reported the results from the SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in Non-Diabetic and Diabetic Subjects) study. Not only was the weight loss that was required for initial randomization to therapy maintained, but further weight loss out to 56 weeks was achieved by patients receiving the drug.

“This trial had 2 phases,” explained SCALE’s lead investigator, Thomas A. Wadden, PhD, professor of psychology in psychiatry at the University of Pennsylvania School of Medicine, and director of the Center for Weight and Eating Disorders, in Philadelphia. “Patients had to participate in a run-in period, where they consumed only 1200 to 1600 calories a day, with a target weight loss of 5% from baseline.” After a run-in period of 4 to 12 weeks, patients were randomized to active treatment, titrated in increments of 0.6 mg liraglutide per/week, to a total of 3 mg, or to placebo (n = 422).

“The reason that the 3 mg dose was chosen, rather than the usual 1.8 mg used in diabetes, is that this dose was found by Rössner and colleagues to have greater efficacy for weight loss.” (Lancet. 2009;374:1606-1616).

The study looked at 3 coprimary end points: the proportion of patients who maintained full run-in weight loss; the proportion of patients who achieved further weight loss after randomization; and the proportion of patients who lost 5% of their weight or more after randomization.

At baseline, the average age of the SCALE patients was 46 years, average weight was 106 kg, and average body mass index (BMI) was 38 kg/m². “It was striking that this study had about one third of patients with a BMI greater than 40 kg/m²,” said Dr. Wadden. “This reminds us of the growing need to find options for heavier patients who are often now thought not to be able to respond to treatment.” He went on to point out that the vast majority of patients enrolled in SCALE were female (82%), and that this is typical of weight-loss studies. Roughly one third of patients had hypertension, but otherwise the patients were relatively healthy.

After an average run-in weight loss of 6%, more patients in the liraglutide group than in the placebo group maintained the run-in weight loss 56 weeks after randomization (81% vs 49%).

Furthermore, liraglutide induced an additional average reduction in weight of 6.1% after randomization, with the majority of these patients losing at least 5%; there was no additional effect in the placebo group. “This is the biggest surprise to me as an obesity researcher. I did not think we would see additional weight loss,” said Dr. Wadden. “I just thought we would see maintenance.”

Reported rates of adverse events were comparable between groups, with a higher than expected rate of subject retention; 25% in the liraglutide group and 31% in the placebo group withdrew from the study. “Dropout rates of 40% at 1 year are not uncommon in weight-loss trials, he explained.

The most common adverse event for liraglutide was nausea (48% of patients). “The important thing about nausea is that patients experience this when you are introducing the drug during the first 4 to 5 weeks of titration, but thereafter it resolves.”

Importantly, given the recent history of weight-loss agents, there were no psychological events reported, no suicidal ideation, and no major depression.

Liraglutide Works, But How?

Liraglutide appears to be acting on a couple of different mechanisms,” explained Dr. Wadden. “There seems to be decreasing gastric emptying, which is associated with improved satiety and decreased intake . . . and it may be operating in the caudal brain stem.” This would make sense for a GLP-1 agent, and would thereby increase satiety, he said.

Eva Tomas-Falco, PhD, instructor in medicine in the division of endocrinology at the Massachusetts General Hospital, Boston, has her own ideas. “I’m very interested in this because we have found in our own studies that when we infuse with GLP-1-like peptides, we also see an effect on body weight. However, you can relate that change to an increase in energy expenditure. Unfortunately, the SCALE study didn’t look at that.”

She is further intrigued because of the great need. “This is pretty much the only [agent] right now that is not only safe for affecting glucose homeostasis, but has this additional property of lowering body weight in obese individuals.”

She did raise one note of caution regarding the drug’s general use. “What we’re looking at here is patients with visceral fat (who often progress to diabetes). For those who are so-called ‘fit obese,’ this probably won’t work.” The mechanisms at work in SCALE’s weight loss, Dr. Tomas-Falco reasoned, would not apply.

American Diabetes Association (ADA) 71st Scientific Sessions: Abstract 1859-P. Presented June 25, 2011.

ADA: ACTID Results Emphasize Diet Alone Over Diet and Exercise

[Diabetes in control](#)

Intensive dietary intervention and dietary intervention combined with an increase in moderate activity were both superior to usual care in a real-world comparison of diabetic patients in the first 6 months after being diagnosed....

Full results of the ACTID study have been published simultaneously in *The Lancet*.

Despite expectations, the addition of exercise to diet provided no additional benefit over diet alone, said lead ACTID investigator, Robert C. Andrews, MB, ChB, PhD, and who is senior lecturer at the University of Bristol, United Kingdom.

“Our study aimed to add to evidence from previous studies that people who exercise or stick to a diet get improvement in their diabetes control. Ours differs in that no one has gone out and done a real-world trial in which they’ve taken all comers.” Nor has diet, with or without exercise, been previously compared in this population, Dr. Andrews noted.

In the ACTID trial, 593 patients in the early stages of type 2 diabetes were randomized to 1 of 3 groups: usual care -- which consisted of a standard, brief education session that offered dietary and exercise advice, with follow-ups at 6 and 12 months; diet alone -- which involved far more detailed dietary information, with more time spent with the patient per visit, and follow-ups at 3, 6, 9, and 12 months; and diet plus exercise -- which involved detailed dietary information and an additional focus on increasing the amount of activity, in this case walking, to at least 30 minutes a day, 5 days a week. Patients in the diet plus exercise group were given motivational literature, a pedometer, and a diary to record daily activity.

The primary end point of the ACTID study was improvement in glycosylated hemoglobin (HbA_{1c}). Study results were reported for 6-month and 1-year time points.

“If you were in the usual care arm, during the first 6 months your diabetes control worsened, whereas in the diet alone and the diet and exercise arms, it got slightly better,” said Dr. Andrews. After 6 months, and according to study protocol, patients were treated to an HbA_{1c} target of 7.5%; again, the usual care group did significantly worse than the other 2 groups ($P = .0001$). Surprisingly, there was no difference between the diet alone and the diet plus exercise groups ($P = .6$).

This initial finding was replicated for the study’s secondary end points of weight loss, insulin resistance, and the amount of medication used to control blood sugar at 1 year. Again, the usual care group fared consistently worse than the other 2 groups; the diet alone and the diet plus exercise groups had beneficial outcomes virtually identical to each other.

“Obviously, the question is: why did we not get an increase [in benefit] with additional activity?” Dr. Andrews said.

One possibility is that the activity chosen, walking, was suboptimal. “A study by Church in *JAMA* [2010;304:2253-2262] suggested that if you do resistance or aerobic exercise alone, you don’t get significant improvement. You have to do a combination.” Alternatively, activity itself might be the wrong focal point. After “comparing activity and waistline circumference at baseline,” Dr. Andrews explained, “we found that waist circumference was not so much related to the amount of moderate activity you had been doing, but to the amount of time you spend doing absolutely nothing -- what’s

called 'sedentary time'." This suggests that it's better to concentrate on changing your patient's sedentary time rather than insisting on more moderate activity, he said.

Dr. Andrews offered one other possible explanation, which he calls "trading." He explained that "after interviewing patients, we found that those in the diet and exercise arm admitted that if they knew they were going to the gym, they could have something extra, some treat just before, and then work out just a bit harder."

Regardless of the reason, Dr. Andrews suggested that the true utility of the results is to stress that in these times of budgetary constraint, diet alone is a legitimate first-line approach to diabetes control. He added that the ACTID program itself was cost effective, and estimated that the savings realized by avoiding the use of diabetes medications covered the cost of the interventions required by those receiving usual care over 1 year.

ADA Attendees Puzzled But Impressed

Commenting at a press briefing during which the ACTID results were highlighted, Sue Kirkman, MD, senior vice president of medical affairs and community information for the ADA, suggested that listeners focus on the big picture.

"I did find it a little surprising that there was no additional benefit of exercise. Perhaps people didn't adhere as well to the diet, or perhaps the diet approach is so powerful at the beginning that exercise doesn't add that much," Dr. Kirkland noted. "But the overall results -- that both lifestyle arms had such obvious benefit -- were no surprise. If you compare the evidence from prediabetes studies, for example, you see that changes in lifestyle, say with modest weight loss, or moderate exercise provide these benefits as well."

Dr. Andrews added, "We're not saying that exercise isn't useful, it simply didn't improve the parameters that we measured. There is clear evidence out there that individuals who exercise have reduced rates of cancer, reduced mortality, and other benefits from exercising, such as enhanced sense of well-being." Include exercise if you can, but dietary change should be the focus of your lifestyle intervention, he emphasized.

Presented at the ADA 71st Scientific Sessions, June 2011 Lancet. Published online June 25, 2011.

ADA: Insulin Pump Suspend Feature Halts Hypoglycemia

[Diabetes in control](#)

Insulin pumps that automatically shut down when blood glucose hits a certain low level decrease the amount of time pediatric patients spend in hypoglycemia....

Sensor-augmented pump therapy with a low glucose suspend mechanism, which shuts the device off when blood sugar levels dip below 70 mg/dL, halved the time patients were hypoglycemic, Thomas Danne, MD, of Hanover Medical School in Germany, and colleagues reported at a scientific session at the American Diabetes Association meeting. "It does work, and it significantly reduces rates of hypoglycemia," Danne said, adding that he believes the technology "is ready for prime-time."

Low glucose suspend technology sounds an alarm when patients appear to be descending into low blood sugar. Patients can respond and turn the alarm off; if they don't, the pump will shut down for two hours, Danne explained, then resume infusion for another four hours. In some cases, after or during that time, patients may have another two-hour cycle of suspension, he said.

Low glucose suspend is an early incarnation of the artificial pancreas, according to Chip Zimlik, PhD, chair of the FDA's critical path initiative on the closed-loop device. It's used with sensor-augmented pump therapy, which lacks a control algorithm -- the hallmark of the artificial pancreas system -- that automatically deploys or withholds insulin on an as-needed basis.

Thus, the patient still controls the insulin dose. Still, having an automatic shut off could potentially be incorporated into a closed-loop system.

The FDA recently released a draft guidance on low glucose suspend technology, which will be followed up by a guidance on two other incarnations of the artificial pancreas: control-to-range and control-to-target, Zimlik said. The goal is to establish unified targets for bringing these devices to market faster, he said.

For their study, Danne and colleagues enrolled 24 patients with type 1 diabetes, whose median age was 10.8 years. Patients were given two weeks of pump training, followed by five weeks of use of the pump with the low glucose suspend function turned on.

Danne said there were more alerts during the day than during the night (76% versus 24%), but there were more shutdowns overnight (84% versus 16%) and that's because patients turn off the devices when the alarm sounds and manage their condition.

"As you may imagine, the patient responds and it's not likely that you'll have the 120-minute suspension during the daytime," Danne said.

When the device did shut down, glucose levels did become elevated, rising a mean of 68.4 mg/dL or about 35 mg/dL per hour.

There were no differences in mean glucose concentrations, glycemic variability, or time spent in the high glucose region with and without the low glucose suspend technology activated.

"There's no risk that you'll lose your good glycemic control by having the low glucose suspend," Danne said. But they did find significant differences in hypoglycemic excursions and time spent in the low glucose region. Time in hypoglycemia fell 50% ($P=0.002$), Danne said.

There were also fewer glucose values below 40 mg/dL when the low glucose suspend technology was turned on.

Danne added that there were no cases of diabetic ketoacidosis, and the device received good rates of patient-reported satisfaction.

William Tamborlane, MD, of Yale School of Medicine in New Haven, Conn., who moderated the session during which the findings were presented, said suspending only when patients reach 70 mg/dL will still lead to hypoglycemic excursions, largely because of a well-known caveat that interstitial sampling doesn't necessarily concur with serum glucose levels. On the other hand, Robert Henry, MD, chief of medicine and science for the ADA, said the 70 mg/dL level is close to the right range, but varies depending on the patient. Even non-diabetic patients can have excursions below that level and be fine, so it may end up being over-responsive, he said.

Tamborlane also pointed out that a closed-loop system would also be able to prevent hyperglycemia, especially during exercise when kids tend to turn their pumps off. During that time, Tamborlane noted, patients can consume a sports drink or other carbohydrate-filled drinks.

Tamborlane pointed out that a device that automatically kicks back into action when needed would be a great benefit. "Having a system that can kick in and also prevent high blood glucose might be a more rational approach than hoping the system will just shut down," he said.

Practice Pearls:

- ◆ Explain that insulin pumps that automatically shut down when blood glucose hits a certain low level decrease the amount of time pediatric patients spend in hypoglycemia.
- ◆ Note that there were no differences in mean glucose concentrations, glycemic variability, or time spent in the high glucose region with and without the low glucose suspend technology activated.

Danne T, et al "The low glucose suspend function in sensor-augmented pump therapy prevents hypoglycemia in children" ADA 2011; Abstract 0150-OR.

ADA: Diabetes Patients Lead Peers to Healthier Status

[Diabetes in control](#)

Training people with diabetes to teach other patients improves utilization of medications and results in lifestyle changes....

Garry Tobin, MD, associate professor of medicine at Washington University and director of the Diabetes Center at Barnes Jewish Hospital, St. Louis stated that patients enrolled in the Diabetes Network of St. Louis achieved a reduction in glycosylated hemoglobin A1c (HbA1c) from 7.38% at baseline to 7.18% ($P=0.001$) after two years of the program.

Dr. Tobin said, "The most important resource in my practice is not my colleagues or other physicians, it is the patients we have in our center."

"We have patients who have had diabetes 50 years and that experience has been able to make them successful in controlling their disease, and this gives them the opportunity to go back out into the community and be successful in helping other people," he said.

The use of the unpaid, volunteer group leaders had measurable success among the 186 patients who agreed to be part of the study. Overall, more than 400 people -- the large majority of whom had type 2 diabetes -- took part in the activities of the 45 groups of patients that attended meetings at 34 sites, said co-investigator Eric Armbrecht, PhD, assistant professor of medicine at St. Louis University.

After two years, in addition to improvement in HbA1c, the researchers reported:

- ◆ Average systolic blood pressure fell three points, from 141 mm Hg to 138 mm Hg ($P=0.026$).
- ◆ Average diastolic blood pressure fell from 78.2 mm Hg to 76.6 mm Hg ($P=0.046$).
- ◆ Average body mass index fell from 34 kg/m² to 33.7 kg/m² ($P=0.025$).

The researchers also demonstrated that blood glucose monitoring increased, consumption of fruits and vegetables increased, and physical activity increased among patients who started the trial with HbA1c greater than 8%.

Armbrecht said the volunteers go through a specific training program that is done in partnership with the Washington University Diabetes Center at Barnes Jewish Hospital.

"Volunteers have about a 25- to 30-hour course of training to prepare them to lead a group of peers that meets in a community setting," he explained. In the St. Louis program, the doctors selected patients they thought would be good group leaders. "The sessions have different topics to focus the conversation, but in each session, one of the common discussion points is an assessment of goal-setting, progress, and a lot of group support."

Martin Abrahamson, MD, associate professor of medicine at the Joslin Clinic/Harvard Medical School, Boston, said, "We think that these programs should go out into the community. We are looking into doing similar programs among our patients."

David Kendall, MD, chief scientific and medical officer at the American Diabetes Association stated that, "These patients reduced their HbA1c, their body mass index didn't go up, their blood pressure went down, they ate better, they did more monitoring." "I think this is additional encouraging evidence that integrating diabetes care support into the community setting at low cost with limited

resources has additional beneficial effects. Given the size of the diabetic epidemic, additional delivery approaches are going to be essential.”

Practice Pearls:

- ◆ Explain that an education program using unpaid volunteers with diabetes as leaders resulted in improved HbA1c in patients who attended the program.
- ◆ Note that blood pressure, BMI, diet, physical activity, and monitoring of blood glucose all also improved following the peer education program.

Presented at the ADA 71st Scientific Sessions, 2011

ADA: Vascular Status Predicts Hypoglycemia

[Diabetes in control](#)

Type 2 diabetes patients with microvascular or macrovascular complications, or those taking certain monotherapies, are more likely to experience hypoglycemia and require outpatient hospital visits....

Jason C. Simeone, PhD, from the University of Rhode Island College of Pharmacy in Kingston, stated that, "The risk of experiencing a hypoglycemic episode was notably higher among patients on insulin monotherapy when compared with patients not taking any anti-diabetes medicine."

"Medications should be carefully chosen for patients at high risk of hypoglycemia, particularly those with microvascular or macrovascular complication, or those taking insulin, meglitinides, or sulfonylureas."

Simeone and his co-researcher, Brian J. Quilliam, PhD, also from the University of Rhode Island College of Pharmacy, scrutinized pharmacy and medical claims from the 2004-2008 MarketScan database, eventually identifying 11,375 cases of type 2 diabetes patients who experienced hypoglycemic events that involved a hospital visit. They compared outcomes in those patients with 68,247 controls.

All patients were over 18-years-old, had type 2 diabetes, were taking an oral antidiabetic drug at entry, and had at least 12 months enrollment in a non-capitated health plan.

After adjusting for clinical factors, the researchers found the following predictors of an outpatient visit for a hypoglycemic event:

- ◆ A microvascular diabetic complication, AOR 1.78 (CI 1.68-1.89)
- ◆ A macrovascular diabetic event, AOR 2.80 (CI 2.64-2.97)
- ◆ Liver disease, AOR 1.54 (CI 1.29-1.82)
- ◆ Insulin plus any oral anti-diabetic agent, AOR 1.91 (CI 1.75-2.09)
- ◆ Meglitinide monotherapy, AOR 1.40 (CI 1.02-1.93)
- ◆ Metformin plus sulfonylurea plus thiazolidinedione, AOR 1.37 (CI 1.24-1.50)
- ◆ Sulfonylurea monotherapy, AOR 1.16 (CI 1.06-1.26)
- ◆ Metformin plus sulfonylurea, AOR 1.13 (CI 1.05-1.22)

In addition, Simeone pointed out that women appeared at greater risk for hypoglycemia compared with men. Older patients (age 50-59) had the lowest odds of hypoglycemia compared with younger patients.

"We found that thiazolidinedione monotherapy, metformin monotherapy, and metformin plus thiazolidinedione combination therapy were protective against having hypoglycemic episodes," Simeone said.

The researchers also determined that patients who were taking medications for other comorbidities were also at increased risk of hypoglycemia. They found significant relationships between the episodes and patients taking trimethoprim, fluoroquinolones, benzodiazepines, warfarin, non-steroidal anti-inflammatory drugs, and fibrates.

Simeone suggested, "Physicians should monitor hypoglycemic events and educate patients with these risk factors." "Alternative medications should be chosen if available for high-risk patients."

Robert Henry, MD, president of medicine and science for the ADA, agreed with Simeone, explaining that, "We try to avoid use of sulfonylureas and secretagogues among patients at risk of hypoglycemia."

The researchers noted that there appeared to be different risks of hypoglycemic events by region, with the highest risks in the southern U.S. and west U.S., and the lowest risks in the Midwest. However, the adjusted analysis did not find that any of those differences reached statistical significance.

Simeone said he undertook the project because data on the risk of hypoglycemia among type 2 diabetes patients on oral medications is lacking even though hypoglycemia is a well-recognized problem in patients with type 1 diabetes, and insulin-treated patients with type 2 diabetes, he said.

Practice Pearls

- ◆ Explain that type 2 diabetes patients had higher odds of needing outpatient care for hypoglycemia if they had micro- or macrovascular complications or were taking insulin.
- ◆ Point out that the study used the 2004-2008 MarketScan database of pharmacy and medical claims.

Simeone J, et al "Predictors of outpatient visits for hypoglycemia in type 2 diabetes patients on oral antidiabetic agents" Diabetes 2011; 60 Supplement (1) A137.

ADA: Even Diet Soda Induces Weight Gain in the Elderly

[Diabetes in control](#)

The perception that diet soft drinks are a benign alternative to highly sweetened beverages might be dangerously wrong....

Diet soft drinks have long been thought to be a healthier alternative to their sugary counterparts; however, past reports have linked increased incidence of obesity, metabolic syndrome, and diabetes to the frequent intake of diet soft drinks.

Sharon P. Fowler, MPH, from the University of Texas Health Science Center at San Antonio, presented the results from the San Antonio Longitudinal Study of Aging. In the study, researchers examined the effect of the long-term consumption of diet soft drinks by a population of individuals 65 to 74 years of age (n = 474).

At baseline, measures of height, weight, and waist circumference were recorded, as was diet soft drink intake. Three additional exams of the study subjects were conducted over an average follow-up of just over 3.5 years (the study was conducted over a 9-year period).

When the results of these observations were compared with those from subjects who did not drink diet soft drinks, the differences were striking. Overall, consumers of diet soft drinks experienced a 70% greater increase in waist circumference than nonconsumers. Further, among elderly drinkers of 2 or more diet soft drinks per day, mean increases in waist circumference were 5 times greater than those recorded for nonconsumers.

“These results suggest that -- amidst the national drive to reduce consumption of sugar-sweetened drinks -- policies that promote the consumption of diet soft drinks may have unintended deleterious effects,” state the study investigators.

Previous work by Ms. Fowler has evaluated the negative effects of diet drinks (*Obesity [Silver Spring]*. 2008;16:1894-1900).

American Diabetes Association (ADA) 71st Scientific Sessions: Abstract 0062-OR. Presented June 25, 2011.

ADA: Intensive Therapy Yields Negligible Benefits in Type 2 Diabetes

[Diabetes in control](#)

In patients diagnosed with type 2 diabetes through screening in general practice, intensive multifactorial treatment improved cardiovascular risk factors, compared with usual care, new findings suggest, but those improvements were very small....

There was only a trend toward a reduction in mortality and cardiovascular events (including heart attack, stroke, and amputation) in intensively treated patients. The differences between usual and intensive care were not statistically significant, reported principal investigator Simon J. Griffin, DM, from the Medical Research Council Epidemiology Unit, Institute of Metabolic Science, in Cambridge, United Kingdom.

Findings from the ADDITION-Europe study were reported at a press briefing held to coincide with the American Diabetes Association (ADA) 71st Scientific Sessions; they were published online simultaneously in *The Lancet*.

According to the researchers, many “patients already have evidence of diabetic complications and potentially modifiable cardiovascular risk factors at the time of diagnosis,” and screening is considered to be an efficient use of resources in diabetes.

The objective of this study was to evaluate whether early intensive multifactorial treatment might improve outcomes, compared with usual care, if initiated soon after detection, by screening and before clinical diagnosis.

The study consisted of 3055 patients (mean age, 60 years) found to have type 2 diabetes on screening; 1377 received usual care and 1678 received intensive treatment. Intensive treatment consisted of usual care plus additional target- and guideline-driven management of hyperglycemia, blood pressure, and cholesterol levels by medical treatment, and the promotion of healthy lifestyles, based on the stepwise regimen used in the Steno-2 and other trials.

The study was conducted in Denmark, the Netherlands, and the United Kingdom. The same approach was used at all centers, although family physicians and patients made the final decisions about prescriptions and choice of individual treatments.

Patients were followed for a mean of 5.3 years. Intensive treatment was associated with slightly, but significantly, increased prescription of treatments and improvements in cardiovascular risk factors (blood pressure and levels of cholesterol and glycosylated hemoglobin [HbA_{1c}]).

The relative reduction in the incidence of first cardiovascular event was lower with usual care than with intensive care, indicating only a nonsignificant trend toward a reduction. Likewise, the incidence of all-cause mortality was lower with usual care, but the difference was not significant.

“Although there is no evidence of harm associated with screening and intensive therapy, the extent to which the complications of diabetes can be reduced by earlier detection and treatment remains unclear,” Dr. Griffin and colleagues note. “Differences were greatest for myocardial infarction and smallest for stroke,” they add.

During the first 2 to 3 years of follow-up, “the event rate was almost the same between the 2 groups, and then the differences started to magnify,” said Torsten Lauritzen, MD, from the

Department of General Practice, School of Public Health, Aarhus University, in Denmark, during the press briefing. “We are going to follow the patients for another 5 years. Hopefully we will see an increasing difference between the 2 groups.”

“One thing that strikes me about this study is how well the routine care group were treated,” said Sue Kirkman, MD, senior vice president of the ADA, in Alexandria, Virginia, during the press conference. “The fact that you didn’t see a significant difference might be because the routine care patients had excellent care, which would have minimized the difference between the 2 groups,” she said.

In a related comment, David Preiss, MRCP, and Naveed Sattar, MD, from the British Heart Foundation and the Glasgow Cardiovascular Research Centre at the University of Glasgow, United Kingdom, noted that the lipid-lowering and antihypertensive therapies now used in the standard care of patients with type 2 diabetes might have diminished the apparent benefit of intensive therapy observed in ADDITION-Europe.

“The key questions now are whether a sizeable reduction in the lead time between diabetes onset and clinical diagnosis can be achieved by implementation of simpler diagnostic criteria (i.e., HbA_{1c}) and, if so, to what extent this development might further reduce cardiovascular and mortality risks in patients with diabetes,” Drs. Preiss and Sattar note.

American Diabetes Association (ADA) 71st Scientific Sessions: Presented June 24, 2011.

ADA: Higher Vitamin D Levels Linked to Lower Diabetes Risk

[Diabetes in control](#)

Higher levels of vitamin D in the blood appear to be associated with a reduced risk for incident diabetes among people at high risk for the disease....

Anastassios G. Pittas, MD, from the division of endocrinology, diabetes, and metabolism at the Tufts New England Medical Center in Boston, Massachusetts, and colleagues presented the findings at the American Diabetes Association 71st Scientific Sessions.

According to Dr. Pittas, vitamin D might play a role in diabetes by improving insulin secretion and insulin sensitivity. "Most of the evidence focuses on a favorable effect in pancreatic beta cells."

To determine the relation between vitamin D status and risk for incident diabetes, the researchers analyzed data from the Diabetes Prevention Program (DPP), a 3-group trial comparing intensive lifestyle modification or metformin with placebo for the prevention of diabetes in patients with prediabetes.

The mean follow-up of the 2039-person cohort was 3.2 years. Plasma vitamin D levels were measured at yearly intervals, and subjects were assessed for incident diabetes. For this analysis, only participants in the intensive lifestyle and placebo groups of the DPP were considered.

Participants with vitamin D levels in the highest tertile had a hazard ratio of 0.74 for developing diabetes, compared with those with vitamin D levels in the lowest .

The findings also suggest a dose-dependent effect for vitamin D levels; the hazard ratio for incident diabetes was lowest in the people with the highest vitamin D levels (50 ng/mL or higher), compared with those with the lowest levels (below 12 ng/mL).

In a subgroup analysis by tertiles of vitamin D, the association was similar in the placebo group and the lifestyle group.

According to Dr. Pittas, "This study offers several methodological advantages over previous studies." Vitamin D status was assessed multiple times during follow-up, not just once at baseline, which might not reflect long-term vitamin D status.

"Our study also includes a large clinically relevant population at high risk for diabetes, with a substantial proportion of nonwhite participants, which improves the external validity of the results," he said. However, he added, "this is an observational study and therefore confounding cannot be excluded. It would be premature to recommend vitamin D specifically for prevention of diabetes."

"This prospective study confirms that there is an association between levels of vitamin D and risk of diabetes, even when correcting for body weight, with no absolute threshold of serum 25-hydroxy vitamin D," said independent commentator Clifford Rosen, MD, from the Jackson Laboratory in Bar Harbor, Maine. Dr. Rosen is a vitamin D researcher and member of the Institute of Medicine Committee that reviewed the evidence on calcium and vitamin D.

"The implications of this study relate to the importance of performing a randomized placebo-controlled trial of vitamin D for the prevention of type 2 diabetes in those at high risk." "In the

interim, clinicians should at least focus on maintaining vitamin D levels in high-risk individuals at or around 20 ng/mL," he added.

American Diabetes Association (ADA) 71st Scientific Sessions: Abstract 0117-OR. Presented June 25, 2011.

ADA: TAK-875 a Novel Agent in the Treatment of Type 2 Diabetes

[Diabetes in control](#)

Takeda Pharmaceuticals recently completed a Phase 2 study with its novel anti-diabetic agent TAK-875, which could help lead to more individualized patient care and diabetes management....

TAK-875 is a selective agonist of GPR40, a G-protein coupled receptor in the islet cells of the pancreas. The activation of GPR40 improves glucose-dependent insulin secretion from the beta cells with minimal hypoglycemia and an improved HbA1c. TAK-875 is thought to produce less hypoglycemia compared to other insulin secretagogues like sulfonylureas or incretin hormones.

Recently, the results from a Phase 2 randomized, double-blind, placebo- and active comparator-controlled, parallel-group, multicenter study evaluating the efficacy, safety, and tolerability of five doses of TAK-875 delivered promising results in favor of the novel agent. When compared to placebo, all doses of TAK-875 produced a statistically significant drop in HbA1c. When compared to the active-control, glimepiride, the 50 mg dose of TAK-875 produced the same reductions in HbA1c at 12 weeks. With a TAK-875 dose of greater than or equal to 25 mg, approximately 33-48% of the patients had an HbA1c less than 7% at week 12, and these results were similar to those of glimepiride. Hypoglycemia incidence was approximately equal between TAK-875 and placebo (2.3 vs. 3.3%), and was significantly lower compared to glimepiride (16.1%). Treatment-emergent events were higher with glimepiride, but in general there was minor discontinuation in any arm of the study that was attributed to adverse events.

TAK-875, with its novel mechanism of action, could lead to a breakthrough in management of type 2 diabetes, pending the results of its Phase 3 studies and market approval. With the development of novel agents, anti-diabetic therapy options are becoming more individualized and are no longer 'one size fits all'.

From: ADA 71st Scientific Sessions: Abstract 0134-LBOR. Presented June 28, 2011.

ADA: Restoring Visual Acuity in Diabetes with VEGF Inhibitor

[Diabetes in control](#)

The vascular endothelial growth factor (VEGF) inhibitor ranibizumab (Lucentis) proves promising in treating diabetic macular edema....

According to the analysis of data from the RIDE and RISE trials, intravitreal injections of ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor, doubled or tripled the proportion of patients with diabetic macular edema who experienced improved visual acuity (as evidenced by regaining three lines on the eye chart) compared with placebo. Standard of care in diabetic macular edema has traditionally been laser photocoagulation, which stabilizes vision but doesn't necessarily restore visual acuity.

In more than 60% of patients treated with ranibizumab, vision improved from the baseline average of 20/80 to 20/40, the visual acuity needed to drive.

Patients received 24 months of intravitreal injections with placebo or ranibizumab and were eligible to receive rescue laser treatments at three months. The rescue treatments used to stabilize vision were used by three quarters of patients treated with placebo, but only in approximately 20-40% of those patients treated with ranibizumab.

Prior studies from the Diabetic Retinopathy Clinical Research Network have also found ranibizumab to be effective in improving visual acuity. The RIDE and RISE trials were designed to elicit FDA approval of ranibizumab for an indication of DME.

Patients treated with ranibizumab also experienced improvement in function, as they scored higher on the National Eye Institute Visual Function Questionnaire compared to those treated with placebo. Improvements were also seen in central foveal thickness, as well as lessening severity of diabetic retinopathy.

Treatment with ranibizumab injections can be costly and are often not covered by insurance. Clinicians have been extrapolating the results to another, more cost-effective anti-VEGF drug bevacizumab (Avastin) based on the results from the CATT study which found that bevacizumab and ranibizumab blocked the same isoform of VEGF.

ADA 71st Scientific Meeting (132-LBOR); June 28, 2011

ADA: Vascular Status Predicts Hypoglycemia

[Diabetes in control](#)

Type 2 diabetes patients with microvascular or macrovascular complications, or those taking certain monotherapies, are more likely to experience hypoglycemia and require outpatient hospital visits, researchers said. The risk of experiencing a hypoglycemic episode was notably higher among patients on insulin monotherapy when compared with patients not taking any anti-diabetes medicine. After adjusting for clinical factors, the researchers found the following predictors of an outpatient visit for a hypoglycemic event: a microvascular diabetic complication, a macrovascular diabetic event, liver disease, insulin plus any oral anti-diabetic agent, Meglitinide monotherapy, Metformin plus sulfonylurea plus thiazolidinedione, Sulfonylurea monotherapy, or Metformin plus sulfonylurea. Simeone J, et al "Predictors of outpatient visits for hypoglycemia in type 2 diabetes patients on oral antidiabetic agents" Diabetes 2011; 60 Supplement (1) A137.

ADA: Tiny Pump Helps Improve Glycemic Control

[Diabetes in control](#)

A matchstick-sized implantable subcutaneous pump that delivers a steady flow of the GLP-1 agonist exenatide (Byetta) maintained improvements in glycemic control over a year, researchers said. The purpose is to increase adherence, while offering greater efficacy and reduced side effects. The pump has to be inserted every three months, but in future studies they hope to expand that to six to 12 months. The device is small and easy to insert and remove. Rosenstock J, et al "Long-term, injection-free treatment with ITCA 650, continuous subcutaneous delivery of exenatide via DUROS device, leads to sustained improved glycemic control and weight loss for 48 weeks in metformin-treated type 2 diabetes" ADA Meeting 2011; Abstract 135-LBOR.

ADA: Public Knows about Diabetes, Yet Takes No Action

[Diabetes in control](#)

Americans are well informed about the risks, dangers, and signs of diabetes, but that knowledge does not appear to translate into actions to prevent or control the disease, researchers reported. Almost 87% of the 3,867 type 2 diabetes respondents in a huge national sampling knew that obesity contributes to chronic disease; more than 75% were aware that type 2 diabetes was as dangerous to health as type 1 diabetes; and 90% were aware that diabetes is more than just a “sugar” disease. Only 57.3% of the people at high risk of developing type 2 diabetes who filled out 8-page questionnaires on health and lifestyle practices said they were even “considering” a plan to lose weight. That’s despite only 23.4% of the people surveyed saying they considered their health excellent; 17.2% of the high-risk cohort said they would rather take medication than change their lifestyle -- about twice the 8.8% of low risk people in the survey who said they would rather look for a silver bullet in a pill bottle than lose weight and exercise. Only 56.3% of those at high risk remembered their doctor advising them to do something about changing their diet. The results for exercise were just as dismal. Green A “Final Results of the SHIELD Study -- Epidemiologic and public policy considerations from a five-year prospective diabetes mellitus study” ADA 2011; P. 146

NC-stat – DPNChek

[Diabetes in control](#)



DPNChek

Fast, accurate and quantitative test that may be used to evaluate peripheral neuropathies such as DPN. It may aid in the early detection, confirmation, and monitoring of DPN. It measures sural nerve conduction velocity - a standard biomarker for subclinical and symptomatic DPN. It is sensitive and specific for DPN, and predictive of its complications. Compact and ergonomic hand-held device designed for ease-of-use with straightforward clinical interpretation

Worst Cocktails for Blood Sugar

[Diabetes in control](#)



Do you know how your favorite libation ranks?

Which are the lowest-carb libations? For people with diabetes, drinking alcohol can be a tricky exercise. Alcohol itself causes blood sugar to drop, but the things people mix with their spirits have widely varying amounts of carbs. So it's hard to know where your blood sugar levels will end up.

People are often surprised by the carb counts of common cocktails. Read on to see what you know. [Follow this link for the Worst Cocktails for Blood Sugar \(pdf\).](#)

ADA: Safety and Efficacy of Once-Monthly Exenatide over 20 Weeks in Patients with Type 2 Diabetes

[Diabetes in control](#)

Exenatide, a GLP-1 receptor agonist, improves glycemic control and body weight with twice daily or once weekly subcutaneous (SC) injections in patients with type 2 diabetes (T2DM)....

A new formulation, exenatide suspension, uses the extended-release microspheres of exenatide once weekly (ExQW) with a triglyceride-based diluent that enables delivery of higher doses with less frequency. The safety and efficacy of 3 monthly doses of exenatide suspension (ExQM; 5, 8, or 11mg SC) or ExQW (2mg) as a reference arm, were assessed in a randomized, open-label, controlled study in 121 patients (36%F, 50±10y, WT 97±19kg, A1C 8.5±1.2%, FPG 185±45mg/dL, diabetes duration 6±5y, mean±SD) with T2DM treated with diet/exercise, metformin (MET), pioglitazone (PIO), or MET+PIO. Across 20wks, patients received 5 monthly ExQM injections or 20 weekly ExQW injections, with high patient retention (94%). Sustained plasma levels were achieved with all ExQM doses.

Greater peak to trough variability was observed with ExQM than ExQW, however mean trough concentrations remained within the therapeutic range with all ExQM doses. The 2 highest ExQM doses achieved levels similar to ExQW. As with ExQW, ExQM approached undetectable levels 8wks after last injection. A1C, FPG, and WT were substantially improved with all doses of ExQM and were comparable to ExQW (Table). Evaluable and ITT results were comparable. No unique safety findings were observed with ExQM relative to ExQW. The most frequent AEs were: ExQM, headache (17-27%) and nausea (17-23%); ExQW, headache (30%) and diarrhea (27%) (ITT). No major or minor hypoglycemia was observed. One AE (vomiting/ExQM) led to withdrawal. There was no evidence of prolonged AE duration with ExQM or ExQW. ExQM was well-tolerated with robust improvements in glycemic control in patients with T2DM, supporting further development of the suspension formulation.

	N	Baseline A1C (%)	[Delta]A1C (%)	A1C [It]7% (Wk20)	[Delta]FPG (mg/dL)	[Delta]WT (kg)
ExQW (2mg)	29	8.6[plusmn]0.2	-1.5[plusmn]0.2	48%	-34[plusmn]9	-1.4[plusmn]0.6
ExQM (5mg)	26	8.4[plusmn]0.2	-1.3[plusmn]0.2	50%	-25[plusmn]8	-1.1[plusmn]0.8
ExQM (8mg)	28	8.6[plusmn]0.2	-1.3[plusmn]0.3	57%	-30[plusmn]10	-0.4[plusmn]0.6
ExQM (11mg)	27	8.4[plusmn]0.3	-1.5[plusmn]0.2	70%	-49[plusmn]9	-1.1[plusmn]0.7
Mean[plusmn]SE [Delta] from baseline to Wk20, Evaluable Population.						

Author(s): LEIGH MACCONELL, JARET MALLOY, WENYING HUANG, BRENDA CIRINCIONE, LARRY SHEN, LISA PORTER: Scientific Sessions Late Breaking Abstract Sunday, June 26, 2011 Abstract -46-LB

ADA: Exenatide/Diet vs. Diet Alone for Treatment of Prediabetes

[Diabetes in control](#)

Exenatide yields beta cell improvement and weight loss in individuals with diabetes but has not been well-studied in individuals with prediabetes....

We recruited healthy volunteers with BMI 25-37 kg/m² with prediabetes as defined by FBG 100-125 mg/dl or 2hr glucose 141-199 mg/dL on screening OGTT. Insulin-mediated glucose uptake was quantified with the modified insulin suppression test with steady-state plasma glucose concentrations (SSPG). Beta cell function was calculated using the insulinogenic index ($\Delta I/\Delta G$).

Subjects were randomized, double-blind, to exenatide (EX), 10 mcg BID, or placebo (P) for 30wks. All subjects took a hypocaloric diet with biweekly oversight by study dietitians for 18wk. During the last 12wks, no dietary counseling was provided.

We hypothesized that individuals assigned to EX would experience greater increase in insulin secretion, weight loss, and improved insulin sensitivity than the P group. 68 subjects were randomized and 10 dropped out. At baseline, subjects were NS different with regard to mean age, BMI(33 kg/m²), sex, SSPG, or insulinogenic index. EX and P subjects had lost 8.8 and 7.8% of initial body weight at 18wks and 8.9 and 8.1%, at 30wks respectively (NS between groups).

Despite reduction in insulin resistance, beta cell function increased in the EX group ($\Delta I/\Delta G$ 1.4 to 1.6). In the P group, beta cell function decreased (2.3 to 2.0) ($p=0.13$). Insulin resistance decreased significantly in both groups, and was correlated with weight loss ($r=0.46$, $p<0.01$). FBG decreased but was NS in both groups. 2hr glucose decreased significantly in both groups, reverting from IGT to NGT on average (NS between groups). Change in FBG was predicted by % weight loss, whereas change in 2hr glucose was predicted by change in insulinogenic index.

In conclusion, obese prediabetic subjects assigned to EX plus hypocaloric diet lose weight, improve insulin sensitivity, and revert from IGT to NGT. Insulin resistance and FBG decrease in proportion to weight loss, whereas 2 hr glucose decreases in proportion to insulinogenic index. Despite reduction in insulin resistance, beta cell function increased with EX, but not P. Otherwise, intensive dietary management alone appears to yield comparable results to EX plus diet.

Author(s): TRACEY MCLAUGHLIN, MARCIA PECK, NICOLE COGHLAN, CINDY LAMENDOLA, DANIELLE WEISS: ADA Scientific Sessions Late Breaking Abstract Sunday, June 26, 2011 Abstract -34LB

ADA: Linagliptin Has Similar Efficacy to Glimepiride but Improved Cardiovascular Safety over 2 Years in Patients with Type 2 Diabetes Inadequately Controlled on Metformin

[Diabetes in control](#)

Type 2 diabetes mellitus (T2DM) often requires combination therapy to maintain glycemic control. Adding a sulfonylurea to metformin therapy improves glycemic control, but can cause hypoglycemia and weight gain. This 2-yr double-blind trial investigated the long-term efficacy and safety of adding linagliptin or glimepiride to ongoing metformin to treat T2DM....

T2DM patients on stable metformin (≥ 1500 mg/d) for ≥ 10 weeks were randomized to linagliptin 5mg/d (N=764) or glimepiride 1–4mg/d (N=755) over 2 years. Efficacy analyses were based on HbA_{1c} change from baseline in the full analysis set (FAS) and per-protocol (PP) population. Safety evaluations included pre-specified, prospective, and adjudicated capture of cardiovascular (CV) events (CV death, non-fatal myocardial infarction or stroke, unstable angina with hospitalization).

Baseline characteristics were well balanced in the 2 groups (HbA_{1c} 7.7% for both). In the PP population, adjusted mean (\pm SE) HbA_{1c} changes from baseline were -0.4% ($\pm 0.04\%$) for linagliptin 5mg/d vs. -0.5% ($\pm 0.04\%$) for glimepiride (mean dose 3mg/d). Mean between-group difference was 0.17% (95% CI, 0.08-0.27%; $p=0.0001$ for noninferiority). Similar results were observed in the FAS population. Far fewer patients experienced investigator-defined, drug-related hypoglycemia with linagliptin than glimepiride (7.5% vs. 36.1%; $p<0.0001$). Body weight was decreased with linagliptin and increased with glimepiride (-1.4 kg vs. $+1.3$ kg; adjusted mean difference, -2.7 kg; $p<0.0001$). CV events occurred in 13 (1.7%) linagliptin patients vs. 26 (3.4%) glimepiride patients revealing a significant 50% reduction in relative risk for the combined CV endpoint (RR, 0.50; 95% CI, 0.26–0.96; $p=0.04$).

In conclusion, when added to metformin monotherapy, linagliptin provides similar HbA_{1c} reductions to glimepiride but with less hypoglycemia, relative weight loss, and significantly fewer adjudicated CV events. A long-term outcomes study (CAROLINA; NCT01243424) is ongoing to confirm the promising CV safety data seen with linagliptin to date. [ClinicalTrials.gov, NCT00622284]

Author(s): BAPTIST GALLWITZ, BARBARA UHLIG-LASKE, SUDIPTA BHATTACHARAYA, SANJAY PATEL, HANS-JUERGEN WOERLE: ADA Scientific Sessions Late Breaking Abstract Sunday, June 26, 2011 Abstract -39-LB

ADA: Efficacy and Safety of Lixisenatide Once-Daily vs. Exenatide Twice-Daily in Type 2 DM Inadequately Controlled on Metformin (GetGoal-X)

[Diabetes in control](#)

This randomized, open-label, parallel-group, multicenter, 24-wk main treatment study, followed by a variable extension of at least 52 wk, compared the efficacy and safety of lixisenatide 20 µg QD and exenatide 10 µg BID in 634 T2DM patients insufficiently controlled on metformin ≥ 1.5 g/day (mean age 57.4 yr, diabetes duration 6.8 yr, BMI 33.6 kg/m², HbA_{1c} 8.0%) [NCT00707031]....

Stepwise dose increases were used in both groups to a maximum 20 µg/day. The primary objective was to demonstrate non-inferiority of lixisenatide vs. exenatide for HbA_{1c} reduction at Wk 24 (predefined non-inferiority margin 0.4%). Hereafter, the 24-wk main treatment period data are presented.

Lixisenatide QD achieved its primary endpoint of non-inferiority in HbA_{1c} reduction vs. exenatide BID (Table). Improvements in mean FPG and the % patients achieving HbA_{1c} <7.0% were comparable between groups (Table). Mean body weight significantly decreased from baseline: 94.5 to 91.7 kg with lixisenatide and 96.7 to 92.9 kg with exenatide. The proportion of patients with AEs and serious AEs was generally comparable between the lixisenatide and exenatide groups. Discontinuations due to AEs (mainly GI events) were 33 (10.4%) lixisenatide and 41 (13.0%) exenatide. Significantly fewer patients experienced symptomatic hypoglycemia with lixisenatide, with 6-fold fewer hypoglycemic events (Table). No severe episodes were reported.

Overall GI tolerability appeared better for lixisenatide vs exenatide, with fewer cases of nausea and vomiting (Table). More lixisenatide patients tolerated the target dose of 20 µg/day (93% vs.83% exenatide). In conclusion, as add-on to metformin, lixisenatide QD was non-inferior to exenatide BID at improving HbA_{1c}, but with less hypoglycemia, slightly less weight loss and better GI tolerability at Wk 24.

Parameter		Lixisenatide	Exenatide	
Mean baseline and 24-week changes in efficacy parameters (mITT population)		N=311	N=305	LS mean difference [95% CI]; p-value
HbA _{1c} (%)	Baseline±SD	7.97±0.82	7.96±0.77	0.17 [0.03 to 0.30] (non-inferior based on upper limit of 95% CI ≤0.4)
	LS mean±SE change from baseline	-0.79 ±0.05	-0.96±0.05	
Fasting plasma glucose (mg/dL)	Baseline±SD	175±37	174±41	4.1 [-0.9 to 9.4]
	LS mean±SE change from baseline	-22.0±2.1	-26.1±2.1	
Body weight (kg)	Baseline±SD	94.5±19.4	96.7±22.8	1.02 [0.46 to 1.58]
	LS mean±SE change from baseline	-2.96±0.23	-3.98±0.23	
Proportion achieving HbA _{1c} <7.0%	n (%)	143 (48.5%)	148 (49.8%)	p=NS
Safety parameters (safety population)		N=318	N=316	p-value
N (%) of patients with symptomatic hypoglycemia *		8 (2.5%)	25 (7.9%)	<0.05
N of hypoglycemic events		8	48	
N (%) of patients with nausea		78 (24.5%)	111 (35.1%)	<0.05
N (%) of patients with diarrhea		33 (10.4%)	42 (13.3%)	NS
N (%) of patients with vomiting		32 (10.1%)	42 (13.3%)	NS

*event with clinical symptoms with either plasma glucose <60 mg/dL or prompt recovery after oral carbohydrate administration if no plasma glucose measurement was available

Authors: JULIO ROSENSTOCK, DENIS RACCAH, LASZLO KORANYI, LAURA MAFFEI, GABOR BOKA, PATRICK MIOSSEC, JOHN E. GERICH- ADA Scientific Sessions Late Breaking Abstract Sunday, June 26, 2011 Abstract -33LB

ADA: CV Risk with Linagliptin in Patients with Type 2 Diabetes: A Pre-Specified, Prospective, and Adjudicated Meta-Analysis from a Large Phase III Program

[Diabetes in control](#)

The cardiovascular (CV) benefit of glucose lowering, particularly if too intensive, in type 2 diabetes mellitus (T2DM) is currently debated. Some modalities have even been reported, unexpectedly, to be associated with worse CV outcomes. To investigate the CV profile of the novel DPP-4 inhibitor linagliptin, a pre-specified meta-analysis of all CV events from 8 phase III randomized, double blind, controlled trials (≥ 12 weeks) was conducted....

CV events were prospectively adjudicated by a blinded independent expert committee. The primary endpoint of this analysis was a composite of CV death, non-fatal stroke, non-fatal myocardial infarction (MI), and hospitalization for unstable angina pectoris (UAP). Other secondary and tertiary CV endpoints were also assessed, including FDA-custom major adverse CV events (MACE).

Of 5239 patients included (mean baseline HbA_{1c} 8.0%) 3319 received linagliptin once daily (5 mg: 3159, 10 mg: 160) and 1920 comparator (placebo: 977, glimepiride: 781, voglibose: 162). Cumulative exposure (person yrs) was 2060 for linagliptin and 1372 for comparators. Overall, adjudicated primary CV events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving comparator. The hazard ratio for the primary endpoint was significantly lower for linagliptin vs. comparator and hazard ratios were similar or significantly lower with linagliptin vs. comparator for all other CV endpoints (TABLE). This is the first pre-specified, prospective, and independently adjudicated CV meta-analysis of a DPP-4 inhibitor in a large Phase III program. Although a meta-analysis, with distinct limitations, the data support a potential reduction of CV events with linagliptin. This hypothesis will be tested prospectively in CAROLINA, an ongoing outcomes trial.

	Linagliptin (n=3319)	Comparator (n=1920)	Hazard ratio Cox proportional model (95% CI)
Primary CV endpoint, n (%)	11 (0.3)	23 (1.2)	
incidence rate/1000 pt-yr	5.3	16.8	0.34 (0.16, 0.70)*
Secondary CV endpoints, incidence rate/1000 pt-yr			
CV death, stroke, or MI	4.8	14.6	0.36 (0.17, 0.78)*
All adjudicated CV events	12.6	23.4	0.55 (0.33, 0.94)*
FDA-custom MACE	4.3	13.9	0.34 (0.15, 0.75)*
Tertiary CV endpoints, incidence rate/1000 pt-yr			
CV death	1.0	1.5	0.74 (0.10, 5.33)
Non-fatal MI	2.9	5.1	0.52 (0.17, 1.54)
Non-fatal stroke	1.0	8.0	0.11 (0.02, 0.51)*
Transient ischemic attack	0.5	2.9	0.17 (0.02, 1.53)
Hospitalization for UAP	0.5	2.2	0.24 (0.02, 2.34)

*Significant lower Hazard ratio (upper 95% CI <1.0; p<0.05).

Authors: ODD-ERIK JOHANSEN, DIETMAR NEUBACHER, MAXIMILIAN VON EYNATTEN, SANJAY PATEL, HANS-JUERGEN WOERLE: ADA Scientific Sessions Late Breaking Abstract Sunday, June 26, 2011 **Abstract No:** 0030-LB