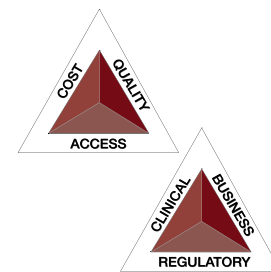


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AMERICAN HEALTH & DRUG BENEFITS®



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ADA 2010: PAYERS' PERSPECTIVES

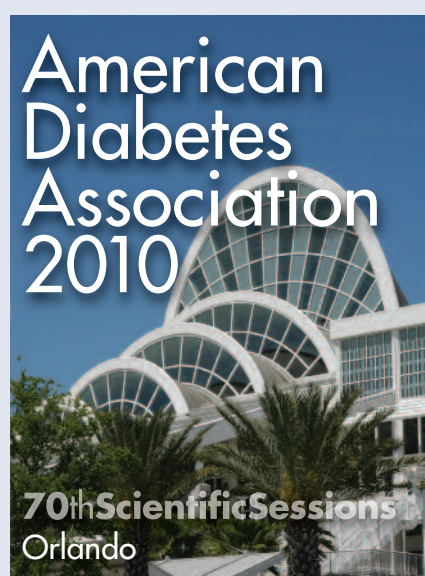
Incretin-Based Therapies Generate Excitement at ADA's Scientific Sessions

By Wayne Kuznar

The 70th scientific sessions of the American Diabetes Association (ADA), held in Orlando from June 25-29, 2010, featured more than 130 abstracts, plenary sessions, symposia, and debates about the merits of incretin-based therapies and their role in the management of type 2 diabetes.

These agents—which encompass 2 distinct classes, the glucagon-like peptide (GLP)-1 receptor agonists, available as injections, and the dipeptidyl peptidase (DPP)-4 inhibitors, taken orally—have demonstrated efficacy in lowering hemoglobin (Hb) A_{1c} levels, although the reduction in HbA_{1c} levels with the GLP-1 receptor agonists is greater.

Furthermore, unlike many other antidiabetes medications, the DPP-4 inhibitors have neutral effects on body weight, whereas the GLP-1 receptor agonists actually cause a reduction in body weight, a significant benefit for patients with diabetes. The risk for hypoglycemia is also low with these agents.



This supplement to *American Health & Drug Benefits* highlights topics of special interest to payers, focusing on the latest developments in approved and investigational incretin-based therapies and the cost of managing patients with diabetes and its associated complications.

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Estimated Lifetime Costs of Type 2 Diabetes: \$180,000 for Women, \$251,000 for Men

By Wayne Kuznar

The economic burden imposed by type 2 diabetes is substantial not only to the individual but to the health-care system and society, according to investigators from the Centers for Disease Control and Prevention (CDC),

Division of Diabetes Translation, Atlanta, GA, who presented data from their recent study at the ADA meeting.

Incidence-based cost estimates of type 2 diabetes, which are needed to evaluate the benefits of a diabetes pre-

Continued on page 3

Diabetes Screening of High-Risk People Is Cost-Effective

By Alice Goodman

Screening for diabetes in all high-risk persons—those with a high body mass index (BMI) and older individuals—would be cost-saving from a health plan perspective, according to a cost analysis of diabetes screening presented at the meeting.

“Screening is infrequently done, in part because it is not clear how best or whom to screen,” said lead investigator, Ranee Chatterjee, MD, clinical research fellow at Johns Hopkins, Baltimore, MD.

She and her colleagues screened for diabetes and prediabetes 1573 volunteers through the use of random plasma glucose and a finger prick test before and after a 1-hour 50-g oral glucose challenge. At a second visit, the subjects underwent testing for hemo-

globin A_{1c} and a standard 2-hour oral glucose tolerance test.

Costs were calculated over a 3-year period, in 2007 dollars, and included the cost of true-positives (treated with generic metformin and medical visits over 3 years) and the cost of false-negatives.

The prevalence of dysglycemia increased with increasing BMI:

- 12% of those with a BMI <25 kg/m²
- 24% with a BMI of 25 kg/m² to 35 kg/m²
- 35% of those with a BMI >35 kg/m².

The prevalence of dysglycemia also increased with increasing age. The 3 age categories investigated were <40 years, 40 to 55, and >55; the average age of the participants was 48 years.

Costs associated with screening the

Continued on page 3

Patients with Diabetes Willing to Pay Extra for Therapies that Help Reduce Weight, SBP, and Hypoglycemia

By Wayne Kuznar

A new pharmacoeconomic analysis presented at the ADA meeting shows that patients with type 2 diabetes are willing to pay more for an antidiabetic treatment that helps them reduce weight and blood pressure, when multiple treatment aspects are considered.

Researchers led by Johan Jendle, MD, PhD, Faculty of Health Sciences, Örebro University Hospital, determined that decreases in weight and systolic blood pressure (SBP) associated with liraglutide compared with glimepiride—as demonstrated in the

phase 3 Liraglutide Effect and Action in Diabetes (LEAD)-2 trial—were the primary drivers behind patients' willingness to pay a higher price to use liraglutide.

The researchers assessed patients' willingness to pay for liraglutide 1.2 mg versus glimepiride 4 mg by applying the 26-week results from LEAD-2 to a willingness-to-pay survey on patients' preferences taken by 461 Swedish patients with type 2 diabetes.

In LEAD-2, liraglutide 1.2 mg/day was compared with glimepiride 4 mg/day

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This supplement was made possible by funding from Novo Nordisk, Inc.

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This publication provides benefit design decision makers the integrated industry information they require to devise formularies and benefit designs that stand up to today's special healthcare delivery and business needs.

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Introduction: Incretin-Based Therapies... *Continued from page 1*

Potential CV Benefits with GLP-1 Agonists and DPP-4 inhibitors

The role of GLP-1 agonists and DPP-4 inhibitors in type 2 diabetes continues to evolve as more evidence is accumulated about these 2 classes, including the potential for cardiovascular (CV) benefits.

Data are beginning to emerge on the positive effect of incretin-based therapies on CV risk factors, an important consideration given the adverse CV risk associated with some oral antidiabetic drugs, such as rosiglitazone.

Specifically, Fonseca and colleagues found reductions in systolic blood pressure with liraglutide in patients with type 2 diabetes, and these reductions appeared to be independent of any antihypertensive drug therapy the patient may already have been receiving (page 6).

In a debate featured on page 9, Nauck and colleagues pointed out that in head-to-head clinical trials of DPP-4 inhibitors and sulfonylureas, the CV event rate was approximately 50% lower in patients treated with DPP-4 inhibitors compared with those receiving sulfonylureas.

In addition, in a 1-year study of once-weekly exenatide (page 7), sustained improvements in systolic blood pressure and the lipid profiles (particularly an increase in

high-density lipoprotein cholesterol levels) were observed with exenatide therapy once weekly.

Hypoglycemia

As Nauck and colleagues also discussed (page 9), severe hypoglycemia is a particular concern with many of the sulfonylureas and insulin, often resulting in hospitalizations and even death. In contrast, the rates of severe hypoglycemia are extremely low with incretin-based therapies, and the rates of hypoglycemia overall are lower with incretin-based therapies compared with sulfonylureas.

Weight Loss

Weight gain is a major concern for patients with diabetes, who are willing to pay more for drugs that enhance weight reduction than for cheaper agents that are weight neutral, suggests Dr Jendle (page 1).

Comparing the effects on weight of the GLP-1 receptor agonist liraglutide with that of the DPP-4 inhibitor sitagliptin, Dr Garber and colleagues found that body weight was reduced by 3.4 kg with liraglutide versus 1.0 kg with sitagliptin (page 6). Weight loss with liraglutide was sustained for 1 year in a study comparing both drugs, as Dr Pratley discusses (page 7).

Composite End Point

Finally, an end point that combines reduction in HbA_{1c} levels, no change in or loss of weight, and absence of hypoglycemia is a valuable clinical end point, given that all 3 are important goals of treating type 2 diabetes. A post-hoc analysis of 5 phase-3 clinical trials of liraglutide (page 8) presented at the meeting revealed that liraglutide allows more patients to reach a composite end point consisting of reduced HbA_{1c} levels to <7% and no hypoglycemia or weight gain than active comparators.

Cost Issues

Hypoglycemia not only leads to adverse clinical outcomes, but has cost consequences and compliance consequences as well. Bron and colleagues found that hypoglycemic episodes predict both the discontinuation of oral antidiabetic therapy and higher costs of care (page 4), with cost differences associated with hypoglycemic episodes approaching \$5000 over 6 months.

In addition, Swedish researchers found that patients with type 2 diabetes are willing to pay extra for treatment with liraglutide than glimepiride based on the superior effects of liraglutide on body weight, systolic blood pressure, and rates of hypoglycemia (page 1). ■

Patients with Diabetes More Willing to Pay Extra... *Continued from page 1*



Johan Jendle, MD, PhD

Patients were willing to pay an extra \$3.48 for the anticipated 2.6-kg reduction in weight with liraglutide compared with the 1.0-kg increase with glimepiride.

as add-on therapy to metformin over 26 weeks (randomized, double-blind phase) in 1091 patients with type 2 diabetes.

The reduction in hemoglobin (Hb) A_{1c} levels was similar between the liraglutide and glimepiride cohorts (0.97% vs 0.98%, respectively), but liraglutide was associated with a 2.8-mm Hg decline in SBP, whereas glimepiride recipients had an SBP increase of 0.4 mm Hg.

In addition, the liraglutide group had a mean body weight reduction of 2.6 kg, whereas glimepiride-treated patients gained a mean of 1 kg. The rate of hypoglycemia was also less with liraglutide versus glimepiride (0.03 vs 1.23 events per patient-year, respectively).

Results from the willingness-to-pay survey were converted from Swedish kronor to US dollars at an exchange rate of 0.1393. The survey revealed that patients were willing to pay the following extra monthly costs for these treatment attributes:

- Weight loss of 6 kg, >\$80
- Weight loss of 3 kg, ~\$80
- Weight loss of 2 kg, ~\$50
- Weight loss of 1 kg, ~\$30
- No hypoglycemic events in a month compared with 2 events, >\$60

- 1% reduction in HbA_{1c} value, >\$60
- No hypoglycemic events in a month compared with 1 event, ~\$50
- No use of glucose test strips versus 1 daily, ~\$20
- No use of glucose test strips versus 3 times weekly, ~\$10.

Overall, patients were willing to pay an additional \$3.62 daily to use liraglutide rather than glimepiride. They were willing to pay an extra \$3.48 for the anticipated 2.6-kg reduction in weight with liraglutide compared with the 1.0-kg increase with glimepiride, and they would also be willing to pay an additional \$0.70/day for the reduction in SBP levels, and \$0.56/day for the decreased risk of minor hypoglycemia with liraglutide versus glimepiride.

The only treatment aspect that favored glimepiride economically was the route of administration. The participants would demand \$1.12/day to accept the injection (irrespective of meal) compared with oral administration in relation to a meal with glimepiride. ■

Estimated Lifetime Costs of Type 2 Diabetes... *Continued from page 1*

vention program, are not available in the United States, the researchers said. They therefore sought to estimate lifetime direct medical costs and indirect productivity loss associated with type 2 diabetes after the initial diagnosis.

A validated diabetes simulation model, developed by the CDC and the research institute RTI International, was used to simulate the natural histories of patients newly diagnosed with type 2 diabetes and track the costs associated with the disease.

Estimated direct medical costs included the cost of diabetes care and complications of diabetes, and indirect costs included productivity loss because of absence from work, "presenteeism" (reduced productivity at work), disability, and premature death.

The estimated total lifetime cost depended on the patient's sex and age at time of diagnosis. The total lifetime cost of type 2 diabetes was \$180,000 for a

female and \$251,000 for a male (Table). These costs are in 2009 US dollars, and future costs were discounted at 3%.

For a person diagnosed at age 30, the lifetime cost was estimated at \$305,000. Of this, \$90,000 was the total medical costs of diabetes care and its associated conditions, including coronary heart disease (CHD), stroke, nephropathy, neuropathy, and retinopathy.

Indirect productivity loss for a person diagnosed at age 30 was estimated at \$215,000. Of the indirect costs, premature death was the major cost component of productivity loss. As shown in the Table, total estimated costs were lower with older age at diagnosis.

Direct medical costs accounted for about 35% of the overall total but grew as a percentage of the total lifetime cost with later age at diagnosis. Indirect costs were the primary drivers of the age and sex variation in total lifetime cost. Of the indirect cost, productivity

	Sex		Age of Diagnosis		
	Female	Male	30 yr	50 yr	60 yr
Total medical cost, \$	67,000	61,000	90,000	74,000	63,000
Diabetes care, \$	19,000	18,000	32,000	23,000	17,000
Total complications, \$	47,000	43,000	58,000	52,000	46,000
Indirect productivity loss, \$	113,000	191,000	215,000	98,000	42,000
Total lifetime cost, \$	180,000	251,000	305,000	172,000	105,000

Source: Zhuo X, et al. Lifetime cost of type 2 diabetes in the US. Poster presented at the American Diabetes Association 2010 Meeting; Orlando, FL; June 25-29, 2010; Poster 0434-PP.

loss associated with premature death was the dominant component.

As much as 70% of the medical cost could be attributed to associated complications. Of the direct medical cost, approximately 50% of the total was for macrovascular complications, and 60% of those costs was incurred during the first 10 years after diagnosis.

The 3 factors most responsible for the high medical cost during that period were:

- Early occurrence of 2 costly complications, CHD and stroke
- The substantial burden of regular diabetes care consisting of glycemic control and control of other diabetes-related conditions
- Increasing mortality. ■

Diabetes Screening of High-Risk People... *Continued from page 1*

entire study population using the plasma glucose challenge test were found to be lower than for no screening—\$216,007 versus \$242,737 for diabetes and prediabetes combined, and \$66,878 versus \$95,710 for diabetes alone.

"The testing costs to identify a patient with disease fell as the risk of disease increased," said Dr Chatterjee. For those with the lowest BMI, the testing cost per person was \$153, but dropped dramatically to \$61 for the highest BMI group. Costs also declined with age.

With screening everyone, "you're detecting more cases, so you're having to treat more true-positives, but you're having fewer false-negatives, which actually costs more than treating true-positives," she said.

Savings per person with screening compared with no screening were greatest—\$253—in the highest BMI group. But screening saved \$73 per person in the lowest BMI group. Screening the oldest age-group (>55 years) saved \$239 per person versus no screening compared with \$65 per person in those aged <40 years.

The opportunity to catch diabetes early would save 7.3% of healthcare costs in those with a BMI of 25 kg/m² to 35 kg/m², and 21.3% of costs in those with the highest BMI.

Screening the 40 to 55 age-group would reduce costs by 8.1% and those aged >55 would save 17.1%.

Of the diabetes tests, "The plasma glucose challenge test, which is the most accurate, is most cost-saving among the highest risk groups, so

we're proposing that it be a test that might be put into practice, both because of its accuracy and its potential cost-effectiveness," said Dr Chatterjee.

A Novel Test to Assess Risk

Juliet E. Berkeley, MD, of Christ Church, New Zealand, presented her poster on the dynamic insulin sensitivity and secretion test (DISST), a novel test for measuring insulin sensitivity that can be performed in approximately 30 minutes.

DISST is a low-cost, low-intensity alternative to the glucose clamp, with the added benefits of measuring beta-cell function and being able to differ-

entiate individual variations in pathophysiology. Dr Berkeley predicts that this novel test will be useful in assessing the risk of diabetes and cardiovascular disease, as well as in evaluating treatment response. This test assesses the glucose, insulin, and C-peptide response to low-dose intravenous glucose and insulin, providing a sensitivity index. It also measures beta-cell function.

The researchers investigated DISST profiles of 73 obese females, who also underwent the glucose clamp and the oral glucose tolerance test. DISST was able to show variations in individual pathophysiology related to insulin

sensitivity and secretion, whereas the results on the glucose clamp were practically indistinguishable for the same women.

"A great strength of the test [DISST] is its dynamic and relatively physiological nature compared with previous tests," Dr Berkeley stated. The comparatively low-dose protocol avoids significant saturation effects. "Many tests require hyperphysiological dosing protocols to produce very strong signals, but these tests have little physiological relevance" as a result of the high dosing. DISST also offers an assessment of insulin secretion, which is not often assessed in other tests. ■

Healthcare Costs, Utilization Lower with Exenatide than with Insulin Glargine

Despite higher total prescription costs, the total medical costs for type 2 diabetes are lower when starting therapy with a glucagon-like peptide (GLP)-1 receptor agonist, such as exenatide, than with insulin glargine, based on an analysis of a large managed care database.

"Improving patients' access to modern therapies, such as exenatide, may not only improve patients' health outcomes but may also result in significant cost-savings for overall management of type 2 diabetes," according to researchers led by Manjiri Pawaskar, PhD, Eli Lilly and Company.

The team compared 7255 patients

who initiated exenatide therapy and 2819 who initiated insulin glargine therapy between June 3, 2005, and June 30, 2007, and who had continuous coverage in managed care plans from 6 months preindex to 12 months postindex.

The groups were matched and controlled for baseline demographics, clinical, resource use, and cost variables. The majority of the patients in both groups were concomitantly receiving at least 1 oral antidiabetic medication.

Preindex per-patient costs were similar—\$11,526 with exenatide and \$11,546 with glargine—but over the

12-month postindex period, the total medical cost was \$19,978 with exenatide compared with \$22,575 with glargine (–\$2597 difference).

Prescription drug costs in the postindex period were \$6509 for patients taking exenatide versus \$5803 for patients taking glargine. Inpatient and outpatient medical costs were lower in the exenatide group.

All-cause hospitalization costs were significantly lower in the exenatide group compared with the glargine group (\$4397 vs \$6307, respectively), because patients treated with exenatide had a 19% lower risk for all-cause hospitalizations.—WK ■

Hypoglycemic Episodes Carry High Direct, Indirect Costs

By Wayne Kuznar

Hypoglycemic events in patients with type 2 diabetes are associated with discontinuation of oral antidiabetic therapy and higher costs of care. The increased likelihood of discontinuing therapy associated with a hypoglycemic episode carries over at least into the following 6-month period, said Morgan Bron, PharmD, Associate Director of Global Health Outcomes, Takeda Pharmaceuticals International, Deerfield, IL.

Discussing hypoglycemic episodes, Dr Bron said that “cost differences were a lot higher than we thought they would be.” The data showed that “instead of the \$2000 range, they were more in the range of \$4000 to \$5000,” she said.

Using a large administrative database of managed care plans (the Ingenix Impact database), she investigated the clinical and economic impact of hypoglycemia in 212,061 patients initiated on ≥ 1 oral antidiabetic drugs.

A total of 4860 (2.29%) patients had at least 1 hypoglycemic episode during the first year after the index date. The risk for hypoglycemia varied among the treatments. In the 6-month interval after the index date, the use of a sulfonylurea or insulin was associated with the largest increase in the risk for hypoglycemia, followed by other oral antidiabetic drugs and thiazolidinediones, said Dr Bron.

The use of metformin had no effect on the risk for hypoglycemia, and dipeptidyl peptidase (DPP)-4 inhibitors were associated with a decreased risk for hypoglycemia.

On multivariate analysis, the use of

sulfonylureas as an index drug increased the risk of hypoglycemia by 58% and insulins increased the risk by 77% in the following 6-month interval. The use of DPP-4 inhibitors was associated with a 21% decrease in the risk for hypoglycemia.



“Instead of the \$2000 range, they [hypoglycemic episodes] were more in the range of \$4000 to \$5000.”

—Morgan Bron, PharmD

Hypoglycemia diagnosis in a given 6-month interval significantly increased the risk for treatment discontinuation—by 27% within the same 6-month interval and by 14% in the following 6-month interval.

After adjusting for confounding factors, incremental annual total costs and diabetes-related total costs were \$5031 higher and \$3751 higher, respectively, in patients with a hypoglycemic episode compared with patients without a hypoglycemic episode. The average total costs were \$18,273 for patients

with a hypoglycemia diagnosis compared with \$8908 for patients without such a diagnosis, and the diabetes-related costs were \$8969 for patients with a diagnosis of hypoglycemia versus \$3220 for patients without a diagnosis of hypoglycemia.

Substantial Economic Burden

Another presentation of 2 separate analyses focused on the substantial economic burden of hypoglycemia, even with nonsevere hypoglycemic events, in type 2 diabetes. Unlike nonsevere hypoglycemic events, the more severe events result in hospitalization and even death (see article on page 9).

The first analysis was a review of 11 studies that reported on the economic burden of hypoglycemia in this patient population. In examining 5 US insurance claims database studies, the researchers found that the medical resource use for hypoglycemia was 13 times greater in patients receiving insulin compared with those treated with sulfonylureas.

Of these, 2 studies (from Germany and Sweden) showed that inpatient care greatly increased the cost per hypoglycemic episode. Three studies that examined indirect costs related to work productivity demonstrated decreased work productivity associated with hypoglycemic episodes, in both insulin- and non-insulin-treated patients.

The Swedish study showed the national economic cost of hypoglycemic events to be €4.25 million in 2005. The high frequency of less-severe hypoglycemic events, and their potential to significantly affect work productivity, indicate their importance from

the payer and societal perspectives, the researchers concluded.

The second study was an online-based survey of 2670 adults with type 1 or type 2 diabetes and at least 1 non-severe hypoglycemic event during the previous month. Nonsevere hypoglycemic events in patients with diabetes have previously been shown to reduce quality of life and alter their behavior (see page 9). Participants were from the United States, United Kingdom, Germany, and France.

This analysis focused on the 972 patients who had a nonsevere hypoglycemic event at work. Insufficient food intake/diet was reported by 47.8% of patients as the reason for the event, and physical exercise/overexertion was cited by 34.8% of patients. Nearly half (46.6%) of the participants used sugar packs or candy to recover from the hypoglycemic event.

As a result of the event, 25.9% of insulin-dependent subjects decreased their normal insulin dose over the next 2 days, and a mean of 7 extra blood glucose tests were conducted in the following week.

One in 5 (19.0%) patients reported absenteeism from work in relation to a nonsevere hypoglycemic event. The average monthly out-of-pocket costs for managing or being prepared for nonsevere hypoglycemic events was \$45.56. “The largest expenses were for extra groceries, purchasing of extra blood glucose test strips, as well as the use of transportation services,” the researchers noted. ■

SEE ALSO page 9

Progression from Prediabetes to Diabetes Raises Healthcare Utilization, Costs

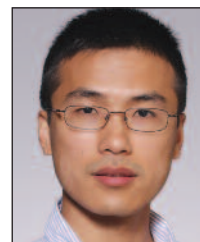
People who progress from prediabetes to type 2 diabetes have significantly higher healthcare utilization and healthcare costs than prediabetics who do not progress to diabetes, researchers from Thomson Reuters in Cambridge, MA, reported.

This retrospective observational study is based on a national claims database of 145,639 persons with prediabetes, which was defined as a primary or secondary diagnosis of impaired glucose tolerance, a fasting plasma glucose of 100 mg/dL to <126 mg/dL, or an oral glucose tolerance test between 140 mg/dL and <200 mg/dL. The index date was the

first date with evidence of a qualifying measure in 1 of these 3 tests.

Claims were followed for at least 12 months before and after the index date. Healthcare utilization and costs (ie, inpatient admissions, emergency department and outpatient visits, other outpatient services and prescriptions) were higher in those with prediabetes who progressed to type 2 diabetes than those who did not progress. A total of 30.6% progressed to type 2 diabetes.

Compared with those who did not progress to diabetes, total medical costs were \$1489 higher in patients who developed type 2 diabetes dur-



“How low the cut-point goes depends on resources available for prevention and the cost and effectiveness of implementing prevention in a large-scale setting.”

— Xiaohui Zhuo, PhD

ing the first 12 months, \$2613 higher during the first 24 months, and \$3847 higher during the first 36 months from the diagnosis of prediabetes.

Outpatient costs were \$414 higher in the first 12 months, \$731 higher in the first 24 months, and \$1001 higher in the first 36 months in those who progressed to diabetes; pharmacy

costs increased by \$474, \$1012, and \$1550 during the first 12, 24, and 36 months, respectively, in those who progressed to type 2 diabetes compared with those who did not.

Patients with baseline hypertension had significantly higher costs in the first 36 months—\$2367 total costs, \$377 inpatient costs, and \$1538 outpa-

Continued on page 5

Progression from Prediabetes to Diabetes... *Continued from page 4*

tient pharmacy costs—compared with no hypertension.

Preventing or delaying the progression from prediabetes to type 2 diabetes may reduce healthcare utilization and costs, the investigators said.

A_{1c} 6% Cost-Effective for Defining Prediabetes

The optimal cost-effective cut-point to define prediabetes for primary prevention is approximately A_{1c} level of 6%, suggests Xiaohui Zhuo, PhD, of the Centers for Disease Control and Prevention, Division of Diabetes Translation, Atlanta, GA.

The American Diabetes Association now recommends using A_{1c} ≥6.5% levels to define diabetes and A_{1c} 5.7% to 6.4% for prediabetes, but “selecting the A_{1c} cutoff to define prediabetes for primary prevention is still subject to debate,” Dr Zhuo said. “No specific A_{1c} level is associated with clear accelerations in the risk of diabetes or other morbidities.”

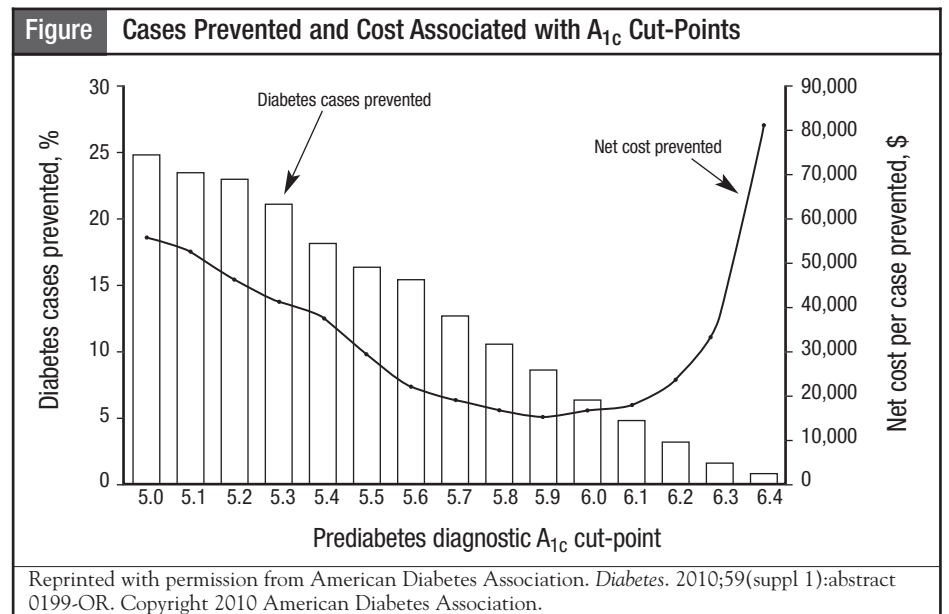
Dr Zhuo noted that, “the economic tradeoff of cut-point selection is difficult.” Choosing a high A_{1c} as the cut-point decreases the number of people eligible for intervention, thereby reducing intervention costs but also the number of cases of diabetes prevented, which can increase diabetes costs upstream, he said. Choosing lower cut-points increases the number of persons for intervention, which escalates the intervention cost.

Dr Zhuo evaluated the cost-effectiveness of different A_{1c} cut-points from 5.0% to 6.4%, calculating the number of diabetes cases prevented and the net cost per case prevented under different A_{1c} cut-points.

For his model, Dr Zhuo used the cost and effectiveness of diabetes prevention from 2 diabetes prevention studies: (1) the Diabetes Prevention Program (DPP), with a per-patient cost of \$1000/year to produce a 55% reduction in the risk for progression to diabetes, and (2) the Diabetes Education & Prevention with a Lifestyle Intervention Offered at the YMCA (DEPLOY), with a per-patient cost of \$300/year to produce a 25% reduction in risk of progression to diabetes.

As expected, the prediabetes population declined dramatically as the A_{1c} cutoff increased—from 77% at an A_{1c} of 5.0% to 3% at an A_{1c} of 6.0%. The prediabetes population curve started to flatten at an A_{1c} level of 5.7%, which constituted 12% of the population. “Increasing the cutoff decreases the cost and health benefit simultaneously,” Dr Zhuo said. The association between A_{1c} cut-points and cost per case of diabetes prevented was U-shaped (Figure).

Using the DPP data, the total cost benefit increased at A_{1c} >5.7%. When adopting DEPLOY as the prevention program, the total cost benefit increased at A_{1c} >5.4%. The lowest cost per case prevented occurred at 5.9%—



about \$20,000, with approximately 9% of cases prevented. Lowering the cut-point from 5.9% to 5.6% prevented about 7% more cases but increased the cost per case prevented by \$28,500, whereas lowering the cut-point from 5.9% to 5.0% prevented 16% more cases but increased costs by \$77,727 per case prevented.

Using DPP, the cost of preventing 1 case of diabetes approached \$80,000 per quality-adjusted life-year (QALY) at a cut-point of 5.6% and was lowered to a QALY of \$40,000 at 5.8%. Using DEPLOY, the cost per QALY was about \$40,000 at a cut-point of 5.6% and slightly more than \$20,000 at 5.8%.

At A_{1c} levels >6.1%, the cost per

QALY actually increases, said Dr Zhuo. “We actually want to move the cut-point a little lower to increase the number of cases prevented and have a reasonable efficiency,” he said.

Therefore, the optimal cut-point to define prediabetes is probably not more than 6.1% but actually a little lower, he said. “How low the cut-point goes depends on resources available for prevention and the cost and effectiveness of implementing prevention in a large-scale setting.”

The selection of prediabetes diagnostic cut-point depends on how policymakers balance preventing cases and cost per case prevented, he concluded.—WK ■

GLP-1 Receptor Agonists

Obesity, Poor Glycemic Control Are Associated with Exenatide Use in Insulin-Treated Patients

By Wayne Kuznar

In clinical practice, exenatide is often started in patients with type 2 diabetes who are receiving insulin therapy, although the prescribing information states that the concurrent use of exenatide with insulin has not been studied and cannot be recommended.

The combination of exenatide with insulin is more likely to be started in obese patients with comorbid conditions, according to a retrospective analysis of a large nationwide database.

“Glycemic control in obese patients with comorbid conditions is difficult to obtain with either drug alone; therefore, despite the absence of clinical evidence to support the combination, it is conceivable that a GLP [glucagon-like peptide]-1 receptor agonist plus insulin was prescribed due to inability to reach treatment tar-

gets while controlling weight gain,” said Irl B. Hirsch, MD, Professor of Medicine, Division of Metabolism, Endocrinology, and Nutrition, University of Washington, Seattle.

The database used for this study included 540,000 patients with type 2 diabetes; of these, the researchers compared 7383 patients who received exenatide and 183,061 who did not.

Among the predictors of exenatide use (regardless of insulin use) were female sex, younger age, body weight ≥200 lb, body mass index (BMI) ≥25 kg/m², white race, hemoglobin (Hb) A_{1c} ≥7%, living in the south, commercial health insurance, and lower creatinine clearance.

In a multivariate analysis, high BMI had the strongest association with exenatide initiation, including patients who

were receiving insulin, oral antidiabetic medications, or both. The 9810 patients who used exenatide as their first incretin-based therapy generally had the following characteristics: white race, age <65 years, weight >200 lb, an HbA_{1c} level of 7% to 9%, blood pressure ≥130/90 mm Hg, living in the south or midwest, having commercial insurance, and having a creatinine clearance <2 mL/min.

The 2740 patients in whom exenatide was initiated while taking insulin were likely to weigh >250 lb, have a BMI >40 kg/m², a creatinine clearance <2 mL/min, a baseline HbA_{1c} >9%, and have Medicare as their payer.

“Research on multiple levels is needed to further evaluate the benefits and risks of combination therapy with a GLP-1 receptor agonist and insulin,”



Irl B. Hirsch, MD

said Dr Hirsch. These include:

- Exploration of the mechanism of action of GLP-1 receptor agonists plus insulin when used in combination
- Safety profile of the combination
- Potential for the GLP-1 agonist to mitigate weight gain associated with insulin therapy
- Potential to obtain greater glycemic control with a lower rate of hypoglycemia compared with insulin alone
- Effect of GLP-1 agonists with different types of insulin. ■

Liraglutide Lowers SBP Independent of Antihypertensive Use

By Wayne Kuznar

A meta-analysis of 6 clinical trials of liraglutide showed that it reduces systolic blood pressure (SBP) independent of antihypertensive drug therapy and in addition to antihypertensive treatment, said Vivian Fonseca, MD, FRCP, FACE, Professor of Medicine and Director, Diabetes Program, Tulane University, New Orleans, at the ADA meeting.

“Multiple risk factor intervention is very important in preventing cardiovascular disease in diabetes, and it suggests that blood pressure lowering is more important than [hemoglobin] HbA_{1c} lowering in terms of preventing cardiovascular death,” Dr Fonseca said.

Liraglutide, a once-daily glucagon-like peptide-1 analog, was studied extensively in the Liraglutide Effect and Action in Diabetes (LEAD) program, which consisted of multiple phase 3 clinical trials in patients at various stages of type 2 diabetes.

Across the phase 3 LEAD trials, liraglutide reduced SBP, but these studies did not control for concomitant antihypertensive treatment.

This meta-analysis by Dr Fonseca and colleagues included 2783 patients

from 6 of the randomized, controlled LEAD trials. The researchers compared the effect of liraglutide 1.2 mg/day (n = 896) or 1.8 mg/day (n = 1363) with placebo (n = 524) on SBP change from baseline to week 26. The researchers took into account the effect of the use of antihypertensive treat-

ment at week 26, the interaction between treatment and use of antihypertensive treatment at week 26, and the interaction between the use of antihypertensive treatment at screening and the use of antihypertensive treatment at week 26.

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“Multiple risk factor intervention is very important in preventing cardiovascular disease in diabetes, and it suggests that blood pressure lowering is more important than HbA_{1c} lowering in terms of preventing cardiovascular death.”

—Vivian Fonseca, MD, FRCP, FACE

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Concomitant antihypertensive medication use reported by ≥5% of the study patients in any treatment group included enalapril, lisinopril, rami-

pril, amlodipine, hydrochlorothiazide, atenolol, and perindopril. There were minor differences in antihypertensive drug use at screening and at week 26 in the liraglutide groups (64.2% and 58.5%, respectively) and the placebo groups (67.6% and 54.8%, respectively).

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Weight Loss, A_{1c} Reduction Seen with Liraglutide

Patients with type 2 diabetes treated with liraglutide lose significantly more body weight than those treated with sitagliptin, based on results from a randomized, open-label study comparing the 2 agents, presented by Alan J. Garber, MD, PhD, Professor of Medicine, Biochemistry and Molecular Biology, and Molecular and Cellular Biology, Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine.

In this post-hoc analysis of a previous trial, Dr Garber and colleagues explored the relationship between change in body weight and change in hemoglobin (Hb) A_{1c} levels after 26 weeks of open-label treatment with liraglutide 1.8 mg/day or sitagliptin 100 mg/day in 429 patients with type 2 diabetes that was not controlled with metformin.

In the previously published study (N = 665), liraglutide reduced mean HbA_{1c} from baseline by 1.5% compared with only 0.9% with sitagliptin. Similarly, body weight was reduced by 3.4 kg with liraglutide compared with only 1.0 kg with sitagliptin.

More liraglutide-treated patients lost more than 3% of their body weight than sitagliptin-treated patients, said Dr Garber.

A total of 51% of patients lost >3% of their body weight with liraglutide compared with 21% with sitagliptin; of these, the mean body weight changes were -6.3 kg in the liraglutide group and -5.3 kg in the sitagliptin group.

Compared with patients who lost ≤3% of body weight while taking liraglutide, those who lost >3% body weight had an additional 0.6% reduction in HbA_{1c}; there was no significant difference in HbA_{1c} reductions in those taking sitagliptin who lost ≤3% or >3% body weight.

Compared with patients who lost ≤3% of body weight while taking liraglutide, those who lost >3% body weight had an additional 0.6% reduction in HbA_{1c}; there was no significant difference in HbA_{1c} reductions in those taking sitagliptin who lost ≤3% or >3% body weight. Within each weight-loss category, however, lira-

glutide reduced HbA_{1c} levels more than sitagliptin.

In addition, Dr Garber said, there seems to be a link between weight loss and additional reductions in HbA_{1c} levels with liraglutide. The beneficial effects associated with weight loss, such as increased insulin sensitivity, may be associated with the incremental glycemic effect of body weight reduction seen with liraglutide, he added.

Some incretin-based therapies promote weight loss (ie, glucagon-like peptide-1 agonists) and some are considered weight-neutral (ie, dipeptidyl peptidase-4 inhibitors). The relationship between weight loss and improved HbA_{1c} has not been well understood, Dr Garber said.

Liraglutide Better than Sitagliptin for Reducing A_{1c}, Regardless of Baseline A_{1c}

Melanie Davies, MD, MB, ChB, Professor of Diabetes Medicine, University of Leicester, England, described the results of a subanalysis of the same study presented by Dr Garber, showing that regardless of patients' baseline HbA_{1c} levels, liraglutide was consistently more effective than sitagliptin in

reducing HbA_{1c} levels during the 26-week study period.

In this subanalysis, patients were divided into 5 categories according to their baseline HbA_{1c} levels (≤7.5%, >7.5%-8.0%, >8.0%-8.5%, >8.5%-9.0%, and >9.0%).

At each baseline category, significantly more liraglutide recipients than sitagliptin recipients achieved an HbA_{1c} level <7%, Dr Davies said. For example, of patients with baseline HbA_{1c} <7.5%, 85% of those in the liraglutide group achieved the ≤7% American Diabetes Association target compared with only 36% in the sitagliptin group.

In addition, mean HbA_{1c} reductions in each baseline group were considerably greater with liraglutide than with sitagliptin.

The mean HbA_{1c} reductions across the 5 baseline HbA_{1c} categories were:

1. In the ≤7.5% category: -0.9% with liraglutide, -0.2% with sitagliptin
2. In the >7.5%-8.0% category: -1.2% with liraglutide, -0.7% with sitagliptin
3. In the >8.0%-8.5% category: -1.4% with liraglutide, -0.9% with sitagliptin
4. In the >8.5%-9.0% category: -1.5% with liraglutide, -1.1% with sitagliptin
5. In the >9.0% category: 2.3% with liraglutide, -1.4% with sitagliptin.—WK ■

Once-Weekly Exenatide Bests 2 Oral Agents and Insulin Glargine on Key End Points

By Wayne Kuznar

In 2 separate studies, a new once-weekly formulation of exenatide offered improved glucose control compared with oral antidiabetic agents that require daily dosing and titration of insulin glargine in the treatment of patients with type 2 diabetes.

Long-acting once-weekly exenatide was also associated with greater weight loss than the oral agents sitagliptin and pioglitazone among patients whose hemoglobin (Hb) A_{1c} levels remained uncontrolled with metformin, and greater weight loss than insulin glargine among patients with type 2 diabetes who remained uncontrolled with multiple agents. Both studies were reported at the ADA meeting and were simultaneously published in the *Lancet*.

Richard Bergenstal, MD, ADA President for Medicine and Science, reported the results of a double-blind study known as DURATION-2, which included 491 patients with type 2 diabetes who were uncontrolled with metformin alone; they were randomized to 1 of 3 treatment groups—exenatide 2

mg injected once weekly, oral sitagliptin 100 mg/day, or 45 mg/day oral pioglitazone.

The primary end point was change in HbA_{1c} level at week 26. In the intent-to-treat analysis, an absolute 1.5% reduction in HbA_{1c} was seen with exenatide compared with a 1.2% reduction with pioglitazone and 0.9% with sitagliptin. Weight loss was also superior with exenatide: -2.3 kg with exenatide, -0.8 kg with sitagliptin, and a gain of 2.8 kg with pioglitazone.

No episodes of major hypoglycemia were reported in any group.

Lead investigator Michaela Diamant, MD, PhD, Associate Professor of Endocrinology, and Scientific Director, Diabetes Centre, VU University Medical Centre, Amsterdam, the Netherlands, reported the results of DURATION-3. In this study, 456 adults with uncontrolled type 2 diabetes with maximum-tolerated doses of antidiabetic drugs were randomized to 26 weeks of additional treatment with once-weekly exenatide or once-daily injections of insulin glargine, starting at 10 IU and

self-titrated to a target glucose level of 4.0 mmol/L to 5.5 mmol/L.

Blinding of the 2 drugs was not possible, but the data analyzers were blinded. HbA_{1c} lowering was significantly better with exenatide (1.5%) than with insulin glargine (1.3%). In addition, 60% of patients using exenatide reached the ADA's HbA_{1c} goal of <7% compared with 48% of patients using insulin.

Patients assigned to exenatide lost a mean of 2.6 kg of body weight at week 26 compared with a 1.4-kg weight gain for insulin glargine. Glycemic response with exenatide was not dependent on body weight.

Once-weekly "exenatide gave superior HbA_{1c} reduction and weight loss," said Dr Diamant. "If we consider convenience and weight, it is important to consider once-weekly exenatide for our patients." She noted that in addi-



Once-weekly "exenatide gave superior HbA_{1c} reduction and weight loss."

—Michaela Diamant, MD, PhD

tion to controlling glucose, "We also need to consider weight gain, avoid hypoglycemia, and most important, convenience to the patient, so they actually use the treatment."

According to Dr Bergenstal, increasingly it is becoming clear "that control of diabetes is more than just glucose; it's glucose, weight, and hypoglycemia," and these 2 studies "are reinforcing that it is possible to do that."

The new once-weekly formulation of exenatide is currently under review by the US Food and Drug Administration. ■

Reductions in A_{1c}, FPG, and Body Weight Sustained for 1 Year in Head-to-Head Study

One year of liraglutide plus metformin treatment is better than sitagliptin plus metformin at sustaining decreases in hemoglobin (Hb) A_{1c} levels, fasting plasma glucose (FPG), and body weight, according to a late-breaking head-to-head study presented at the meeting.

Both agents target the incretin system. Liraglutide is a glucagon-like peptide-1 analog that increases insulin secretion and decreases glucagon secretion independently of glucose, increases satiety, and leads to weight loss.

Sitagliptin inhibits dipeptidyl peptidase-4 and increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner, but does not affect satiety or weight.

In adults with type 2 diabetes who were already taking metformin, liraglutide 1.2 mg/day or 1.8 mg/day was compared with sitagliptin 100 mg/day in a 26-week randomized trial, which was then extended to another 26 weeks.

Richard Pratley, MD, Professor of Medicine and Director, Diabetes and

Metabolism Translational Unit, University of Vermont, Colchester, and colleagues presented data showing that after 1 year, liraglutide at either dose was associated with greater reductions in HbA_{1c}, FPG, and body weight compared with sitagliptin, with more patients reaching target HbA_{1c} <7%.

Mean decreases in HbA_{1c} were 1.3% for liraglutide 1.2 mg, 1.5% for liraglutide 1.8 mg, and 0.9% for sitagliptin. In addition, 50.3% of patients achieved the target HbA_{1c} of <7% with liraglutide 1.3 mg, 63.3% with liraglutide 1.8 mg, and 27.1% with sitagliptin.

Reductions in FPG at 26 weeks were maintained through the end of 52 weeks:

- 30.6 mg/dL with liraglutide 1.2 mg
- 36.0 mg/dL with liraglutide 1.8 mg
- 10.8 mg/dL with sitagliptin.

Weight loss at 26 weeks was also sustained to 1 year:

- 2.8 kg with liraglutide 1.2 mg and 3.7 kg with liraglutide 1.8 mg
- 1.2 kg with sitagliptin.

The proportion of patients who

Continued on page 8

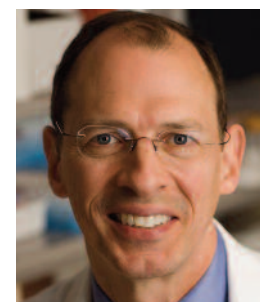
Taspoglutide: Good Glycemic Control but Increased Adverse Events

Data from 3 ongoing phase 3 trials (known as the "T-emerge" series) of the investigational, once-weekly injectable human glucagon-like peptide (GLP)-1 analog, taspoglutide, were presented at the ADA meeting.

In T-emerge 4, taspoglutide 10 mg titrated to 20 mg weekly was compared with placebo and sitagliptin 100 mg/day orally in 666 patients with type 2 diabetes inadequately controlled with metformin. Reductions in hemoglobin (Hb) A_{1c} were 0.89% with sitagliptin compared with 1.23% with 10 mg taspoglutide and 1.30% with 20 mg taspoglutide. Of the taspoglutide group, 65% achieved an HbA_{1c} <7% compared with 50% of the sitagliptin group, reported Richard Bergenstal, MD, Executive Director, International Diabetes Center, Park Nicollet, Minneapolis, MN, and President for Medicine and Science of the ADA.

Mean weight loss was 2.6 kg with the high-dose taspoglutide compared with 0.9 kg with sitagliptin. As with other GLP-1 receptor agonists, "the most common adverse events with taspoglutide were related to GI tolerability," Dr Bergenstal said. Nausea and vomiting occurred in >40% of the taspoglutide recipients.

"Among patients reporting nausea



Richard Bergenstal, MD

or vomiting, there was predominantly a single episode that tended to occur early in treatment on the day of injection," said Dr Bergenstal.

Adverse events leading to discontinuation exceeded 16% in both taspoglutide groups compared with only 1.6% of patients receiving sitagliptin.

T-emerge 5 included 1049 insulin-naïve adults with type 2 diabetes inadequately controlled with metformin plus a sulfonylurea. Taspoglutide 10 mg or 20 mg twice weekly demonstrated noninferiority to insulin glargine once daily in reducing HbA_{1c} levels, and more patients assigned to taspoglutide achieved an HbA_{1c} level of ≤6.5%. The 20-mg taspoglutide group had a mean weight loss of 4.1 kg versus 0.4 kg for insulin glargine recipients.

T-emerge 2 included 1189 patients with type 2 diabetes inadequately controlled with metformin with or without a thiazolidinedione; they were randomized to taspoglutide and exenatide. The change in HbA_{1c} was similar between the 2 drugs, as was weight loss. Nausea or vomiting were more common with taspoglutide.

Taspoglutide's manufacturer has delayed submitting the agent for approval for 12 to 18 months to examine hypersensitivity reactions.—WK ■

More Patients Reaching Composite End Point with Liraglutide than Comparator Drugs: A_{1c} <7%, No Weight Gain or Hypoglycemia

By Alice Goodman

A post-hoc analysis of 5 phase 3 studies comparing liraglutide with other antidiabetic drugs supports the superiority of this new glucagon-like peptide (GLP)-1 analog to reach the clinically relevant composite end point that includes reduced hemoglobin (Hb) A_{1c} to <7%, no hypoglycemia, and no weight gain.

These 3 components are key factors in developing treatment recommendations for diabetes, said Bernard Charbonnel, MD, Head of Internal Medicine, Endocrinology and Diabetes Department, University Hospital of Nantes, France. Hypoglycemia and weight gain are common side effects of many therapies for type 2 diabetes.

All 5 trials were part of the Liraglutide Effect and Action in Diabetes (LEAD) program, with similar randomized controlled designs; comparator drugs were glimepiride, sulfonylureas, metformin, insulin glargine, rosiglitazone, and exenatide in various combinations.

In each LEAD trial, significantly more patients treated with liraglutide 1.2 mg/day or 1.8 mg/day reached the composite end point (range, 16.1%-38.8%) than those treated with comparator agents (range, 3.6%-28.9%).

In 5 LEAD trials, liraglutide 1.8 mg at 26 weeks was associated with 1% to

1.5% HbA_{1c} reduction, as well as weight loss, no major hypoglycemic events, and only a few minor hypoglycemia events, said Dr Charbonnel.

Recent trials “have highlighted the risk of hypoglycemia in patients with intensive glycemic control and a strict A_{1c} target of <6.5%.”

—Bernard Charbonnel, MD

Recent studies conducted in large numbers of patients with type 2 diabetes and with long-term follow-up “have highlighted the risk of hypoglycemia in patients with intensive glycemic control and a strict A_{1c} target of <6.5%, and <6% in the ACCORD [Action to Control Cardiovascular Risk in Diabetes] trial,” he said.

Weight gain has also been a problem with other oral antidiabetic medications, he noted.

In 4 of the LEAD trials, liraglutide was significantly ($P = .012$) superior to comparator drugs in achieving the primary end point of HbA_{1c} <7% versus comparator drugs. In the fifth trial, a similar proportion of patients in all 3 arms achieved HbA_{1c} <7%.

In LEAD-1, 16% to 24% of patients treated with liraglutide 1.2 mg or 1.8 mg plus sulfonylurea achieved the composite end point compared with 3.6% of those receiving rosiglitazone 4 mg plus sulfonylurea.

In LEAD-2, when used in combination with metformin, significantly more patients receiving liraglutide achieved the composite end point than with glimepiride 4 mg/day combined with metformin (31.2%-34.7% vs 12.9%, respectively).

In LEAD-3, the composite was reached by 32.4% in patients randomized to 1.2 mg/day of liraglutide,

38.2% of those taking 1.8 mg/day of liraglutide, and 7.7% of those assigned to 8 mg/day of glimepiride.

In LEAD-5, 38.8% of those treated with liraglutide 1.8 mg plus metformin and sulfonylurea met the primary end point compared with 10.7% of those taking glargine plus metformin plus sulfonylurea.

In LEAD-6, which compared liraglutide 1.8 mg plus metformin and/or sulfonylurea versus exenatide 10 mg plus metformin and/or sulfonylurea, 39% versus 29% of patients, respectively, met the composite end point, but the differences were not significant. ■

Reductions in A_{1c}, FPG... *Continued from page 7*

achieved a composite end point of an HbA_{1c} <7% with no weight gain and no hypoglycemia was 38.9% with liraglutide 1.2 mg, 49.9% with liraglutide 1.8 mg, and 18.6% with sitagliptin. The rate of minor hypoglycemia over 1 year was low in both treatment groups.

Gastrointestinal (GI) adverse events (AEs) were more common in patients taking liraglutide than sitagliptin. Withdrawal rates because of GI AEs in the first 26 weeks were 3.4% with liraglutide

1.2 mg, 4.6% with liraglutide 1.8 mg, and 0.5% with sitagliptin; the rates in the second phase were 0.5% and 0.9% with liraglutide 1.2 mg and 1.8 mg, respectively, compared with 0% with sitagliptin.

Nausea initially occurred more often with liraglutide than with sitagliptin, but the incidence of nausea was <2% in all groups in weeks 27 to 52. Investigators noted that nausea in recipients of liraglutide was transient and decreased in incidence after week 3.—WK ■

DPP-4 Inhibitors

Saxagliptin plus Metformin Combination Superior to Monotherapy for Initial Type 2 Diabetes Treatment

By Wayne Kuznar

The combination of saxagliptin plus metformin was superior to either drug alone as initial therapy to achieve sustained glycemic control in patients with type 2 diabetes. The combination was well-tolerated over a total of 76 weeks (24-week phase 3 trial, 52-week extension trial). Results of the 52-week extension trial were reported by Andreas Pfützner, MD, Institute for Clinical Research and Development, Mainz, Germany.

“The study suggests that the combination of saxagliptin plus metformin may be an attractive first-line therapy for type 2 diabetes mellitus,” Dr Pfützner told attendees at the 2010 ADA meeting.

Saxagliptin is the latest dipeptidyl peptidase-4 inhibitor to be approved for treatment of adults with type 2 dia-

betes. The original 24-week multicenter, double-blind, active-controlled trial randomized 1306 treatment-naïve patients in a 1:1:1:1 ratio to saxagliptin 5 mg plus metformin, saxagliptin 10 mg plus metformin, saxagliptin 10 mg plus placebo, or metformin plus placebo.

Baseline hemoglobin (Hb) A_{1c} level was 8% to 12%; mean body mass index was 30 kg/m²; mean age was around 52 years, and approximately 33% to 40% of patients were aged ≥65 years.

This 52-week analysis included 1103 patients. The combinations of saxagliptin 5 mg or 10 mg plus metformin achieved substantial reductions in HbA_{1c} level at week 24 and week 76 versus either drug alone.

Of those treated with the combination of both drugs, 60% achieved target HbA_{1c} <7% at week 24, and 51% were

still at target at week 76.

In the saxagliptin plus placebo group, 22% and 15% of patients achieved HbA_{1c} <7% at weeks 24 and 76, respectively; in the metformin plus placebo group, 41% and 35% of patients achieved HbA_{1c} at weeks 24 and 76, respectively.

“The combination of saxagliptin plus metformin may be an attractive first-line therapy for type 2 diabetes mellitus.”

—Andreas Pfützner, MD

A similar pattern was observed for the change in fasting plasma glucose

level from baseline and postprandial glucose level from baseline, with the combinations having a superior effect over either drug alone at week 24, and these effects sustained by week 76.

The percentage of patients who discontinued their assigned treatment at week 76 was about 30% in the 2 combination arms versus 56% with saxagliptin monotherapy and 42% with metformin monotherapy.

Saxagliptin plus metformin combinations had acceptable safety. Approximately 66% of all patients in the study experienced at least 1 adverse event. Discontinuation as a result of adverse events was reported in about 4% of all groups. The incidence of hypoglycemia was low and was not increased in the groups receiving combination therapy.

Experts Debate Whether Sulfonylureas Should Be Written Off in Favor of DPP-4 Inhibitors

By Wayne Kuznar

Dipeptidyl peptidase (DPP)-4 inhibitors are relatively new to the oral antihypoglycemic armamentarium, whereas sulfonylureas have been used in clinical practice for 5 decades. Does newer mean better, and has the time come to replace sulfonylureas with this newer class of agents?

Michael Nauck, MD, Head of the Diabetes Centre, Diabeteszentrum Bad Lauterberg, Germany, and David R. Matthews, FRCP, Professor of Diabetes Medicine, Oxford Centre for Diabetes, Endocrinology, and Metabolism, England, debated this issue at the 2010 ADA meeting.

Both classes of drugs effectively lower hemoglobin (Hb) A_{1c} and both work within the pancreatic beta cell but by different mechanisms. Glucagon-like peptide (GLP)-1 is a hormone secreted by the intestine after ingestion of nutrients, an effect that is reduced in patients with type 2 diabetes. Native GLP-1 is degraded rapidly by DPP-4, but DPP-4 inhibitors reduce serum DPP-4 activity to prolong the half-life of GLP-1, which has insulinotropic activity only on glucose stimulation, Dr Nauck said.

Therefore, he added, DPP-4 inhibitors would be expected to have low rates of hypoglycemia, and they perform well in this regard.

Rates of hypoglycemia are lower with DPP-4 inhibitors compared with sulfonylureas, he said. Furthermore, recovery of hypoglycemia is delayed with sulfonylureas. "I am not as concerned about hypoglycemia as I am about severe hypoglycemia," Dr

Nauck said, and DPP-4 inhibitors clearly perform better than sulfonylureas in this regard. The rate of severe hypoglycemia is as high as 1.5% over 2 years with sulfonylureas but is rare with DPP-4 inhibitors, he pointed out.

"I am most concerned about hospitalization...and deaths due to severe hypoglycemia," said Dr Nauck. The combined rate of hospitalizations and deaths resulting from severe hypoglycemia, which he termed "lethality," is 5.7% with sulfonylureas. Sulfonylurea-induced severe hypoglycemia "translates into about 80 unnecessary deaths per year in the United States," he said.

In studies comparing the 2 classes of agents, body weight changes consistently favor the DPP-4 inhibitors, and superior effects on lipid profiles were observed in patients treated with DPP-4 inhibitors compared with those treated with sulfonylureas, he said.

Sulfonylureas can have negative effects on ischemic preconditioning; this effect and the weight gain induced by these agents are associated with cardiovascular (CV) risk. In 2 trials in which DPP-4 inhibitors and sulfonylureas were compared head to head and in which CV events were reported, the rate of CV events was nearly half with the DPP-4 inhibitors, Dr Nauck said.

Dr Matthews did not propose that either class is better than the other but said that sulfonylureas will retain a place in the therapeutic armamentarium, even with the rise of DPP-4 inhibitors and other incretin-based therapies. More than 40 years of experience

with sulfonylureas have shown that they safely and effectively lower blood glucose. In contrast, long-term data with DPP-4 inhibitors are lacking.



Sulfonylurea-induced severe hypoglycemia "translates into about 80 unnecessary deaths per year in the United States."

—Michael Nauck, MD

"I am not saying that sulfonylureas are better than DPP-4 inhibitors. What I am saying is that there is no information about DPP-4 inhibitors as related to glycemic outcomes," Dr Matthews said.

In a testament to the utility of sulfonylureas, Dr Matthews reviewed several large, longitudinal, randomized, controlled clinical trials. In the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evalu-

ation (ADVANCE) trial, intensive blood glucose control using gliclazide modified release resulted in a 14% relative risk reduction in major microvascular events compared with a conventional strategy.

In the United Kingdom Prospective Diabetes Study, intensive blood glucose control with insulin and/or a sulfonylurea reduced the incidence of microvascular but not macrovascular complications compared with conventional treatment.

In defense of the CV safety of sulfonylureas, Dr Matthews offered that although there were more deaths in the tolbutamide recipients in the University Group Diabetes Program, patients in this arm had a frequency of baseline electrocardiographic abnormalities that was 30% higher than the comparator arms.

Dr Matthews acknowledged that hypoglycemia does occur with sulfonylureas, but he said that hypoglycemia is not a true side effect of sulfonylureas, but rather "too much" of the effect. The lesson is to use caution in dosing, as with most other drugs. Part of the weight gain that occurs with sulfonylureas may be the result of the body defending against hypoglycemia.

With a global pandemic in obesity, and consequently type 2 diabetes, as well as the strained budgets of many countries worldwide, especially developing countries, sulfonylureas should maintain a place in the treatment of type 2 diabetes, Dr Matthews emphasized. ■

Linagliptin Improves Glycemic Control as Add-On Therapy to Metformin

Adding linagliptin—an investigational selective inhibitor of dipeptidyl peptidase (DPP)-4 with predominantly nonrenal excretion—to metformin in patients with type 2 diabetes with inadequate glycemic control results in significant and clinically meaningful reductions in fasting plasma glucose (FPG) and 2-hour postmeal glucose without weight gain.

These were the findings from a multicenter, 24-week, randomized, placebo-controlled, double-blind, parallel-group study, as presented during a poster session by Marja-Riitta Taskinen, MD, PhD, Professor of Medicine, University of Helsinki, Department of Medicine, Biomedicum, Finland.

Linagliptin was compared with placebo as add-on therapy to metformin in 700 patients with a hemoglobin (Hb) A_{1c} level that remained between 7% and 10% despite met-

Linagliptin reduced the mean FPG from baseline by 21 mg/dL more than placebo.

formin monotherapy, or between 6.5% and 9.0% for patients previously treated with additional oral antihyperglycemic drugs. Patients were randomized in a 3:1 ratio to linagliptin or

placebo. All patients discontinued previous antidiabetic medications other than metformin (≥ 1500 mg/day) for 6 weeks before randomization to linagliptin or placebo.

After 24 weeks of treatment, linagliptin was associated with a significantly greater (0.64%) reduction in HbA_{1c} than placebo. Patients who received linagliptin with baseline HbA_{1c} $\geq 7.0\%$ were more than 4 times as likely to achieve an HbA_{1c} $< 7.0\%$ than those receiving placebo (26.2% vs 9.2%, respectively; odds ratio, 4.40), said Dr Taskinen.

Linagliptin reduced the mean FPG from baseline by 21 mg/dL more than placebo.

Linagliptin plus placebo showed a significant change in placebo-adjusted postmeal glucose levels of -67.1 mg/dL compared with placebo plus metformin.

The proportion of patients who reported at least 1 adverse event was similar between the linagliptin and placebo groups (52.8% and 54.2%, respectively). Hypoglycemia was rare, occurring in 5 patients receiving placebo (2.8%) and 3 patients taking linagliptin (0.6%).

The change in body weight from baseline to 24 weeks was similar between the 2 treatment groups (-0.5 kg with placebo vs -0.4 kg with linagliptin).—WK ■

Type 2 Diabetes, Associated Complications, and Cost Concerns

Gary M. Owens, MD

President, Gary Owens Associates, Philadelphia, PA

Diabetes is one of the most important and challenging disease states for managed care organizations (MCOs) in 2010 and beyond. The epidemic of diabetes is, in part, driven by the growing epidemic of obesity and the changing demographics in the United States, as the first wave of baby boomers reach their sixties.

According to 2007 data published by the Centers for Disease Control and Prevention¹:

- Total cost of diagnosed diabetes in the United States is \$174 billion—\$116 billion in direct medical costs and \$58 billion in indirect costs, such as disability, work loss, and premature mortality
- 23% of people aged ≥60 years have diabetes
- 23.6 million children and adults in the United States—7.8% of the population—have diabetes
- 1.6 million new cases of diabetes are diagnosed in people aged ≥20 years each year
- 5.7 million people have undiagnosed diabetes
- Adults with diabetes have cardiovascular disease death rates approximately 2 to 4 times higher than adults without diabetes
- The risk for stroke is 2 to 4 times greater among people with diabetes than in those without the disease.

It is therefore easy to infer that for MCOs and the employer groups they serve, diabetes and its related conditions represent one of the largest categories of medical and pharmacy

spending. Population management strategies have been directed at this disease, and pharmacy management strategies that include a broad range of approaches, from value-based benefit designs to closely managed step-therapy programs, have been tried.



Much needs to be learned about how to get patients to be adherent to their medications, diet, and exercise.

Yet none of these approaches yields adequate results, because more than 50% of the diabetic population remains inadequately controlled, with hemoglobin (Hb) A_{1c} levels >7%.

In one retrospective claims database analysis, Schmittiel and colleagues revealed even more grim findings. Their data showed that in a large population of type 2 diabetic patients, even those patients who

were adherent to their medications and whose physicians made medication adjustments appropriately, only 27% of them reached the goal for HbA_{1c}, lipids, and blood pressure—3 essential factors necessary to help control microvascular and macrovascular complications of type 2 diabetes.²

In reading this publication, we learn that the total lifetime cost of type 2 diabetes is substantial. In fact, for a person diagnosed with the disease at age 30, the total lifetime cost is estimated at more than \$300,000, with about 33% of this in direct medical costs and the rest in lost productivity over the lifetime of the patient.

We also learn that more than 70% of the direct medical costs of the disease are a result of macrovascular complications, such as stroke or myocardial infarction. In addition, according to these presentations from the annual meeting of the American Diabetes Association, the cost of treating such factors as hypoglycemia in diabetic patients is also a major cost factor.

Therefore, it is essential that health plans and their providers closely manage these patients, balancing the potential long-term complications of undertreatment with the immediate and costly issues associated with overtreatment.

The issue of screening and the potential delay of the onset of type 2 diabetes is of great interest. Compared with pre-diabetic patients who did not progress to type 2 diabetes, those who did progress had significantly more hospital admissions, emergency department

visits, and office visits, as discussed in this publication.

All this leads to some relatively obvious conclusions from a health plan perspective of managing large populations of diabetic patients.

First, it is important that we have new treatment options in the quest to better manage diabetes, and agents with newer mechanisms of action will add significant value to the treatment of this population. Yet it is important to keep in mind that pharmaceutical innovation alone will not result in better management of diabetes.

I have often heard it said at the Pharmacy & Therapeutics Committee meeting that, “what we need is not more drugs to treat the disease, but better strategies to engage patients and their physicians to do the right things.” Much needs to be learned about how to get patients to be adherent to their medications, diet, and exercise. Likewise, getting physicians to manage their patients to goal and according to guidelines is a major challenge.

In conclusion, we must not forget that to adequately manage type 2 diabetes, an equal amount of time and effort also needs to be invested in better understanding human behavior, and how to motivate patients and their doctors to change their approach to diabetes. ■

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Payers Lead Healthcare Reform toward Prevention of Chronic Disease

By Wayne Kuznar

Through new partnerships, payers can help make significant changes to improve the care and prevention of diabetes in the United States, according to Deneen Vojta, MD, Senior Vice President of the UnitedHealth Center for Health Reform and Modernization.

In the future, payers will play a significant role in the advancement of healthcare delivery, Dr Vojta said.

“With health reform, we have an amazing opportunity to begin to change the way care is delivered in this country, particularly preventive care and chronic care,” she said. “In our new world of health reform, we have some new rules and new opportunities to make sure that the 30 [million] to 50 million people who have access continue to get access to quali-

ty, and that the system is sustainable in the long run.”

Payers today must broaden their traditional roles as claims processors and risk aggregators to include a role in the reduction of health risks. If this does not occur, the costs of healthcare will only escalate further, Dr Vojta said.

“In 2010, we as insurers need to take pride in becoming major players in prevention,” Dr Vojta pointed out. The current healthcare system must be changed, and payers will play an interesting role in effecting this change, she continued.

Payers will need to use their assets to reach out to patients and physicians to engage in behavior change in managing care. “In essence, we change from a transactional role to a transformational role,” she said.

This transformational role will require insurers to play a greater role in prevention, support, and innovation; focus on improving care quality and outcomes; emphasize efficiency; and partner with others to bring good ideas to scale.

Dr Vojta showcased the Diabetes Prevention and Control Alliance as an example of such a partnership. This alliance, introduced in April 2010, marks the first time in the United States that a health plan is paying for evidence-based diabetes prevention and control programs.

Research funded by the Centers for Disease Control and Prevention (CDC) demonstrated the success of a pilot initiative to reduce the risk for the development of diabetes through lifestyle changes. The CDC, the YMCA, and UnitedHealth Group joined together, in partnership with

Walgreens, to develop the Diabetes Prevention and Control Alliance.

“This new partnership enables this program to be rolled out across the country to stem the rising tide of diabetes and prediabetes,” Dr Vojta said. ■

The Diabetes Prevention and Control Alliance Goals:

- Identification of individuals who match prediabetic profiles
- Contacting and screening eligible patients through various channels
- Enrolling patients in the 16-week program, delivered over 20 weeks
- Offering patients pharmacist support to provide diabetes education, medication management, behavioral intervention, and monitoring for complications.

Role for Incretin-Based Therapies in the Management of Type 2 Diabetes Is Expanding

Based on an interview with Alan J. Garber, MD, PhD

Professor of Medicine, Biochemistry, and Molecular Biology, and Molecular and Cellular Biology Division of Diabetes, Endocrinology and Metabolism, Baylor College of Medicine, Houston, TX



In an interview with *American Health & Drug Benefits*, Dr Alan J. Garber weighed in on the role that incretin-based therapies may occupy in light of emerging data, including those presented at the 70th scientific sessions of the American Diabetes Association (ADA).

As more clinical experience is obtained with incretin-based therapies in the treatment of patients with type 2 diabetes, the more it appears that these agents are becoming preferred classes of oral and injectable antihyperglycemic drugs.

Dipeptidyl peptidase (DPP)-4 inhibitors as well as glucagon-like peptide (GLP)-1 agonists address some major limitations of other established therapies for type 2 diabetes, namely, weight gain and hypoglycemia.

Longer-term data are confirming the durability of the effect, said Dr Garber. "We have 2-year data with liraglutide. The drug effect looks quite stable and appears durable for 2 years," he said.

Combined End Point Reveals Full Clinical Utility

A new post-hoc combined end point of achievement of a hemoglobin (Hb) A_{1c} target <7% with no hypoglycemia and no weight gain is gaining in popularity among clinical trial investigators to showcase differences between antihyperglycemic drugs. "It's an artificial end point but it has been created to demonstrate the kind of thinking you have in the primary care arena," said Dr Garber. "Primary care doctors are not looking solely to get blood glucose under control. They are very worried about hypoglycemia, particularly after the ACCORD situation."

In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, the rate of hypoglycemic events that required care from a medical professional with intensive glucose control was almost triple the rate compared with standard control (10% vs 3.5%, respectively). Patients who had 1 or more episodes of severe hypoglycemia had an increase in mortality compared with those without any episodes, at adjusted hazard ratios of 1.41 in the intensive-treatment group and 2.30 in the standard-treatment group.

"Primary care doctors do not like weight gain, and having to explain it to their patients, and the patients do not like it either. It's just a way of

showing that in terms of clinical concerns in primary care, this is a more useful drug," Dr Garber said.

Differences among Incretin-Based Therapies

The incretin effect—the phenomenon by which oral glucose elicits a larger increase in plasma insulin level compared with the same amount of glucose given intravenously—is reduced in type 2 diabetes. Because the insulinotropic effect of GLP-1 is preserved in patients with type 2 diabetes, giving GLP-1 as replacement therapy partially restores incretin activity. GLP-1 is susceptible to degradation by DPP-4; the DPP-4 inhibitors act by reducing serum DPP-4 activity, thereby increasing levels of endogenously secreted GLP-1.

Clinical differences between the 2 classes of incretin-based therapies are starting to emerge with the recent publication (Pratley RE, et al. *Lancet*. 2010;375:1447-1456) of a head-to-head, 26-week, open-label study between the GLP-1 agonist liraglutide and the DPP-4 inhibitor sitagliptin, known as the 1860-LIRA-DPP-4 study.

Data from the 52-week extension study were presented at the ADA meeting. This was a study of patients not achieving adequate glycemic control with metformin. Patients with a mean baseline HbA_{1c} of about 8.5% were randomized to liraglutide 1.2 mg/day or 1.8 mg/day or to sitagliptin 100 mg/day. Liraglutide was more significantly effective than sitagliptin in terms of absolute reduction of HbA_{1c} (1.2% and 1.5% vs 0.9%, respectively), proportion of subjects achieving goal HbA_{1c} (55% vs 20%), and weight loss (approximately 3 kg vs 1 kg).

"The 1860-LIRA-DPP-4 study basically showed that when you take liraglutide versus sitagliptin, there's better glucose reduction, more weight loss, and about the same amount of hypoglycemia [with liraglutide]," Dr Garber said. "An extension of the study out to 1 year showed that patients continue to do well with liraglutide....It suggests, quite frankly, that the degree of GLP-1 receptor saturation with an injectable compound [that has much higher levels of GLP-1] is probably important mechanistically in terms of producing glucose reduction that is greater in degree and longer in durability," he observed.

Cardiovascular Risk Profiles

The impact that any type 2 diabetes treatment has on cardiovascular risk is heightened, given the recent controversy surrounding rosiglitazone and the risk for heart attacks.

Patients taking GLP-1 agonists have favorable blood pressure changes, as well as beneficial changes in inflammatory markers for cardiovascular risk and left-ventricular ejection fraction.

"Blood pressure lowering is a class effect for the GLP-1 receptor agonists. They all lower systolic blood pressure," Dr Garber said. "They're all probably direct-acting antagonists of insulin resistance."

"Primary care doctors are not looking solely to get blood glucose under control. They are very worried about hypoglycemia."

—Alan J. Garber, MD, PhD

Risk of Acute Pancreatitis Update

Concerns of acute pancreatitis with incretin-based drugs have been raised, leading the US Food and Drug Administration to issue safety alerts for exenatide and sitagliptin. Whether incretin-based therapies are responsible for pancreatitis or whether these events reflect an increased risk in patients with type 2 diabetes had not been clear, but recent data do not support an increased risk for pancreatitis with incretin-based therapies, according to Dr Garber.

"If you actually look at the data [for these agents], there doesn't look like there is an increase in pancreatitis," he said. "Patients with diabetes have been getting pancreatitis for years. Diabetic patients are just swimming in a sea of risk factors for pancreatitis; they're overweight, they have gallstone disease at a high rate, they have dyslipidemia. So in general, when you look at most databases, patients with diabetes have triple the rate of pancreatitis than nondiabetics."

Indeed, retrospective examinations of health claims databases show that patients receiving incretin-based therapies are not different from the general population in terms of pancreatitis risk. In one such analysis comparing patients who received new prescriptions either for exenatide (n = 9951) or

for sitagliptin (n = 23,951) and a non-diabetic control group (n = 1,113,392), all of whom were followed for 6 to 18 months, adjusted hazard ratios for pancreatitis were 0.86 with exenatide and 1.01 with sitagliptin compared with the control group.

In a nested case-control study based on a review of 25,000 patients from a US healthcare insurance claims database treated with exenatide and 235,000 patients treated with other antidiabetic medications for a 3-year period, current, recent, or past use of exenatide was not associated with an increased rate of acute pancreatitis compared with other antidiabetic medications, according to the data presented at the ADA meeting.

Potential of Once-Weekly Therapy

Longer-acting GLP-1 agonists are starting to capture attention. "Once-weekly exenatide long-acting release is just as effective as or slightly more effective than twice-daily," Dr Garber said. The key issue will be whether delivery devices for once-weekly formulations of GLP-1 agonists will be user friendly.

"It's going to be a battle of patient preferences," he said. "Is once-weekly [exenatide] that much better than twice-daily?"

The longer-acting agents have been shown to have a smaller impact on postprandial excursions compared with twice-daily exenatide, possibly because of the lack of continued effect on gastric emptying.

Once-weekly taspoglutide suffered a setback as clinical trials have uncovered hypersensitivity reactions in a very small proportion of patients; that led to the withdrawal from these studies. As a result, regulatory filing of taspoglutide has been delayed.

Future Role of Incretin Therapies

The incretin-based therapies "are real contenders for second-line therapy after metformin fails," Dr Garber said. "In some patients, they may be first-line therapy when metformin is not well-tolerated, because the alternative is a sulfonylurea, which gives you hypoglycemia and weight gain, and there's nothing good about either."

"In short [incretin-based therapies] are good drugs, and they got better with closer study," Dr Garber concluded. ■

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