

The Unique Role of Incretin-Based Therapy in Type 2 Diabetes

Supported by an educational grant from
Novo Nordisk Inc.

The Unique Role of Incretin-Based Therapy in Type 2 Diabetes is supported by an educational grant from Novo Nordisk Inc. It has been accredited by the American Association of Diabetes Educators (AADE) for nurses, dietitians, and pharmacists.

Susan A. Cornell, PharmD, CDE, FAPhA, FAADE



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Midwestern University
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Downers Grove, IL**

The following program is a taped presentation by Susan A. Cornell.

Susan A. Cornell is the assistant director of experiential education and an associate professor in the department of pharmacy practice at Midwestern University Chicago College of Pharmacy in Downers Grove, Illinois.

Dr. Cornell is also a clinical pharmacy consultant and certified diabetes educator, specializing in community and ambulatory care practice. She has over 24 years of practice in community pharmacy where she has practiced as a clinical pharmacist, diabetes educator and preceptor, as well as, the inaugural coordinator of the ADA recognized Dominick's Pharmacy Diabetes Self-Management Education program through 2004.

Dr. Cornell received her bachelor of pharmacy at the University of Illinois, College of Pharmacy in 1986 and her Doctor of Pharmacy at Midwestern University in May of 2002.

Dr. Cornell's current clinical practice is with the Access Community Health Network, where she trains, educates, and supervises students from the colleges of medicine, pharmacy, and health sciences, as they provide diabetes education classes for patients in numerous underserved community clinics.

Dr. Cornell recently completed her term as President of the Illinois Pharmacists Association in October 2011. She has received numerous awards and recognitions, including the 2010 Teacher of the Year Award, the 2010 American Association of Colleges of Pharmacy, Student Engaged Community Service Award, the 2008 American Association of Diabetes Educators Fellow Award, 2008 American Pharmacists Association Fellow award, the 2005 Midwestern University Golden Apple Teaching Award. She is an active member of the American Diabetes Association, and the American Association of Diabetes Educators, where she served on their board of directors from 2004 to 2007. Dr. Cornell has given numerous presentations to various healthcare professionals and community groups and has published and contributed to many peer-reviewed, professional written and online publications.

We will now join Dr. Cornell.

Objectives

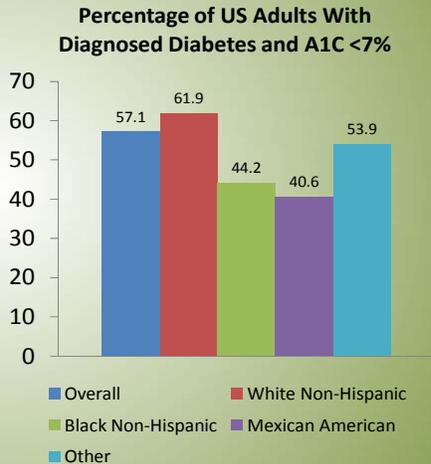
- Discuss the major characteristics and functions of endogenous incretins and the mechanisms of action of the GLP-1 agonists and DPP-4 inhibitors
- Explain how to incorporate strategies that improve A1C levels by using incretin-based treatments as monotherapy for selected patients with recently diagnosed type 2 diabetes
- Describe how incretin-based therapies can be incorporated into dual- and triple-agent regimens, resulting in a higher proportion of patients who achieve the American Diabetes Association A1C target of <7%

After completing this activity, participants should be able to:

- Discuss the major characteristics and functions of endogenous incretins and the mechanisms of action of the GLP-1 agonists and DPP-4 inhibitors
- Explain how to incorporate strategies that improve A1C levels by using incretin-based treatments as monotherapy for selected patients with recently diagnosed type 2 diabetes
- Describe how incretin-based therapies can be incorporated into dual- and triple-agent regimens, resulting in a higher proportion of patients who achieve the American Diabetes Association A1C target of <7%

Need for Improved Glycemic Control in the US

- Lowering A1C to around or below 7% is linked to:
 - Significantly decreased rates of microvascular and neuropathic complications
 - Long-term decrease in macrovascular disease (if A1C reduction is implemented soon after diagnosis)
- Many US adults with diagnosed diabetes do not have A1C of <7%



Cheung BM, et al. *Am J Med.* 2009;122:443–453.

Glycemic control is essential for diabetes management. The Diabetes Control and Complications Trial (DCCT), Kumamoto study, and UK Prospective Diabetes Study (UKPDS) conclusively showed that lowering the A1C to below or around 7% is associated with significantly decreased rates of microvascular and neuropathic complications. Similarly, the DCCT/Epidemiology of Diabetes Interventions and Complications Study and the UKPDS demonstrated that lowering the A1C to around or below 7% is associated with a long-term decrease in macrovascular disease, as long as this A1C reduction is implemented soon after the diagnosis of diabetes.

Therefore, reasonable goals for many nonpregnant adults with diabetes are <7% according to the American Diabetes Association (ADA) and $\leq 6.5\%$ according to the American Association of Clinical Endocrinologists (AACE). (Note that A1C goals for pregnant women are <6.0% according to the ADA and $\leq 6.0\%$ according to the AACE.)

Despite the desirability of maintaining an A1C level below 7%, many people with diabetes have not reached this goal. The graph on this slide shows the percentage of US adults with diagnosed diabetes whose A1C was less than 7%. The data source is the 2003–2006 wave of the National Health and Nutrition Examination Survey, the last wave to undergo intensive analysis. Individuals who were not currently at goal included 42.9% of the overall US population, 38.1% of white non-Hispanics, 55.8% of black non-Hispanics, 59.4% of Mexican Americans, and 46.1% of other ethnic groups. These statistics show that dramatic improvements in the treatment of diabetes are needed. One approach to improving diabetes care is to develop agents that lower glucose in novel ways.

Pathophysiology of Type 2 Diabetes

- Progressive pancreatic islet dysfunction
 - Qualitative and quantitative abnormalities in insulin secretion from beta-cells
 - Unrestrained glucagon secretion from alpha-cells
- Insulin resistance in muscle and adipose tissue
- Dysregulated hepatic glucose production
- Qualitative and quantitative abnormalities in amylin secretion
- Derangements in function of incretin hormones, GLP-1 and GIP

GLP-1 = glucagon-like peptide 1;
GIP = glucose-dependent insulintropic polypeptide.

Pratley RE. *Medscape J Med.* 2008;10:171.
Pratley RE. *Diabetes Care.* 2010;33:1691–1692.

Type 2 diabetes is a progressive metabolic disorder characterized by functional defects in several organs. Patients experience progressive pancreatic islet dysfunction, including qualitative and quantitative abnormalities in insulin secretion from beta-cells and unrestrained glucagon secretion from alpha cells. They also have insulin resistance in muscle and adipose tissue, as well as dysregulated hepatic production.

Patients also exhibit qualitative and quantitative abnormalities in the secretion of amylin. Amylin, like insulin, is secreted by pancreatic beta-cells. It is secreted in response to nutrient stimuli and works together with insulin to suppress glucagon secretion. It also helps regulate gastric emptying, thereby influencing the rate at which glucose enters the blood.

Type 2 diabetes is also characterized by derangements in the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). The incretin hormones are discussed in greater detail in the next slides.

Physiologic Role of Incretin Hormones

- GLP-1 and GIP are incretin hormones released from GI tract during food ingestion
- Increase insulin secretion from beta-cells in a glucose-dependent manner
- Additional effects of GLP-1
 - Regulates rate of gastric emptying
 - Decreases postprandial glucagon secretion from pancreatic alpha-cells
 - Promotes satiety and reduces appetite
- GLP-1 and GIP promote beta-cell proliferation in animals

GI = gastrointestinal.

Pratley RE. *Medscape J Med.* 2008;10:171.
Pratley RE. *Diabetes Care.* 2010;33:1691–1692.

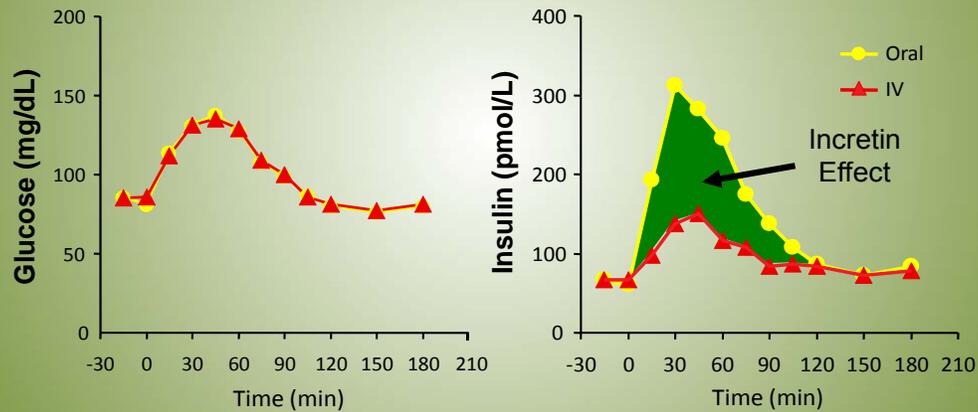
The incretin hormones GLP-1 and GIP are secreted from specialized endocrine cells, called enteroendocrine cells, in the gastrointestinal (GI) tract. Incretin hormones are secreted in response to nutrients entering the gut. GLP-1 secretion is stimulated by glucose, amino acids, and fat, and GIP secretion is stimulated by fat and, to a lesser extent, by glucose. Studies conducted in the 1970s and 1980s showed that oral ingestion of glucose led to a greater insulin response than intravenous (IV) administration of an equivalent amount of glucose. This phenomenon, called “the incretin effect,” is discussed further on the next slide.

GLP-1 has some additional effects that have not been observed with GIP. GLP-1 regulates the rate of gastric emptying, so that nutrients are gradually delivered to the small intestine and absorbed into the circulation. Because nutrients are absorbed gradually, the demand for insulin is also gradual. GLP-1 also reduces postprandial glucagon secretion from pancreatic alpha-cells, helping to maintain the counterregulatory balance between insulin and glucagon. GLP-1 promotes satiety, leading to reduced food intake and weight loss.

Both GLP-1 and GIP have been shown to promote pancreatic beta-cell proliferation in animals, but this effect has not been demonstrated in humans.

The Incretin Effect: Insulin Secretion Is Greater in Response to Oral vs IV Glucose

Effects in Healthy Volunteers



IV = intravenous.

Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498.
Nauck MA, et al. *Diabetologia.* 1986;29:46-52.

Beginning in the 1960s, studies in healthy volunteers showed that oral ingestion of glucose led to a greater insulin response than IV administration of glucose. This phenomenon, which is due to the action of GLP-1 and GIP, is known as “the incretin effect.”

This slide depicts the incretin effect. In the graph on the left, the yellow line represents serum glucose levels following oral ingestion of glucose and the red line represents glucose levels following IV infusion of an equivalent amount of glucose. Subjects had similar blood glucose (BG) levels regardless of the route of administration.

The graph on the right shows the levels of secreted insulin in subjects who received glucose by the oral route (yellow line) or the IV route (red line). Considerably more insulin was secreted when glucose was administered by the oral route. The difference in the amount of insulin secreted following oral and IV administration of equivalent amounts of glucose is called the “incretin effect,” because the markedly greater secretion of insulin following oral administration results from the actions of incretin hormones.

Further research has shown that approximately 60% of postprandial insulin secretion is due to the effects of incretins.

Rationale for Incretin-Based Therapies

- In many persons with type 2 diabetes, GLP-1 secretion is normal, but response of insulin to GLP-1 is diminished
- Continuous infusion of native intact GLP-1 restores more physiologic balance between insulin and glucagon secretion, but native GLP-1 is quickly degraded by DPP-4, a ubiquitous enzyme
- Pharmacologic interventions to increase plasma GLP-1 levels have been developed

DPP-4 = dipeptidyl peptidase-4.

Pratley RE. *Rev Diabet Stud.* 2008;5:7394.
Nauck MA, et al. *Diabetologia.* 1993;36:741-744.

In many persons with type 2 diabetes, GLP-1 secretion is normal, but the response of insulin to GLP-1 is diminished. However, diabetic beta-cells can still respond to high levels of GLP-1.

Nauck and colleagues performed a study in which patients whose diabetes was inadequately controlled by diet and sulfonylurea therapy received a continuous infusion of IV saline or native intact GLP-1. After less than 4 hours of GLP-1 treatment, the patients' plasma glucose decreased to normal fasting levels and glucagon levels were also reduced. The study showed that GLP-1 infusion can restore a more physiologic balance between insulin and glucagon secretion in patients with type 2 diabetes.

Despite these demonstrated benefits, continuous infusion of native GLP-1 is impractical. Furthermore, native GLP-1 has an elimination half-life of only 1 to 2 minutes, because it is inactivated by dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme.

Collectively, these findings suggested to researchers that pharmacologic interventions that would increase plasma GLP-1 levels without rapid degradation by DPP-4 might be promising approaches to the treatment of diabetes. Two types of pharmacologic approaches to increase GLP-1 levels have been developed. The first modifies native GLP-1 to make it resistant to the effects of DPP-4 and the second works indirectly, by inhibiting the action of DPP-4.

Common Effects of GLP-1 Agonists and DPP-4 Inhibitors

- Two classes of incretin-based therapies
 - GLP-1 agonists: modify native GLP-1 to make it resistant to effects of DPP-4
 - DPP-4 inhibitors: inhibit action of DPP-4
- Members of both classes
 - Enhance insulin secretion
 - Suppress glucagon secretion
 - Reduce postprandial hyperglycemia

Pratley RE and Gilbert M. *Rev Diabet Stud.* 2008;5:73–94. Davidson JA. *Mayo Clin Proc.* 2010;85(Suppl):S27–S37. Freeman JS. *Cleve Clin J Med.* 2009;76(Suppl 5):S12–S19.

The 2 classes of incretin-based therapies are GLP-1 receptor agonists, which are usually called “GLP-1 agonists,” and DPP-4 inhibitors. GLP-1 agonists modify native GLP-1 to make it resistant to the effects of the DPP-4 enzyme. As their name suggests, DPP-4 inhibitors inhibit the action of DPP-4.

These classes of glucose-lowering agents have several important common effects. They enhance insulin secretion, suppress glucagon secretion, and reduce postprandial hyperglycemia. Some preclinical data suggest that the incretin-based therapies also preserve beta-cell function by stimulating cell proliferation and inhibiting apoptosis, but this effect has not been demonstrated in humans.

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There are also some important differences between the GLP-1 agonists and the DPP-4 inhibitors. The increase in the level of GLP-1 is in the pharmacological range (greater than 5 times) after administration of a GLP-1 agonist and in the physiological range (2 to 3 times) after administration of a DPP-4 inhibitor.

Once medication concentrations reach steady state, a sustained increase in the GLP-1 concentration is observed in patients treated with a GLP-1 agonist. In contrast, GLP-1 levels are postprandially increased in patients treated with a DPP-4 inhibitor.

GLP-1 agonists suppress the appetite, induce a sense of satiety, and reduce body weight. However, DPP-4 inhibitors do not have a significant effect on appetite, satiety, or weight.

Another important difference between these classes of incretin-based therapy is that GLP-1 agonists are administered by subcutaneous injection, while DPP-4 inhibitors are administered orally.

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A finding that supported the development of incretin-based therapies for individuals with type 2 diabetes is that _____.

- a. the function of the incretin hormones is often deranged in this population
- b. incretin hormones are released from the GI tract only after carbohydrate ingestion
- c. incretin hormones continuously promote insulin secretion in this population
- d. intermittent administration of native GLP-1 normalizes plasma glucose levels

Answer to Checkpoint 1

The correct answer is **a**.

A finding that supported the development of incretin-based therapies for individuals with type 2 diabetes is that the function of the incretin hormones is often deranged in this population.

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Introduction to GLP-1 Agonists

Agents Approved for Use in the US or in Late-Phase Development*

Agent (Brand Name)	Manufacturer	Program	US Status
ExBID (Byetta®) [†]	Amylin	–	Approved, 4/05
Liraglutide (Victoza®) [†]	Novo Nordisk	LEAD	Approved, 1/10
ExQW (Bydureon™)	Amylin	DURATION	FDA CRL, 10/10
Albiglutide (Syncria®)	GlaxoSmithKline	–	Phase 3
Dulaglutide [‡]	Lilly	AWARD	Phase 3
Lixisenatide (Lyxumia®)	sanofi-aventis	GETGOAL	Phase 3
Taspoglutide	Ipsen	T-Emerge	Phase 3; development suspended

*Effective June 2011. [†]Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

[‡]Known until recently as LY2189265. Will not be discussed in this activity.

CRL = complete response letter; ExBID = exenatide twice daily; ExQW = exenatide once weekly; FDA = US Food and Drug Administration.

US FDA. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

Pollack A. Available at: <http://prescriptions.blogs.nytimes.com/2010/10/19/f-d-a-rejects-new-diabetes-drug>.

GlaxoSmithKline. Available at: http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10025.htm.

Umpierrez GE, et al. *Diabetes Obes Metab*. 2011;13:418–425.

Christensen M, et al. *Expert Opin Investig Drugs*. 2011;20:549–557.

Ipsen. Available at: <http://www.ipson.com/sites/default/files/communiques-presse/PR%20Q1%202011%20sales%20Final%20EN.pdf>

This slide shows GLP-1 agonists that are approved for use in the US or in late-phase clinical development as of July 2011. Exenatide twice daily (ExBID) has the brand name Byetta®. It is marketed by Amylin Pharmaceuticals, Inc. It was approved by the US Food and Drug Administration (FDA) in April 2005. Liraglutide, marketed under the name Victoza®, is manufactured by Novo Nordisk Inc. It received FDA approval in January 2010. The acronym for its phase 3 development program is “LEAD.” Both ExBID and liraglutide are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Exenatide once weekly (ExQW), which has the brand name Bydureon™, is being developed by Amylin. Its phase 3 development program is called “DURATION.” In October 2010 the FDA issued a complete response letter (CRL), requiring a cardiac safety study to be conducted. (Recall that a CRL is the letter used by the FDA to communicate the decision to a drug manufacturer that its new drug application will not be approved in its current form.) Albiglutide, dulaglutide, and lixisenatide are now under investigation in phase 3 clinical trials. Albiglutide has the brand name Syncria® and is being developed by GlaxoSmithKline. Dulaglutide, which was identified until recently as LY2189265, is being developed by Eli Lilly & Company. The acronym for its development program is AWARD. Lixisenatide, which has the brand name Lyxumia®, is being developed by sanofi-aventis. The name of its development program is “GETGOAL.” Taspoglutide was under development by Ipsen and Hoffman La Roche Inc in the T-Emerge program. However, at the end of 2010, Roche announced that it would not continue as a development partner due to concerns about treatment-emergent GI adverse events (AEs) and hypersensitivity reactions in phase 3 clinical trials. In February 2011, Ipsen announced that it was suspending development of taspoglutide while it sought a new partner. A June 2011 presentation in which Ipsen described its future development activities did not include taspoglutide. Therefore, taspoglutide will not be discussed in this activity.

Pharmacologic & PK Differences Among GLP-1 Agonists

Agent	Description	T_{max} , $t_{1/2}$	Active Metabolites, Significant Interactions	Elimination
ExBID	Synthetic analog of extendin-4 found in saliva of <i>Heloderma suspectum</i> (lizard); 53% homology to native GLP-1	2.1 h 2.4 h	None	Mainly renal; not recommended for patients with ESRD or severe renal impairment
Liraglutide	Acelated analog of human GLP-1; 97% homology to native GLP-1	8–12 h 13 h	None	Mainly metabolized by proteolytic degradation; use caution in patients with renal impairment
ExQW	Exenatide suspended in PLG microspheres	2–5 wk NR	None	Renal
Albiglutide	GLP-1 dimer genetically fused to human albumin	3–5 d 6–7 d	NR	NR
Dulaglutide	GLP-1 IgG4-Fc fusion protein	~70 h ~4 d	NR	NR
Lixisenatide	Extendin-4-like GLP-1 agonist modified C-terminally	~2 h ~3 h	NR	Renal

ESRD = end-stage renal disease; IgG4 = immunoglobulin G4; NR = not reported; PLG = poly D, L-lactic-co-glycolic acid; $t_{1/2}$ = elimination half-life; T_{max} = time to maximum plasma concentration.

Byetta.® PI. Sept. 2010. Victoza®. PI. Dec. 2010. Gilbert MP, Pratley RE. *Am J Med.* 2009;122 (Suppl):S11–S24. Bischoff LA, et al. *Expert Opin Pharmacother.* 2011;12:1297–1303. St Onge EL, Miller SA. *Expert Opin Biol Ther.* 2010;10:801–806. Umpierrez GE, et al. *Diabetes Obes Metab.* 2011;13:418–425. Christensen M, et al. *Expert Opin Investig Drugs.* 2011;20:549–557.

The GLP-1 agonists are synthetic peptides with varying chemical and pharmacokinetic characteristics. Their wide ranges of time to maximum plasma concentration (T_{max}) and elimination half-life ($T_{1/2}$) values explain why the dosing intervals for these agents range from twice daily to once weekly. The GLP-1 agonists for which data have been reported lack active metabolites and do not engage in clinically significant drug interactions.

ExBID is not recommended for use in patients with end-stage renal disease (ESRD) or severe renal impairment (creatinine clearance [CrCl] <30 mL/min) and should be used with caution in patients with renal transplantation. No dosage adjustment is required in patients with mild renal impairment (CrCl 50–80 mL/min). Caution should be used when treatment is initiated or the dosage is increased in patients with moderate renal impairment (CrCl 30–50 mL/min). Liraglutide appears to be eliminated by generalized proteolysis, with no single organ having demonstrated major involvement. There is limited experience with liraglutide in patients with mild, moderate, and severe renal impairment, including ESRD. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. Although no dose adjustment is recommended for patients with any degree of renal impairment, liraglutide should be used with caution in this population. Neither ExBID nor liraglutide has been studied in patients with hepatic impairment. Because of their elimination pathways, hepatic dysfunction is not expected to affect their blood concentrations, and there are no restrictions about using ExBID or liraglutide in patients with any degree of hepatic impairment. However, caution should be used when administering one of these agents to a patient with liver impairment.

Pharmacologic & PK Differences Among GLP-1 Agonists

Agent	Description	T _{max} , t _{1/2}	Active Metabolites, Significant Interactions	Elimination
ExBID	Synthetic analog of extendin-4 found in saliva of <i>Heloderma suspectum</i> (lizard); 53% homology to native GLP-1	2.1 h 2.4 h	None	Mainly renal; not recommended for patients with ESRD or severe renal impairment
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Byetta.[®] Pl. Sept. 2010. Victoza.[®] Pl. Dec. 2010. Gilbert MP, Pratley RE. *Am J Med.* 2009;122 (Suppl):S11–S24. Bischoff LA, et al. *Expert Opin Pharmacother.* 2011;12:1297–1303. St Onge EL, Miller SA. *Expert Opin Biol Ther.* 2010;10:801–806. Umpierrez GE, et al. *Diabetes Obes Metab.* 2011;13:418–425. Christensen M, et al. *Expert Opin Investig Drugs.* 2011;20:549–557.

Patients beginning treatment with ExBID should receive a 5 µg dose, given twice daily, for the first month. Based on clinical response, the dose can then be increased to 10 µg, twice daily, if warranted. ExBID can be administered at any time within the 60-minute period before the morning and evening meals, or before the 2 main meals of the day, approximately 6 hours or more apart. It should not be administered after a meal.

Liraglutide should be initiated with a dose of 0.6 mg per day for 1 week. After that, the dose should be increased to 1.2 mg. If warranted, the dose can be further increased to 1.8 mg. Liraglutide is administered once daily. It can be administered at any time of day, without regard to meals.

In phase 3 clinical trials, ExQW is being administered at a dose of 2 mg. Albiglutide is being administered once weekly at a dose of 30 mg. Dulaglutide is being administered once weekly at doses of 0.75 mg and 1.5 mg. Lixisenatide is being administered once daily, within 1 hour before breakfast. The initial dose is 10 µg for 2 weeks, followed by a maintenance dose of 20 µg.

Delivery Systems for Approved GLP-1 Agonists

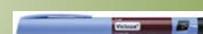
- Disposable pen (similar to insulin pen)
 - Byetta®: 5 µg (1.2 mL) and 10 µg pens (2.4 mL); each dispenses 60 doses
 - Victoza®: same 3 mL pen used for 0.6 mg, 1.2 mg, or 1.8 mg dose
- Disposable single-use pen needles
 - Byetta®: 29, 30, or 31G pen needle
 - Victoza®: 32G NovoFine® or NovoTwist® pen needle
- Pen must be prepared before initial use; priming not needed before each dose



Byetta® 5 µg Pen



Byetta® 10 µg Pen



Victoza® Pen

Byetta.® Prescribing information. September 2010.
Victoza.® Prescribing information. December 2010.

The 2 approved GLP-1 agonists, ExBID (Byetta®) and liraglutide (Victoza®), are administered with disposable pens that are similar to insulin pens. There are 2 different Byetta® pens, each dispensing 60 doses of ExBID. The pen used to administer 5 µg doses has a total capacity of 1.2 mL, and the pen used for 10 µg doses has a total capacity of 2.4 mL. The 5 µg pen has an orange and blue label and the 10 µg pen has a yellow and blue label. Both have dark blue caps. The Victoza® pen contains 3 mL of liraglutide and can be used to administer liraglutide doses of 0.6, 1.2, or 1.8 mg. The Victoza® pen is light blue, with a burgundy label.

Both Byetta® and Victoza® pens use disposable, single-use pen needles. Needles of 29G through 31G can be used with Byetta® pens. Novo Nordisk recommends that a 32G NovoFine® or NovoTwist® pen needle be used with the Victoza® pen.

Instructions for storing, using, and disposing of Byetta® and Victoza® pens are similar to those for insulin pens. Byetta® and Victoza® pens must be prepared before they are used for the first time (or if dropped), but unlike insulin pens, they do not need to be primed before each use. The manufacturers' websites have useful print materials and videos to help patients learn to use these pens.

Delivery Systems for Approved GLP-1 Agonists

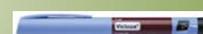
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- Pen must be prepared before initial use; priming not needed before each dose



Byetta® 5 µg Pen



Byetta® 10 µg Pen



Victoza® Pen

Byetta.® Prescribing information. September 2010.
Victoza.® Prescribing information. December 2010.

This slide shows mean A1C reductions from baseline in phase 3 clinical trials of GLP-1 agonists. The duration of phase 3 trials was typically 12 to 26 weeks. An important exception was the liraglutide monotherapy trial (LEAD-3), which lasted for 52 weeks. As shown in the table, mean A1C reductions ranged from 0.7% to 1.5% when a GLP-1 agonist was given as monotherapy. According to the 2009 ADA/EASD Consensus Statement, expected decreases in A1C when other glucose-lowering drugs are administered as monotherapy are 1.0% to 2.0% with metformin, 1.5% to 3.5% with insulin, 1.0% to 2.0% with a sulfonylurea, 0.5% to 1.4% with a thiazolidinedione (TZD), 0.5% to 0.8% with an α -glucosidase inhibitor, 0.5% to 1.5% with a glinide, 0.5% to 1.0% with pramlintide, and 0.5 to 0.8% with an FDA-approved DPP-4 inhibitor. Thus, the A1C reductions observed with GLP-1 agonist monotherapy compare favorably with those attained with other glucose-lowering drugs. Reported reductions ranged from 0.5% to 1.5% when a GLP-1 agonist was given with 1 or 2 oral glucose-lowering drugs. There was a reduction of 1.7% when ExBID was given with basal insulin. Combination therapy with a GLP-1 agonist and basal insulin may eventually prove to be a very effective regimen. Using the A1C reduction data shown in this table to draw conclusions about the relative efficacy of the various GLP-1 agonists is not useful, due to differences in study populations, baseline A1C values, and methodologies. Some studies in which two GLP-1 agonists were compared directly have been completed and others are in progress. Comparative data are reported later in this presentation.

A1C Reductions From Baseline With GLP-1 Agonists in Phase 3 Trials*

Agent	MONO	+ MET	+ SU	+ MET, + SU	+ TZD (or + TZD, + MET)	+ Basal Insulin
ExBID, 5 µg	-0.7	-0.5	-0.5	-0.7	-	-
ExBID, 10 µg	-0.9	-0.9	-0.9	-0.9	-0.7	-1.7
Liraglutide, 1.2 mg	-0.8	-1.0	-1.1	-	-1.5	-
Liraglutide, 1.8 mg	-1.1	-1.0	-1.1	-1.3	-1.5	-
ExQW, 2 mg	-1.5	-1.5	-	-1.5	-	-
Lixisenatide, 20 µg	-0.8	-	-	-	-	-

*Phase 3 data not yet reported for albiglutide and dulaglutide.

- = Data not yet available; MET = metformin; MONO = Monotherapy; NS = not studied; SU = sulfonylurea; TZD = thiazolidinedione; red text = upper end of range; green text = lower end of range.

Byetta.[®] Prescribing information. September 2010. Victoza.[®] Prescribing information. December 2010.

Bischoff LA, et al. *Expert Opin Pharmacother.* 2011;12:1297–1303.

Buse JB, et al. *Ann Intern Med.* 2011;154:103–112.

Gerich JE, et al. 46th EASD Annual Meeting; September 20–24, 2010; Abstract 830.

This slide shows median changes in body weight from baseline to end point in phase 3 clinical trials of GLP-1 receptor agonists. These data demonstrate that promotion of weight reduction is an important characteristic of this therapeutic class. Overall, weight reduction was greatest when GLP-1 agonists were administered as monotherapy, with mean reductions ranging from 2.0 kg to 2.9 kg. However, weight loss also occurred when GLP-1 agonists were given as a component of double or triple therapy, with decreases ranging from 0.1 kg to 2.8 kg.

Because many patients with type 2 diabetes are overweight and treatment with insulin, sulfonylureas, TZDs, and glinides often results in weight gain, the weight-reducing potential of the GLP-1 agonists is an especially beneficial characteristic. Approximately 30% of GLP-1 agonist-treated patients experience significant weight loss, defined as weight loss of more than 7%.

Effects of GLP-1 Agonists on Cardiovascular Risk Parameters

- Reduce BP (especially SBP) independently of weight loss
- Decrease triglycerides by $\geq 20\%$
- Reduce levels of C-reactive protein, plasminogen activator inhibitor, brain natriuretic peptide
- Promote vasodilation and improve endothelial function
- Increase sodium excretion
- Modestly increase heart rate

BP = blood pressure;
SBP = systolic blood pressure.

Okerson T, Chilton RJ. *Cardiovasc Ther*. 2010 Dec 19.
Bergental R, et al. ADA 69th Scientific Sessions, 2009. Abstract 165-OR.
Buse JB, et al. *Lancet*. 2009;374:39-47.

In addition to their effectiveness in reducing BG levels and body weight, GLP-1 agonists have shown beneficial effects on cardiovascular risk parameters. They reduce BP, especially systolic BP (SBP), and this reduction appears to be largely independent of weight loss. After 1 year of treatment with ExQW, for example, mean reductions from baseline were 6.2 mmHg for SBP and 2.8 mmHg for diastolic BP (DBP). GLP-1 agonist therapy often decreases triglyceride levels by 20% or more, and this reduction also appears to be independent of weight loss. Other beneficial effects on lipid levels have also been reported, but they have not been observed consistently and may be related to weight loss. In clinical trials, improvements in several surrogate markers of cardiovascular disease risk were reported, with reduced levels of C-reactive protein, plasminogen activator inhibitor, and brain natriuretic peptide. In human laboratory studies, GLP-1 agonists promoted vasodilation, improved endothelial function, and increased sodium excretion.

The only potentially harmful cardiovascular effect of GLP-1 therapy is a modest increase in heart rate (HR), which has often been observed. In the LEAD-6 study, for example, mean HR increases were 3.28 beats per minute (BPM) with liraglutide 1.8 mg/day and 0.69 BPM with ExBID 10 $\mu\text{g}/\text{day}$. The long-term clinical significance of this increase in HR is unknown.

The effects of GLP-1 therapy on cardiovascular parameters are now undergoing further study in many clinical trials.

Reduction in the Risk of CVD Events With GLP-1 Agonist Therapy

- Retrospective insurance claims analysis
- Patients with no recent history of CVD event assigned to ExBID (n = 39,275) or non-ExBID cohort (n = 381,218)
- Higher rates of prior CVD, comorbidities, and risk factors in ExBID cohort
- ExBID patients less likely to have:
 - CVD event (HR = 0.81; $P = 0.01$)
 - CVD-related hospitalization (HR = 0.88; $P = 0.02$)
 - All-cause hospitalization (HR = 0.94; $P < 0.001$)

CVD = cardiovascular disease;
HR = hazard ratio.

Best JH, et al. *Diabetes Care*. 2011;34:90–95.

Although GLP-1 agonists have a generally beneficial effect on cardiovascular risk parameters, the more important question is whether treatment with a GLP-1 agonist reduces the risk of cardiovascular disease (CVD) events. To begin to address this question, Best et al. performed a retrospective analysis of LifeLink database pharmaceutical insurance claims for the period June 2005 to March 2009. Patients with no history in the previous 9 months of myocardial infarction, ischemic stroke, or coronary revascularization were assigned to the ExBID or non-ExBID cohorts. Patients in the non-ExBID cohort were treated with another glucose-lowering drug or combination of drugs, including insulin. Out of a potential pool of almost 1.3 million patients with at least 1 claim for a glucose-lowering drug, 39,275 patients met all eligibility criteria and were included in the ExBID cohort and 381,218 patients were included in the non-ExBID cohort. Exenatide initiators had evidence of greater use of other glucose-lowering therapies before the initial exenatide prescription and were also more likely to have obesity, diabetic retinopathy, peripheral neuropathy, hyperlipidemia, hypertension, and ischemic heart disease than nonexenatide initiators.

The analysis showed that patients in the ExBID cohort were significantly less likely to have a CVD event or hospitalizations than those in the non-ExBID cohort. Hazard ratios for exenatide-treated patients were 0.81 for a CVD event, 0.88 for CVD hospitalization, and 0.94 for all-cause hospitalization. The investigators speculated that this reduction in CVD events and hospitalization may have resulted from greater reduction of hyperglycemia with less hypoglycemia and/or improvement in risk factors, including weight, BP, and lipids. Prospective studies are now evaluating the effects of GLP-1 agonists on CVD outcomes.

Frequently Reported Adverse Effects of GLP-1 Agonist Therapy

- GI disorders, usually transient and of mild or moderate intensity, are most common AEs
 - Nausea, 28–44%
 - Vomiting, 13–17%
 - Diarrhea, 11–17%
- Risk of GI disturbance can be reduced by following manufacturer's recommendations about dose titration
- Mild injection-site reactions may occur

Campbell RK. *Clin Ther.* 2011;33:511–527. Wilding JP, Hardy K. *BMJ.* 2011;342:d140.

The most frequently reported adverse effects of GLP-1 agonist treatment are GI disorders. These disturbances are typically transient, resolving within the first month of therapy, and of mild or moderate intensity. In clinical trials, reported ranges for the most common GI AEs were 28–44% for nausea, 13–17% for vomiting, and 11–17% for diarrhea. Following manufacturers' recommendations about dose titration can reduce the risk of GI disorders.

Since the GLP-1 agonists are administered by subcutaneous injection, patients may experience mild reactions, such as itching and rashes, at the injection site. The risk of these reactions can be minimized by following the instructions in the product-specific Medication Guide.

Other frequently reported AEs in clinical trials were nonspecific disorders, such as headache and nasopharyngitis.

Incidence of Hypoglycemia With GLP-1 Agonists in Phase 3 Trials

- Hypoglycemia classification
 - Minor: BG ~55 mg/dL and patient able to self-treat
 - Major: treatment by another person required
- Monotherapy
 - Similar incidence of any hypoglycemia similar with placebo and GLP-1 agonist (0–12%)
 - No major hypoglycemia reported
- Combination therapy
 - Hypoglycemia nearly always associated with SU or basal insulin treatment
 - Any (major) hypoglycemia incidence
 - SU-containing regimen: 8–36% (0–2%)
 - Insulin-containing regimen: 25% (0)
 - Other combinations: 1.2–11% (0–0.1%)

Byetta.® Prescribing information. September 2010. Victoza®. Prescribing information. December 2010. Buse JB, et al. *Ann Intern Med.* 2011;154:103–112. Bischoff LA, et al. *Expert Opin Pharmacother.* 2011;12:1297–1303. Gerich JE, et al. 46th EASD Annual Meeting; September 20–24, 2010; Abstract 830.

In analyses of clinical trial data for the GLP-1 agonists, episodes of hypoglycemia are classified as “minor” and “major.” Criteria for minor hypoglycemia vary somewhat, but generally include a BG reading of about 55 mg/dL and the presence of symptoms that the patient can treat independently. Major hypoglycemia is defined as an episode requiring treatment by a person other than the patient. Because GLP-1 agonists increase insulin production in a glucose-dependent manner, the incidence of minor hypoglycemia in phase 3 monotherapy studies has been similar to that observed with placebo, ranging from 0% to 12%. No episodes of major hypoglycemia have been reported. In phase 3 combination therapy studies, the incidence of hypoglycemia has largely depended on the hypoglycemic risk profile of the glucose-lowering agent or agents with which the GLP-1 agonist was used. Thus, the highest rates of hypoglycemia were reported when a GLP-1 agonist was administered with a sulfonylurea or basal insulin. When a GLP-1 agonist was given with a sulfonylurea, reported ranges were 8% to 36% for any hypoglycemia and 0% to 2% for major hypoglycemia. When a GLP-1 agonist was given with insulin, the incidence of any hypoglycemia was 25% and no episodes of major hypoglycemia were reported. When a GLP-1 agonist was given with another combination, reported ranges were 1.2% to 11% for any hypoglycemia and 0% to 0.1% for major hypoglycemia. The prescribing information (PIs) for ExBID and liraglutide include the recommendation that the dose of a sulfonylurea be lowered during coadministration with the GLP-1 agonist. Consideration should also be given to reducing the dose of other insulin secretagogues, such as repaglinide and nateglinide.

Other Safety Issues With GLP-1 Agonist Therapy

- Pancreatitis
 - Rare cases reported during clinical trials and postmarketing period
 - No conclusive data establishing risk of pancreatitis with GLP-1 treatment
 - Observe patients for signs and symptoms when initiating therapy or increasing dose
 - Use with caution (or consider another treatment) in patient with pancreatitis history
- Thyroid C-cell tumors
 - Dose- and duration-dependent tumors in liraglutide-treated rats and mice
 - Liraglutide contraindicated in patients with personal or family history of MTC and in those with MEN 2

MEN 2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid carcinoma.

Byetta.[®] Prescribing information. September 2010. Victoza.[®] Prescribing information. December 2010.

EASD. Available at: http://www.easd.org/easdwebfiles/statements/Elashoff_Commentary.pdf.

Garg R, et al. *Diabetes Care*. 2010;33:2349–2354. Gonzalez-Perez A, et al. *Diabetes Care*. 2010;33:2580–2585.

Other safety issues are the possible risk of pancreatitis during treatment with a GLP-1 agonist and the risk of developing thyroid C-cell tumors during treatment with liraglutide. Rare reports of pancreatitis, especially acute pancreatitis, have been reported in patients who received a GLP-1 agonist in a clinical trial or during the postmarketing period. However, it is not currently known whether treatment with a GLP-1 agonist increases the odds of developing pancreatitis. The risk of pancreatitis is slightly elevated in persons with type 2 diabetes compared to those without diabetes, and current smoking, alcohol intake of ≥ 30 units (≥ 300 mL) per week, previous history of GI disease, and current use of acetaminophen or an ACE inhibitor significantly increase this risk. Patients treated with a GLP-1 agonist should be instructed to report signs or symptoms of pancreatitis to their health care provider, and patients should be carefully monitored for the development of pancreatitis at the beginning of GLP-1 therapy and when the dose is increased. For patients with a history of pancreatitis, the prescribing information (PI) for Byetta[®] recommends that other glucose-lowering options be considered and the Victoza[®] PI recommends that liraglutide be used with caution.

Liraglutide is known to cause dose- and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is currently unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Therefore, liraglutide treatment is contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Patients should be counseled regarding the risk and symptoms of thyroid tumors before beginning treatment with liraglutide.

Combination Therapy With Basal Insulin and a GLP-1 Agonist*

Parameter	ExBID + Insulin Glargine (n = 137)	Placebo + Insulin Glargine (n = 122)	P-value for Comparison
A1C change from BL	-1.74	-1.04	<0.001
Patients with A1C ≤7% at endpoint, %	60	35	<0.001
Weight change from BL, kg	-1.8	+1.0	<0.001
Incidence of minor hypoglycemic events, %	25	29	NS
Discontinued due to AEs, %	9.5	0.8	<0.010

*Investigational therapy not currently approved by FDA.
BL = baseline.

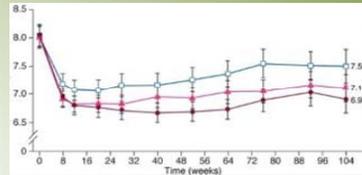
Buse JB, et al. *Ann Intern Med.* 2011;154:103–112.

Several studies have shown that basal insulin replacement can result in the attainment of A1C targets in up to 60% of patients when the insulin dose is systematically adjusted using structured titration regimens. Addition of prandial insulin is currently the treatment of choice for patients without an adequate response to basal insulin. Another investigational approach is adding a GLP-1 agonist to basal insulin. The rationale for this combination is that basal insulin provides glycemic control during the postabsorptive period while a GLP-1 receptor agonist controls postprandial glucose. In addition to complementing the mechanism of basal insulin, GLP-1 agonists promote modest weight loss and are associated with a low risk of hypoglycemia. Many of the studies that have assessed the combination of basal insulin and a GLP-1 agonist have been small, with methodological limitations.

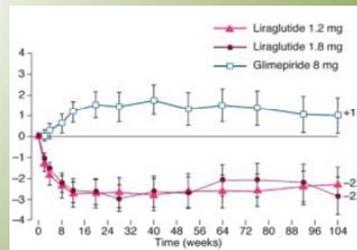
The most important study of combination therapy reported to date was a double-blind, placebo-controlled, multicenter, 30-week trial in which 137 patients were randomized to receive ExBID at a dose of 10 µg twice daily with insulin glargine and 122 patients were randomized to receive placebo with insulin glargine. At study end point, the mean A1C reduction from baseline was 1.74% in the ExBID group and 1.04% in the placebo group. Sixty percent of patients in the ExBID group and 35% of those in the placebo group attained an A1C of ≤7% at end point. Both of these differences were statistically significant. The mean weight change from baseline at end point was a decrease of 1.8 kg in the ExBID group and an increase of 1.0 kg in the placebo group. The incidence of minor hypoglycemic events was similar—25% with ExBID and 29% with placebo. No patients in the ExBID group and one patient in the placebo group experienced major hypoglycemia. There was a significantly higher discontinuation rate due to AEs in the ExBID group (9.5%) than in the placebo group (0.8%). Consistent with the tolerability profile of the GLP-1 agonists, there was a significantly higher incidence of nausea, diarrhea, vomiting, headache, and constipation in the ExBID group than in the placebo group. Other studies are now assessing the efficacy and safety of long-term treatment with a GLP-1 agonist and basal insulin.

Long-Term Safety and Efficacy of GLP-1 Agonist Therapy

- Benefits of GLP-1 agonists persist with long-term therapy
- In LEAD-3, patients received monotherapy with liraglutide 1.2 mg or 1.8 mg or glimepiride 8 mg for ≤ 2 years
- Liraglutide provided significant, sustained improvements in glycemic control and body weight compared with glimepiride, with significantly fewer hypoglycemic episodes



Mean Change in A1C Over Time, %



Mean Weight Change Over Time, kg

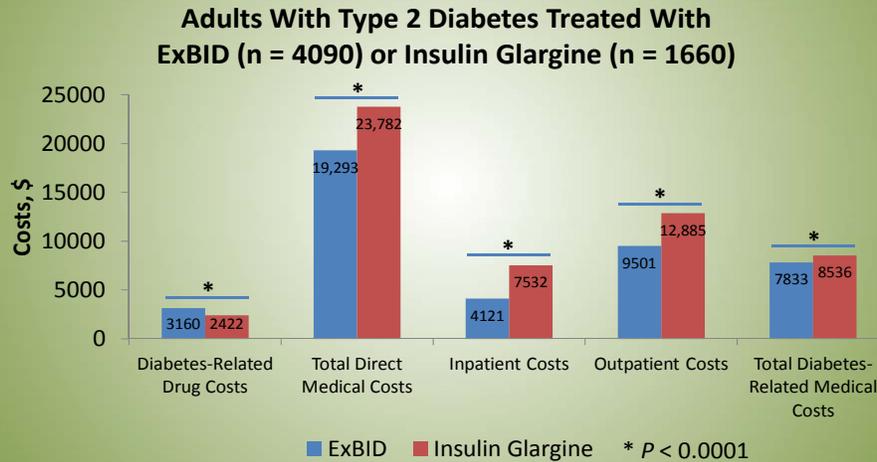
Garber A, et al. *Diabetes Obes Metab.* 2011;13:348–356.

Studies with ExBID, liraglutide, and ExQW have shown that the benefits of GLP-1 agonist therapy persist during long-term treatment. The graphs on this slide show changes in mean A1C and weight over time in the LEAD-3 study. LEAD-3 was a monotherapy study in which participants were randomized to receive liraglutide 1.2 mg, liraglutide 1.8 mg, or glimepiride 8 mg. Phase 1 of the study was a 52-week, double-blind, double-dummy trial and phase 2 was a 52-week open-label extension. Thus, patients received liraglutide or glimepiride for up to 104 weeks. Forty-three percent of the 746 patients who were originally randomized completed the study. Mean A1C reductions from baseline to 2 years were significantly greater with each dose of liraglutide than with glimepiride. For the 2-year completer population, reductions were 0.9% with liraglutide 1.2 mg, 1.1% with liraglutide 1.8 mg, and 0.6% with glimepiride.

As shown in the lower graph, mean body weight decreased over the first 12 weeks of therapy in both liraglutide groups, and these decreases were maintained over 2 years. At end point, mean weight reduction was 2.8 kg with liraglutide 1.8 mg and 2.3 kg with liraglutide 1.2 mg. In contrast, the mean weight change from baseline in the glimepiride group was 1.0 kg. Differences between each liraglutide dose and glimepiride were statistically significant.

Over 2 years, minor hypoglycemia occurred in 12% of the liraglutide 1.2 mg group, 10% of the liraglutide 1.8 mg group, and 26% of the glimepiride group. The rate of minor hypoglycemia was significantly lower with each dose of liraglutide than with glimepiride. Consistent with the findings of other studies, nausea was the most common AE in liraglutide-treated patients. The incidence of nausea over 2 years was 29% with liraglutide 1.2 mg, 31% with liraglutide 1.8 mg, and 9% with glimepiride. However, nausea in liraglutide-treated patients was most frequently reported early in the trial and its frequency remained below 5% throughout the extension.

Costs of GLP-1 Agonist Therapy



Misurski D, et al. *Appl Health Econ Health Policy*. 2009;7:245–254.

A disadvantage of the GLP-1 agonists is that they are more costly than some other classes of glucose-lowering agents. However, several recent studies have shown that the higher acquisition costs of a GLP-1 agonist are offset by a reduction in other medical costs. For example, the graph on this slide summarizes the results of a study that used data from a large, nationwide administrative claims database to compare costs among patients with type 2 diabetes who initiated therapy with ExBID or insulin glargine. The study included 4090 ExBID initiators and 1660 insulin glargine initiators. Eligible patients had received at least 2 prescriptions for an oral glucose-lowering agent in the 6 months before the first use of ExBID or insulin glargine and had continuous insurance coverage from 6 months before to 12 months after initiation of study medication.

The study found that patients treated with ExBID had significantly higher annual costs for diabetes-related drugs than those treated with insulin glargine. However, patients who received ExBID also had significantly lower total direct medical costs, inpatient costs, outpatient costs, and total diabetes-related medical costs. An important limitation of this study is that participants' duration of diabetes was not determined. Clearly, diabetes duration is a major determinant of the cost of diabetes treatment.

Comparative Trial: Liraglutide vs ExBID

LEAD-6: 26-Week, Randomized, Open-Label, Phase 3 Trial, N = 464
Patients Received GLP-1 Treatment With MET ± SU

Variable	Liraglutide 1.8 mg n = 233	ExBID 10 µg n = 231	P-Value for Comparison
Mean baseline A1C, %	8.2	8.1	NS
Mean baseline FPG, mg/dL	176	171	NS
Mean A1C ↓, %	1.12	0.79	< 0.0001
Mean FPG ↓, mg/dL	29	11	< 0.0001
A1C <7%, %	54	43	0.0015
Weight ↓, kg	3.2	2.9	0.2235
Nausea, %	26	28	NR
Minor hypoglycemia, %	26	34	NR
Major hypoglycemia, %	0	0.8	NR

FPG = fasting plasma glucose.

Buse JB, et al. *Lancet*. 2009;374:39–47.

Results of relatively few comparative clinical trials of GLP-1 agonists have been reported to date. One of these is the LEAD-6 study, which is comparing liraglutide 1.8 mg with ExBID 10 µg. Part 1 of this trial was a 26-week, randomized, open-label, phase 3 study that included 464 randomized patients, 233 assigned to receive liraglutide and 231 assigned to receive ExBID. Patients also received metformin, a sulfonylurea, or both. Mean baseline A1C and FPG levels were similar in the 2 treatment groups.

At the 26-week study end point, treatment with liraglutide resulted in significantly greater mean reductions from baseline in A1C, FPG, and weight than treatment with ExBID. A significantly greater proportion of liraglutide- than ExBID-treated patients met the ADA A1C target of <7%. The investigators credited the larger reduction in A1C values to the greater reduction in FPG that occurred with liraglutide. Although the incidence of nausea was similar in the 2 treatment groups, nausea resolved more quickly in liraglutide-treated patients. Lower rates of minor and major hypoglycemia were reported with liraglutide.

Comparative Trial: ExQW vs ExBID

DURATION-5: 24-Week, Randomized, Open-Label, Phase 3 Trial, N = 252
Patients Received GLP-1 Treatment With MET, a SU, a TZD, or Any Combination

Variable	ExQW 2 mg n = 129	ExBID 10 µg n = 123	P-Value for Comparison
Mean baseline A1C, %	8.5	8.3	NS
Mean baseline FPG, mg/dL	173	168	NS
Mean A1C ↓, %	1.6	0.9	< 0.0001
Mean FPG ↓, mg/dL	35	12	< 0.0008
A1C <7%, %	58	30	0.0015
Weight ↓, kg	2.3	1.4	NS
Nausea, %	14	35	NR
Minor hypoglycemia, %	3.9	3.2	NR
Major hypoglycemia, %	0	0	NR

Blevins T, et al. *J Clin Endocrinol Metab.* 2011;96:1301–1310.

Another comparative trial of GLP-1 agonists was DURATION-5, which is comparing ExQW 2 mg with ExBID 10 µg. Part 1 of this trial was a 24-week, randomized, open-label, phase 3 study that included 252 randomized patients, 129 assigned to receive liraglutide and 123 assigned to receive ExBID. Patients also received metformin, a sulfonylurea, a TZD, or any combination of those oral agents. Mean baseline A1C and FPG levels were similar in the treatment groups.

At the 24-week study end point, treatment with ExQW resulted in significantly greater mean reductions from baseline in A1C and FPG than treatment with ExBID. A significantly greater proportion of ExQW- than ExBID-treated patients met the ADA A1C target of <7%. Weight loss was numerically greater in the ExQW group, but the difference was not statistically significant. The incidence of nausea reported in the ExQW group (14%) was less than half of that reported in the ExBID group (35%). The incidence of minor hypoglycemia was low in both groups, although it was slightly higher in patients treated with ExQW. Major hypoglycemia was not reported in either group. The investigators concluded that continuous GLP-1 receptor agonism with ExQW resulted in superior glycemic control, with less nausea, compared with ExBID.

Case 1: Patient Profile

- Olivia, a 58-year-old Hispanic female
- Widow with 3 teenage children
- Human resources manager for large corporation
- Height, 63 in; weight, 172 lb; BMI, 30.5 kg/m²
- 10-pound weight gain in past year
- “No time” for physical activity
- 5-year history of type 2 diabetes
- No diabetes-associated complications, normal renal function

This case describes a patient who is an appropriate candidate for treatment with a GLP-1 agonist.

Olivia is a 58-year-old Hispanic female who returns to her healthcare provider for a routine physical examination. Her husband died suddenly 15 months ago and she has 3 active teenage sons, one of whom is driving. She works as a human resources manager for a large corporation.

Olivia is 63 inches tall, weighs 172 pounds, and has a BMI of 30.5 kg/m². She has gained 10 pounds over the past year. She attributes this weight gain to eating snack food in the mid-afternoon when she feels low on energy. She says that she often has second helpings of her favorite foods when she feels stressed by her responsibilities as a single parent. Between her work schedule, a 30-minute commute to work, and driving her 2 younger children to athletic practices and games, she says that she has no time for physical activity.

Olivia was diagnosed with type 2 diabetes 5 years ago. Currently she has no diagnosed diabetes complications. Testing last year revealed normal renal function. She has no other health issues.

Case 1: Current Regimen, Blood Pressure, and Laboratory Values

- Metformin 1000 mg twice daily
- Glipizide extended release 10 mg once daily

Parameter	Olivia's Value	ADA Recommendation
A1C, %	8.4	<7.0
FPG, mg/dL	187	70–130
PPG, mg/dL	Not measured	<180
SBP/DBP, mmHg	141/88	<130/80
LDL-C, mg/dL	114	<100*
HDL-C, mg/dL	33	>50 [†]
Triglycerides, mg/dL	194	<150

PPG = postprandial glucose; Red type = does not meet ADA goal.

*Goal for individuals without overt cardiovascular disease (CVD). Goal is <70 mg/dL in individuals with overt CVD.

[†]Goal in women. Goal is >40 mg/dL in men.

American Diabetes Association. *Diabetes Care*. 2011;34(Suppl 1):S11–S61.

Olivia's current pharmacologic regimen is metformin 1000 mg twice daily and glipizide extended release 10 mg once daily. Both agents are well tolerated.

As the table shows, her blood glucose values, blood pressure, and lipid levels do not meet the goals recommended by the ADA.

Her A1C is 8.4%, her FPG level is 187 mg/dL and her PPG value was not measured. Thus, her A1C level exceeds the ADA target by 1.4% and her FPG exceeds the high end of the recommended range by 57 mg/dL.

Olivia's blood pressure is 141/88, whereas the ADA recommends values of <130/80. Recall that the ADA standards also state that patients with a SBP of 130–139 mmHg or a DBP of 80–89 mmHg may be given lifestyle therapy alone for a maximum of 3 months. Then, if targets are not achieved, they should be treated with a regimen that contains either an ACE inhibitor or an angiotensin receptor blocker (ARB). Patients with more severe hypertension, defined as SBP of ≥140 mmHg or DBP of ≥90 mmHg at diagnosis or follow-up, should receive pharmacologic therapy in addition to lifestyle therapy. Thus, Olivia is a candidate for an antihypertensive agent on the basis of her SBP value and a candidate for lifestyle therapy on the basis of her DBP value.

Olivia's LDL-C value is 114 mg/dL, and thus exceeds the ADA target for patients without overt cardiovascular disease by 14 mg/dL. Her HDL-C value is 33 mg/dL and is thus 17 mg/dL below the recommended value of 50 mg/dL for women. Her triglyceride level is 194 mg/dL, thus exceeding the ADA-recommended value of 150 mg/dL by 44 points. Recall that the ADA recommends statin therapy, regardless of baseline A1C levels, for patients with diabetes who do not have overt cardiovascular disease but who are over age 40 and have one or more other CVD risk factors, such as obesity.

Case 1: Considerations in Selecting a Treatment Regimen

- Olivia's A1C and FPG are not at goal
- She has obesity, mild hypertension, and dyslipidemia

Treatment	Considerations
Increase MET dose from 2000 mg/d to maximum (2500 mg/d)	Unlikely to have substantial effect on BG values
Increase glipizide extended release dose from 10 mg/d to maximum (20 mg/d)	Might have beneficial effect on BG values, but could also lead to further weight gain and hypoglycemia
Add a TZD	Might bring BG values to goal, but could result in further weight gain
Add a DPP-4 inhibitor	Would reduce BG levels, but probably not sufficiently; unlikely to affect weight
Add a GLP-1 agonist	Might bring BG values to goal and have beneficial effects on weight, BP, and lipids
Add a statin	Combined with MNT, likely to bring lipid levels to goal

MNT = medical nutrition therapy.

Nathan DM, et al. *Diabetes Care*. 2009;32:193–203.

In determining the optimal treatment regimen for Olivia, several considerations are important. Her A1C and FPG are not at goal and it is probable that her PPG level also exceeds the ADA goal of <180 mg/dL. Additionally, Olivia has obesity, mild hypertension, and dyslipidemia.

There are several treatment options for Olivia. Her metformin dose could be increased from 2000 mg/day to the maximum dose of 2500 mg/day, but this small increase would probably not have a substantial effect on Olivia's BG values. Additionally, the maximum clinically effective dose of metformin is 1000 mg twice daily. Her dose of glipizide extended release could be increased from 10 mg/day to the maximum dose of 20 mg/day. This dose escalation might have a beneficial effect on her BG values, but it would probably not be sufficient to bring Olivia to goal. Furthermore, this approach could lead to further weight gain and episodes of hypoglycemia, which would be very undesirable for someone who spends much of her time driving a car. Adding a TZD to Olivia's regimen might bring her BG values to goal, but it could also result in additional weight gain. Adding a DPP-4 inhibitor would reduce Olivia's BG levels, but probably not sufficiently. Furthermore, DPP-4 inhibitor therapy would probably not reduce her weight.

Considering Olivia's overall situation, adding a GLP-1 agonist is her best option. It might bring her BG values to goal while also exerting beneficial effects on her weight, blood pressure, and lipid levels. Since she is over age 40 and has obesity and hypertension, it would be appropriate for Olivia to begin statin therapy at this point even if her lipid values met ADA goals.

Olivia's health care provider also referred her to a registered dietitian for medical nutrition therapy (MNT). Olivia was very pleased with this referral, since it would give her the opportunity to explore healthy weight loss options, learn about nutritious food choices that might boost her energy level in the afternoon, and learn about healthy responses to stress. The health care provider also encouraged her to look for opportunities to get some aerobic exercise as part of her daily routine, such as walking briskly in the park while her sons are at soccer practice.

Case 1: Treatment Regimen and Three-Month Results

- Metformin 1000 mg twice daily, **glipizide extended release 5 mg** once daily, and **liraglutide 1.2 mg** once daily
- Simvastatin 20 mg once daily
- Weight reduction: 9 pounds

Parameter	Olivia's Value	ADA Recommendation
A1C, %	7.3	<7.0
FPG, mg/dL	139	70–130
PPG, mg/dL	176	<180
SBP/DBP, mmHg	135/79	<130/80
LDL-C, mg/dL	95	<100*
HDL-C, mg/dL	47	>50 [†]
Triglycerides, mg/dL	163	<150

Green type = meets ADA goal; red type = does not meet ADA goal.

*Goal for individuals without overt cardiovascular disease (CVD). Goal is <70 mg/dL in individuals with overt CVD.

[†]Goal in women. Goal is >40 mg/dL in men.

American Diabetes Association. *Diabetes Care*. 2011;34(Suppl 1):S11–S61.

After learning about GLP-1 agonist therapy and how to use a disposable pen, Olivia began receiving a glucose-lowering regimen that included 3 agents. Following titration of the GLP-1 agonist, her new regimen included metformin 1000 mg twice daily, glipizide extended release 5 mg once daily, and liraglutide 1.2 mg once daily. Note that Olivia's former dose of glipizide was reduced by 50%, an approach recommended when a sulfonylurea is administered together with an incretin-based therapy to reduce the risk of hypoglycemia. Olivia also began statin therapy, taking simvastatin at a dose of 20 mg once daily.

Olivia found MNT to be very helpful, and lost 9 pounds over a 3-month period. She said that she had become very creative about finding ways to get extra exercise while doing routine chores around the house.

Olivia had substantial improvement in her BG values, blood pressure, and lipid levels after 3 months of treatment with her new glucose-lowering regimen and a statin. In the table, values that are at goal are shown in green and those that not at goal are shown in red. Although Olivia's A1C still exceeded the A1C goal, it had decreased by 1.1% and was 7.3%—nearly at goal. At 139 mg/dL, her FPG was approaching the recommended range and her PPG was at goal. Weight loss and treatment with a GLP-1 agonist appear to have had beneficial effects on Olivia's blood pressure. Her SBP dropped by 6 points, from 141 mmHg to 135 mmHg and thus remained slightly elevated, while her DBP dropped by 9 points, from 88 to 79 mmHg, and thus was within the recommended range. Statin therapy, weight loss, and treatment with a GLP-1 agonist also seem to have had a favorable effect on Olivia's lipid levels. Her LDL-C level fell from 114 to 95 mg/dL and thus was at goal. Her HDL-C level rose from 33 mg/dL to 47 mg/dL and thus approached the ADA target of 50 mg/dL for women. Her triglyceride level decreased by 31 mg/dL, to 163 mg/dL. Although this value remained above target, it was greatly improved.

In view of the substantial progress she has made and the fact that all values are at or approaching goal, Olivia will continue her current regimen for 3 more months. At that point a decision will be made about whether her regimen of glucose-lowering agents should be modified in some way, whether she should begin treatment with an ACE inhibitor or ARB, and whether her statin dose should be increased.

Checkpoint 2

Typical effects of GLP-1 agonist therapy include _____.

- a. weight loss and a slight reduction in the heart rate
- b. low risk of hypoglycemia when given with a sulfonylurea and a modest reduction in DBP
- c. possible nausea that often diminishes over time and reduced triglyceride levels
- d. a modest increase in SBP and a low risk of hypoglycemia when given as monotherapy

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Answer to Checkpoint 2

The correct answer is **c**.

Typical effects of GLP-1 agonist therapy include possible nausea that often diminishes over time and reduced triglyceride levels.

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Typical effects of GLP-1 agonist therapy include possible nausea that often diminishes over time and reduced triglyceride levels.

Introduction to DPP-4 Inhibitors

Agents Approved for Use in the US or in Late-Phase Development*

Agent (Brand Name)	Manufacturer	US Status
Linagliptin (Tradjenta™) [†]	Boehringer Ingelheim	Approved, 5/11
Saxagliptin (Onglyza™) [†]	Bristol-Myers Squibb	Approved, 7/09
Sitagliptin (Januvia®) [†]	Merck	Approved, 10/06
Alogliptin (Nesina®)	Takeda	FDA CRL, 6/09
Vildagliptin (Galvus®) [‡]	Novartis	Data resubmission to FDA not planned, 10/08
Dutogliptin [‡]	Phenomix, Forest	Phase 3 trials terminated, 2/11

*Effective June 2011.

[†]Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

[‡]Will not be discussed in this activity.

US FDA. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011.

Januvia®. Prescribing information. April 2011. Takeda. Available at: http://www.takeda.com/press/article_34760.htm.

Novartis. Available at: <http://www.novartis.com/newsroom/media-releases/en/2008/1249901.shtml>.

Trading Markets.com. Available at: http://www.tradingmarkets.com/news/stock-alert/frx_phmx-forest-laboratories-terminates-agreement-with-phenomix-for-dutogliptin-phx1149-934212.html.

This slide shows the DPP-4 inhibitors that are approved for use in the US or in late-phase clinical development as of June 2011. Linagliptin has the brand name Tradjenta™. It is marketed by Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company. It was approved by the FDA in May 2011. Saxagliptin, marketed under the name Onglyza™, is marketed by Bristol-Myers Squibb Company and AstraZeneca Pharmaceuticals LP. It received FDA approval in July 2009. Sitagliptin® has the brand name Januvia®. It is marketed by Merck & Co., Inc. Linagliptin, saxagliptin, and sitagliptin are all indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes. Alogliptin, which has the brand name Nesina®, is being developed by Takeda Pharmaceutical Company Limited. In June 2009 the FDA issued a complete response letter, requiring a cardiac safety study to be conducted. Vildagliptin, which has the brand name Galvus®, is marketed by Novartis. It is currently available in over 50 countries, but not the US. In 2007, after receiving what was then called “an approvable letter” from the FDA, Novartis entered into discussions with the FDA to determine how issues preventing the US approval of vildagliptin could be addressed. Several clinical trials, some of which are still continuing, were also initiated. However, Novartis announced in 2008 that resubmission of the New Drug Application for vildagliptin is not planned in the foreseeable future. Dutogliptin was being developed by Phenomix Corporation and Forest Laboratories, but phase 3 clinical trials with dutogliptin were terminated in February 2011. Therefore, neither vildagliptin nor dutogliptin will be covered in this activity.

Pharmacologic and PK Characteristics of DPP-4 Inhibitors

Agent	Ex Vivo DPP-4 Inhibition, %		Metabolism	Elimination
	Maximum	24 H Postdose		
Linagliptin	~80%	~70	~90% eliminated unchanged; exposure decreased by CYP3A4 or P-gp inducers	Biliary (>70% unchanged as parent), <6% via kidney
Saxagliptin	~80%	~70	Hepatically metabolized to active metabolite via CYP3A4/5	Renal (12-29% as parent, 21-52% as metabolite)
Sitagliptin	~97%	~80	Not appreciably metabolized	Renal (>80% unchanged as parent)
Alogliptin	~90%	~75	Not appreciably metabolized	Renal (>70% unchanged as parent)

CYP = cytochrome P450; P-gp = P-glycoprotein; PK = pharmacokinetic.

Deacon CF. *Diabetes Obes Metab.* 2011;13:7-18. Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011. Januvia®. Prescribing information. April 2011.

This table summarizes some major pharmacologic and pharmacokinetic (PK) characteristics of the 3 approved DPP-4 inhibitors and alogliptin. All of these agents are highly selective for the DPP-4 enzyme, and none has shown any significant activity on other important enzymes, such as quiescent cell proline dipeptidase, DPP-8, or DPP-9. Ex vivo studies using human plasma demonstrated that all of these agents are potent inhibitors of DPP-4, with maximum inhibition ranging from 80% to 97% and inhibition remaining in the 70% to 80% range at 24 hours postdose.

Although 3 of the DPP-4 inhibitors are not appreciably metabolized, saxagliptin is hepatically metabolized by cytochrome P450 (CYP) isoenzymes 3A4 and 3A5 to produce the active metabolite 5-hydroxy saxagliptin. Ketoconazole significantly increases saxagliptin exposure, and clinically relevant increases in saxagliptin plasma concentrations are anticipated with other strong CYP3A4/5 inhibitors, such as clarithromycin, itraconazole, and ritonavir. The usual recommended daily dose of saxagliptin is 2.5 mg or 5 mg, but dose should be limited to 2.5 mg during coadministration with a strong CYP3A4/5 inhibitor. Although linagliptin is not appreciably metabolized, it is a CYP3A4 and P-glycoprotein (P-gp) substrate, and strong inducers of CYP3A4 or P-gp such as rifampin decrease linagliptin exposure to subtherapeutic concentrations. Patients who must take a CYP3A4 or P-gp inducer should use a different glucose-lowering agent.

Another important difference among the DPP-4 inhibitors involves their elimination pathways. Unlike the other DPP-4 inhibitors, which are eliminated by the kidney, linagliptin is eliminated almost entirely by the liver. In contrast to saxagliptin and sitagliptin, linagliptin can be given without dose modification in patients with renal impairment. (Since alogliptin is not currently approved for use in the US, recommendations about its use in special populations are not available.) Dose modifications with the DPP-4 inhibitors are discussed further in the next slide.

Approved and Standard Investigational Doses of DPP-4 Inhibitors

- All DPP-4 inhibitors should be taken orally, once daily, with or without food
- Dose titration at the beginning of therapy is not required

Agent	Standard Dose	Moderate Renal Impairment	Severe Renal Impairment or ESRD	Other
Linagliptin	5 mg	5 mg	5 mg	None*
Saxagliptin [†]	2.5, 5 mg	2.5 mg	2.5 mg	2.5 mg with strong CYP3A4/5 inhibitors
Sitagliptin [†]	100 mg	50 mg	25 mg	None
Alogliptin	12.5, 25 mg [‡]	ND	ND	ND

ESRD = end-stage renal disease; ND = not determined.

*Should not be used by patients who must take a CYP3A4 or P-gp inducer.

[†]Assess renal function before initiating therapy and periodically thereafter.

[‡]Investigational doses in phase 3 clinical trials.

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011. Januvia®. Prescribing information. April 2011. Andukuri A, et al. *Diabetes Metab Syndr Obes.* 2009;2:117–126.

All DPP-4 inhibitors should be taken orally, once daily, with or without food. In contrast to some of the GLP-1 agonists, dose titration at the beginning of therapy is not needed.

The recommended dose of linagliptin is 5 mg. Since it is eliminated almost exclusively by the liver, no dose reduction is needed for patients with any degree of renal impairment. Linagliptin, like the other approved DPP-4 inhibitors, can be used in patients with hepatic impairment without dose modification. As previously mentioned, linagliptin should not be used by patients who require ongoing therapy with a CYP3A4 or P-gp inducer.

Saxagliptin should be administered at a dose of 2.5 mg or 5 mg. Patients with moderate or severe renal impairment and those with ESRD should receive the 2.5 mg dose. As mentioned previously, the 2.5 mg dose is also recommended when saxagliptin is taken in combination with a strong CYP3A4/5 inhibitor.

The standard dose of sitagliptin is 100 mg. The dose should be reduced to 50 mg for patients with moderate renal impairment and to 25 mg for those with severe renal impairment or ESRD. Candidates for saxagliptin or sitagliptin therapy should have their renal function assessed before beginning treatment and have periodic renal function assessments thereafter to ensure that dose modification is not needed.

In phase 3 clinical trials, alogliptin has been administered at doses of 12.5 mg and 25 mg. Since alogliptin is not currently approved for use in the US, recommendations about dose modification are not available.

A1C Reductions (%) From Baseline With DPP-4 Inhibitors*

Agent	MONO	+ MET	+ SU	+ MET, + SU	+ TZD (± MET/± SU)	Insulin (± MET)
Linagliptin, 5 mg	-0.4	-0.5	-0.5	-0.7	-1.1	-
Saxagliptin, 2.5 mg	-0.4 [†]	-0.6	-0.5	-	-0.7	-
Saxagliptin, 5 mg	-0.5 [†]	-0.7	-0.6	-	-0.9	-
Sitagliptin, 100 mg	-0.6 -0.8 [†]	-0.7	-0.3	-0.6	-0.9 -2.4 [†]	-0.6
Alogliptin, 12.5 mg	-0.6 [†]	-0.6	-0.4	-	-0.7 -1.6 [†]	-0.6
Alogliptin, 25 mg	-0.6 [†]	-0.6	-0.5	-	-0.8	-0.7

Red text = upper end of range; green text = lower end of range.

*In phase 3 trials with a duration of 24 or 26 weeks.

[†]All patients were treatment-naïve.

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011. Januvia®. Prescribing information. April 2011. Andukuri A, et al. *Diabetes Metab Syndr Obes.* 2009;2:117–126. Rosenstock J, et al. *Diabetes Obes Metab.* 2009;11:1145–1152.

This slide shows mean A1C reductions from baseline at the end points of phase 3 clinical trials of DPP-4 inhibitors. The linagliptin, saxagliptin, and sitagliptin trials had a duration of 24 weeks and the alogliptin trials lasted for 26 weeks. In the monotherapy trials, A1C reductions ranged from 0.4% to 0.6% in studies that included previously treated patients and from 0.4% to 0.8% in studies that enrolled only treatment-naïve patients.

In combination trials in which a DPP-4 inhibitor was added on to existing therapy, A1C reductions ranged from 0.3% to 1.1%. Reductions of 1.6% and 2.4% were reported in combination studies in which all patients were treatment naïve. Overall, the greatest reductions occurred with a DPP-4 inhibitor was administered with a TZD, with or without metformin or a sulfonylurea.

Collectively, the results of these studies show that the A1C reductions attained with the DPP-4 inhibitors are somewhat less than those observed with GLP-1 agonists.

Other Beneficial Effects of DPP-4 Inhibitor Therapy

- Neutral effect on weight and caloric intake
 - Beneficial for many older adults, since muscle and total body protein mass are preserved
- Post hoc analyses suggest that risk of CV events may be reduced
 - Relative risk of CV events with saxagliptin vs comparators: 0.44 (95% CI, 0.24 to 0.80)
- Inconsistent data concerning effects on CV risk factors (eg, blood pressure, lipids)

CV = cardiovascular.

Dicker D. *Diabetes Care*. 2011;34 (Suppl 2):S276–S278.
Frederich R, et al. *Postgrad Med*. 2010;122:16–27.

In addition to reducing BG levels, available data suggest that treatment with a DPP-4 inhibitor may confer additional benefits to patients. Unlike many other classes of glucose-lowering agents, the DPP-4 inhibitors have a neutral effect on weight and caloric intake. This effect is particularly beneficial for many older adults, since muscle and total body protein mass are preserved during treatment.

Post hoc analyses of registration trials suggest that DPP-4 therapy may be associated with a reduced risk of cardiovascular (CV) events. For example, a pooled analysis of 8 clinical trials of saxagliptin found that the relative risk of experiencing a CV during treatment with saxagliptin relative to treatment with a comparator was 0.44. This finding, along with retrospective data for other members of this therapeutic class, suggest that DPP-4 treatment may reduce the risk of CV events in patients with type 2 diabetes. Ongoing CV outcome studies are investigating this issue prospectively.

To date, there is no consistent evidence suggesting that DPP-4 inhibitor therapy has a beneficial effect on blood pressure, lipids, or other CV risk factors.

Combination Therapy With Basal Insulin and a DPP-4 Inhibitor (+ Metformin)*

Parameter	SITA + Insulin Glargine + MET (n = 16)	Insulin Glargine + MET (n = 16)	P-value for Comparison
A1C change from BL	-1.5 [†]	-1.2 [†]	NS
% of patients with A1C ≤7% at endpoint	88	63	NS
Weight change from BL, kg	+0.1	+0.4	NS
Incidence of minor hypoglycemia, %	25	37	NS
TC change from BL, mg/dL	-10	+12 [†]	< 0.01
LDL-C change from BL, mg/dL	-11 [†]	+3	<0.5

BL = baseline; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

*Study also had ExBID arm; data not reported here.

[†]P < 0.05 vs baseline.

Arnolds S, et al. *Diabetes Care*. 2010;33:1509–1515.

Ongoing studies are investigating the effects of adding a DPP-4 inhibitor to basal insulin. This slide shows the results of a 4-week, open-label, proof-of-concept study in adults with type 2 diabetes and a mean A1C of 8.1%. Sixteen patients were randomized to continue their treatment with insulin glargine plus metformin, and 16 patients were randomized to add-on treatment with sitagliptin plus insulin glargine and metformin. (The study also had an ExBID arm, but those data are not reported here.)

Both treatments were shown to be highly effective at end point, significantly reducing the mean A1C from baseline. The mean 1.49% decrease seen with adjunctive sitagliptin did not differ significantly from the 1.23% decrease seen with insulin glargine plus metformin.

The most noteworthy effect of sitagliptin augmentation was its beneficial effects on total cholesterol and LDL cholesterol levels. Total cholesterol decreased by 10 mg/dL in the adjunctive sitagliptin group and increased by 12 mg/dL in the insulin glargine plus metformin group. This increase was a statistically significant change from baseline. The difference between the adjunctive sitagliptin group and the insulin glargine plus metformin group was also statistically significant. In addition, treatment with adjunctive sitagliptin resulted in a statistically significant reduction in the LDL cholesterol level from baseline at endpoint, while patients in the insulin glargine plus metformin group had a nonsignificant increase from baseline. At endpoint, the difference between the 2 groups was statistically significant. Data from longer-term studies are needed to determine whether the favorable effects of adjunctive sitagliptin on plasma lipids are sustained.

Frequently Reported AEs in Patients Receiving a DPP-4 Inhibitor*

Adverse Reactions Reported in $\geq 5\%$ of Patients and More Commonly Than in Patients Given Placebo in Phase 3 Monotherapy Studies, %

Agent	Headache	Nasopharyngitis	Skin-Related	URTI	UTI
Linagliptin, 5 mg	–	5.8	–	–	–
Saxagliptin, 2.5 mg	6.5	–	–	–	–
Saxagliptin, 5 mg	6.5	–	–	7.7	6.8
Sitagliptin, 100 mg	–	5.2	–	–	–
Alogliptin, 12.5 mg	6.8	–	12.8	–	–
Alogliptin, 25 mg	7.5	–	15.2	–	–

*Excluding hypoglycemia.

URTI = upper respiratory tract infection; UTI, urinary tract infection.

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011. Januvia®. Prescribing information. April 2011. DeFronzo RA, et al. *Diabetes Care*. 2008;31:2315–2317. Deacon CF. *Diabetes Obes Metab*. 2011;13:7–18.

Overall, the DPP-4 inhibitors are very well tolerated, and few differences among the safety profiles of the various DPP-4 inhibitors have emerged. During clinical trials, most treatment-emergent AEs, including nausea and other GI-related events, were reported at similar levels in patients who received a DPP-4 inhibitor and placebo. The lower GLP-1 concentrations seen with DPP-4 inhibitor therapy help to explain why GI AEs are reported infrequently with the DPP-4 inhibitors and more frequently with the GLP-1 agonists.

This table shows the frequency of AEs reported in at least 5% of patients and more commonly in patients given a DPP-4 inhibitor than placebo in phase 3 monotherapy studies. The most commonly reported AEs were headache and minor infections, including nasopharyngitis, upper respiratory tract infection (URTI), and urinary tract infection (UTI). The next slide provides additional information about infections in patients treated with a DPP-4 inhibitor.

Skin-related ARs, consisting mostly of pruritus, were reported in 12.8% of patients who received alogliptin at a dose of 12.5 mg/day and in 15.2% of those receiving alogliptin 25 mg/day. During the preclinical development programs for vildagliptin and saxagliptin, necrotic skin lesions were observed in monkeys. The mechanism underlying these lesions remains unclear, and similar lesions have not been reported during clinical trials of DPP-4 inhibitors despite intensive surveillance.

Incidence of Hypoglycemia With DPP-4 Inhibitors in Phase 3 Trials

- Monotherapy
 - Incidence of any hypoglycemia similar with DPP-4 inhibitor and placebo (0–3%)
 - No major hypoglycemia reported
- Combination therapy
 - Highest incidence of hypoglycemia when given with insulin or a SU
 - Any (major) hypoglycemia incidence
 - Insulin-containing regimen: 16–27% (0–0.6%)
 - SU-containing regimen: 0.8–23% (0–1.0%)
 - Other combination: 0–9% (0%)

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011. Januvia®. Prescribing information. April 2011. Andukuri A, et al. *Diabetes Metab Syndr Obes*. 2009;2:117–126. Rosenstock J, et al. *Diabetes Obes Metab*. 2009;11:1145–1152.

During phase 3 clinical trials of DPP-4 inhibitor therapy, the reported frequency of any hypoglycemia was very low and similar to or lower than that reported for placebo. In monotherapy trials, the incidence of any hypoglycemia was 0% to 3% and no episodes of major hypoglycemia were reported. In combination therapy trials, the highest incidence of hypoglycemia was reported when a DPP-4 inhibitor was given with insulin or a sulfonylurea. When a DPP-4 inhibitor was given with basal insulin, reported ranges were 16% to 27% for any hypoglycemia and 0% to 0.6% for major hypoglycemia. Ranges were 0.8% to 23% for any hypoglycemia and 0% to 1% for major hypoglycemia when a DPP-4 inhibitor was given with a sulfonylurea. When a DPP-4 inhibitor was given with another combination, the reported range was 0% to 9% for any hypoglycemia and no major hypoglycemia was reported.

The PIs for linagliptin, saxagliptin, and sitagliptin caution that a lower dose of secretagogue may be required to reduce the risk of hypoglycemia when the DPP-4 inhibitor is used in combination with an insulin secretagogue. The PI for sitagliptin also cautions that a lower insulin dose may be required during administration with a DPP-4 inhibitor.

Other Safety Issues With DPP-4 Inhibitor Therapy

- Hypersensitivity reaction (rare)
 - Angioedema, urticaria, skin exfoliation
 - Typically occurs early in treatment
 - ACE inhibitor treatment increases risk
- Pancreatitis (rare)
 - Diabetes increases risk
 - Meta-analyses find no increased risk with DPP-4 inhibitor therapy
- Decreased dose-related mean absolute lymphocyte count with saxagliptin, but clinically relevant adverse reactions not seen

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011. Januvia®. Prescribing information. April 2011. Waeber B, et al. *Rev Med Suisse*. 2010;6:28–31. Engel SS, et al. *Int J Clin Pract*. 2010;64:984–990.

Hypersensitivity reactions (HSRs), including angioedema, urticaria, exfoliative skin conditions, cutaneous vasculitis, bronchial hyperreactivity, and anaphylaxis, are rare adverse effects of DPP-4 inhibitor therapy. HSRs typically occur during the first 3 months of treatment, especially during concomitant treatment with an angiotensin converting enzyme (ACE) inhibitor. The mechanism for these reactions is currently unknown. However, both DPP-4 and ACE promote the inactivation of the proinflammatory peptides bradykinin and substance P. Therefore, an accumulation of bradykinin and substance P could potentially lead to HSRs. Health care providers should familiarize patients with the clinical manifestations of HSRs before they begin DPP-4 inhibitor therapy and instruct them to report a possible HSR immediately.

During clinical trials and postmarketing surveillance, a very low incidence of pancreatitis has been reported in patients with a DPP-4 inhibitor. During the clinical trial program for linagliptin, for example, pancreatitis was reported in 0.2% of linagliptin-treated patients and in no patients who received placebo. As mentioned previously, diabetes itself increases the risk of pancreatitis, and patients may have other risk factors that predispose them to pancreatitis. Thus far, meta-analyses have not found an increased incidence of pancreatitis in patients treated with DPP-4 inhibitors relative to patients receiving other treatments for diabetes. However, health care providers should educate candidates for DPP-4 inhibitor therapy about the symptoms of pancreatitis and instruct them to report any symptoms promptly.

During clinical trials, a dose-related mean decrease in the absolute lymphocyte count (ALC) was observed with saxagliptin. From a baseline mean ALC of 2200 cells/ μ L, a pooled analysis of five 24-week placebo-controlled clinical trials found a mean decrease of approximately 120 cells/ μ L with saxagliptin 5 mg and no mean decrease with saxagliptin 2.5 mg. The proportion of patients who had an ALC of less than 750 cells/ μ L was 0.5% with saxagliptin 2.5 mg, 1.5% with saxagliptin 5 mg, and 0.4% with placebo. Decreases in lymphocyte count were not associated with clinically relevant adverse reactions. However, the ALC should be measured if a saxagliptin-treated patient develops an unusual or prolonged infection.

Long-Term Safety and Efficacy of DPP-4 Inhibitor Therapy

52-Week Data From Noninferiority Trials Comparing
a DPP-4 Inhibitor + Metformin With a Sulfonylurea + Metformin

Parameter	Linagliptin		Saxagliptin		Sitagliptin	
	LINA 5 mg + MET (n = 778)	GLIM + MET (n = 781)	SAXA 5 mg + MET (n = 428)	GLIP + MET (n = 430)	SITA 100 mg + MET (n = 588)	GLIP + MET (n = 584)
Baseline A1C, %	7.7	7.7	7.7	7.6	7.7	7.6
Mean change, %	-0.4	-0.6	-0.6	-0.7	-0.5	-0.6
Baseline FPG, mg/dL	164	167	162	161	166	164
Mean change, mg/dL	-9	-16	-9	-16	-8	-8
Hypoglycemia incidence, %	5*	32	3 [†]	36	5 [†]	32

GLIM = glimepiride; GLIP = glipizide; LINA = linagliptin; SAXA = saxagliptin; SITA = sitagliptin.
*P < 0.0001 vs glimepiride. [†]P-value for comparison with glipizide not reported.

Tradjenta™. Prescribing information. May 2011. Onglyza™. Prescribing information. February 2011.
Januvia®. Prescribing information. April 2011. Göke B, et al. *Int J Clin Pract*. 2010;64:1619–1631.
Nauck MA, et al. *Diabetes Obes Metab*. 2007;9:194–205.

As part of the drug approval process for a DPP-4 inhibitor, the DPP-4 inhibitor is compared to a sulfonylurea in a long-term noninferiority trial. Patients with an inadequate response to metformin are randomized to receive add-on treatment with a DPP-4 inhibitor or a sulfonylurea. This table shows 52-week data for the currently approved DPP-4 inhibitors. Patients randomized to a sulfonylurea received glimepiride in the linagliptin trial and glipizide in the saxagliptin and sitagliptin trials. The baseline A1C values of participants ranged from 7.6 to 7.7%. In each trial, the mean A1C reduction from baseline attained with a DPP-4 inhibitor was noninferior to that achieved with a sulfonylurea. A1C reductions ranged from 0.4 to 0.6% with a DPP-4 inhibitor and from 0.6 to 0.7% with a sulfonylurea. Similarly, mean FPG reductions from baseline with a DPP-4 inhibitor, which ranged from 8 to 9 mg/dL, were noninferior to the reductions of 8 to 16 mg/dL seen with a sulfonylurea.

All treatments were well tolerated, and except for hypoglycemia, the incidence of AEs were similar with a DPP-4 inhibitor and a sulfonylurea. The AE profile observed with the DPP-4 inhibitors was similar to that observed in 24-week studies. However, the frequency of hypoglycemia was substantially higher in patients who received a sulfonylurea. The incidence of hypoglycemia ranged from 3 to 5% with a DPP-4 inhibitor and from 32 to 36% with a sulfonylurea. These studies showed that long-term treatment with a DPP-4 inhibitor results in sustained glycemic control and is well tolerated.

Approved and Investigational Fixed-Dose Combination Products

Agents Approved for Use in the US or in Late-Phase Development*

Product (Brand Name)	Manufacturer	US Status
Sitagliptin + metformin (Janumet®)	Merck	Approved, 3/07
Saxagliptin + metformin ER (Kombiglyze™ XR)	Bristol-Myers Squibb	Approved, 11/10
Alogliptin + metformin	Takeda	FDA CRL, 6/09
Alogliptin + pioglitazone	Takeda	FDA CRL, 6/09
Sitagliptin + metformin ER	Merck	Phase 3

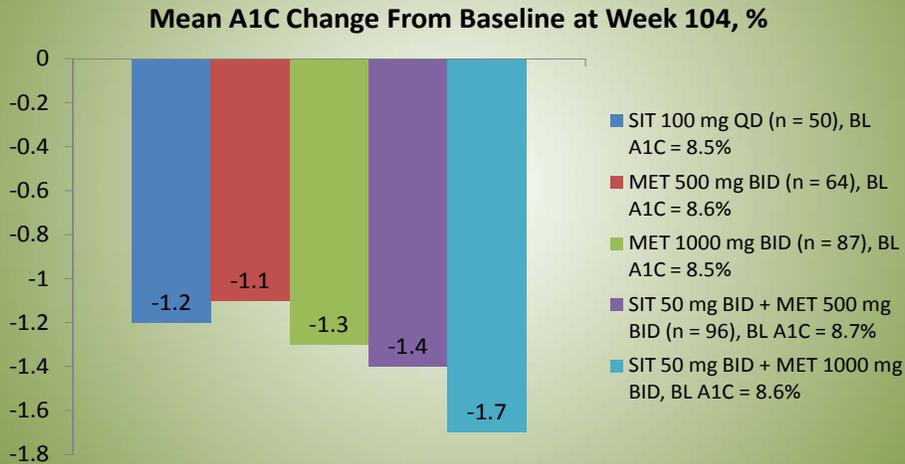
ER = extended-release.
*Effective June 2011.

Janumet®. Prescribing information. April 2011. Kombiglyze™ XR. Prescribing information. November 2010. Merck & Co., Inc. Available at: <http://merck.com/research/pipeline/home.html?WT.svl=mainnav>. Takeda Pharmaceuticals North America, Inc. Research and development. Available at: http://www.tpna.com/research_development/default.aspx. Accessed June 8, 2011.

Since the DPP-4 inhibitors are oral agents that are often taken with other glucose-lowering drugs, fixed-dose combination products that contain a DPP-4 inhibitor are a convenient option for many patients. Two combination products are currently available and others are in development. Janumet®, which includes sitagliptin and the immediate-release formulation of metformin (metformin HCl), was developed by Merck and approved by the FDA in March 2007. Janumet® is available in 2 fixed-dose tablet presentations, one containing 50 mg of sitagliptin plus 500 mg of metformin, the other containing 50 mg of sitagliptin plus 1000 mg of metformin. Janumet® should generally be taken twice daily with meals, with gradual dose escalation, to reduce the GI side effects associated with metformin. The maximum recommended daily dose is 100 mg of sitagliptin plus 2000 mg of metformin. Kombiglyze™ XR, which includes saxagliptin and the extended-release (ER) formulation of metformin, was developed by Bristol-Myers Squibb and approved by the FDA in November 2010. Kombiglyze™ XR is available in 3 fixed-dose tablet presentations: 5 mg of saxagliptin plus 500 mg of metformin ER, 2.5 mg of saxagliptin plus 1000 mg of metformin ER, and 5 mg of saxagliptin plus 1000 mg of metformin ER. Kombiglyze™ XR should generally be taken once daily with the evening meal, with gradual dose titration to reduce the GI side effects of metformin. The maximum daily recommended dose is 5 mg for saxagliptin and 2000 mg for metformin ER.

In addition to these approved products, Takeda has developed fixed-dose combinations of alogliptin plus metformin and alogliptin plus pioglitazone. As mentioned earlier, the US approval of alogliptin has been delayed while Takeda performs a cardiac safety study required by the FDA. Merck is developing a fixed-dose combination of sitagliptin plus metformin XR, which is intended to replace Janumet®.

Initial Combination Therapy With Sitagliptin and Metformin Over 2 Years



BL = baseline.

Williams-Herman D, et al. *Diabetes Obes Metab.* 2010;12:442–451.

The long-term effects of initial combination therapy with sitagliptin and metformin were studied in a 54-week randomized, double-blind, multinational study with a 50-week double-blind extension period. Patients were randomized to receive sitagliptin 100 mg QD, metformin 500 mg BID, metformin 1000 mg BID, sitagliptin 50 mg BID plus metformin 500 mg BID, or sitagliptin 50 mg BID plus metformin 1000 mg BID. Baseline A1C values ranged from 8.5% to 8.7%. Of the 1091 patients originally randomized, 685 entered the 50-week extension study and 517 completed all 104 weeks of treatment.

As the graph shows, substantial mean A1C reductions from baseline were observed in all treatment groups at week 104, with decreases ranging from 1.1% to 1.7%. At each metformin dose studied, the reduction in A1C was greater with the coadministration of sitagliptin and metformin than with the administration of metformin alone. Glycemic improvement was also greater with sitagliptin plus metformin than with sitagliptin alone.

After 104 weeks of treatment, the incidence of AEs was generally similar in the coadministration groups and their respective metformin monotherapy groups. The incidence of any hypoglycemia ranged from 1.1% in the sitagliptin monotherapy group to 4.9% in the sitagliptin 50 mg BID plus metformin 1000 mg BID group. The incidence of major hypoglycemia was 3.1% in the metformin 500 mg BID group. No other episodes of major hypoglycemia were reported.

Since metformin is associated with GI AEs, the incidence of these AEs was of particular interest. GI AEs were reported in 21% of the sitagliptin 100 mg BID group and in 33% of both the metformin 1000 mg BID group and the sitagliptin 50 mg BID plus metformin 1000 mg BID group.

Cost-Effectiveness of DPP-4 Inhibitor Therapy

- The negative impact of the side effects and RoA of sitagliptin is minuscule, and smaller than that of glyburide or ExBID
- Long-term treatment with sitagliptin is less expensive and more effective than long-term treatment with ExBID

Loss in QoL (Disutility) Due to Side Effects/Administration Route

Effect	GLYB	ExBID	SITA
Weight gain/loss	-0.0031	0.0013	0
Hypoglycemia	-0.0064	-0.0005	-0.0002
Nausea/GI	0	-0.0005	0
URTI	0	0	-0.0001
Injectable	0	-0.0032	0
Overall disutility*	-0.0095	-0.0029	-0.0003

GLYB = glyburide; ICER = incremental cost-effectiveness ratio;
 QALY = quality-adjusted life years; QoL = quality of life;
 RoA = route of administration.

Cost-Effectiveness Analysis

Agent	Drug Cost, \$	Total Cost, \$	QALY [†]	ICER [‡]
GLYB	65,205	146,950	15.2143	-
SITA	85,418	167,163	15.3335	\$169,572
ExBID	89,054	170,799	15.2998	Dominated

*A disutility is a loss in QoL; overall values are weighted.

†A QALY is the product of the number of years of life times the quality of those years, as measured from 0 (indifference between life and death) to 1 (full health).

‡ICER = (costs of treatments intended to prevent diabetes-related complications)/(QALYs gained).

Dominated means that ExBID was more expensive and less effective than sitagliptin.

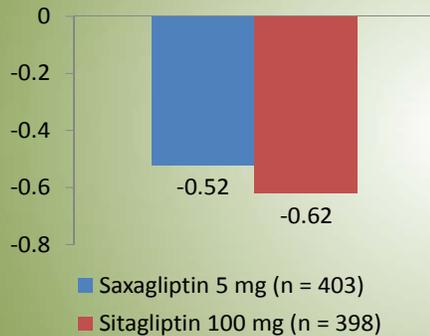
Sinha A, et al. *Diabetes Care*. 2010;33:695-700.

The cost-effectiveness of incretin-based therapies for US patients is only beginning to be studied. This slide summarizes an analysis of the costs and consequences of long-term second-line therapy with glyburide, sitagliptin, or ExBID for adults. The analysis assumed that these agents, in combination with metformin, are similarly effective at preventing the major consequences of diabetes. However, as shown in the table on the left, the harmful impact on patients' quality of life (QoL) due to side effects and the route of administration is greatest with glyburide, intermediate with ExBID, and smallest with sitagliptin. The disutilities of glyburide are weight gain and hypoglycemia. Disutilities of ExBID are undesired weight loss (in a small proportion of patients), a low risk of hypoglycemia, a risk of nausea and other GI side effects, and the fact that it is given by subcutaneous injection. The disutilities of sitagliptin are a very low risk of hypoglycemia and a risk of minor URTI.

As shown in the table on the right, drug costs and other direct medical costs were calculated to be lowest with glyburide, intermediate with sitagliptin, and highest with ExBID. The number of quality-adjusted life years (QALY) saved by glucose-lowering therapy was highest with sitagliptin, intermediate with ExBID, and lowest with glyburide. (Recall that a QALY is the product of the number of years of life provided by a treatment times the quality of those years, as measured from zero [indifference between life and death] to 1 [full health]). In this analysis, the incremental cost-effectiveness ratio (ICER) was calculated by dividing the costs of treatment intended to prevent diabetes-related complications by the number of QALYs gained. Compared to glyburide, sitagliptin was associated with an ICER of \$169,572 per QALY saved and ExBID with an ICER of \$278,935. According to these calculations, ExBID was "dominated" by sitagliptin, meaning that it was found to be more expensive and less effective than sitagliptin.

Saxagliptin Is Noninferior to Sitagliptin

A1C Reduction From Baseline at Week 18, %*



*Between-group difference was 0.09% (95% CI, -0.01 to 0.20%). Noninferiority was shown if upper limit of CI interval was <0.3%.

Incidence of Most Common AEs and Hypoglycemia, %

Event	SAXA + MET	SITA + MET
Influenza	5.7	5.8
UTI	5.7	5.3
Nasopharyngitis	4.0	4.0
Headache	2.7	2.3
Diarrhea	2.5	2.5
URTI	2.2	1.0
Any hypoglycemia	3.2	2.8
Major hypoglycemia	0	0.2

Scheen AJ, et al. *Diabetes Metab Res Rev.* 2010;26:540–549.

The noninferiority of saxagliptin to sitagliptin as a glucose-lowering agent was shown in a randomized, double-blind, phase 3b, 18-week multicenter clinical trial that included adult patients whose glycemia was inadequately controlled with metformin. During the study, 403 patients were randomized to receive add-on therapy with saxagliptin and 398 patients were randomized to add-on therapy with sitagliptin. The primary efficacy analysis was a comparison of the mean change in A1C from baseline at week 18. The noninferiority of saxagliptin to sitagliptin was confirmed if the upper limit of the 2-sided 95% confidence interval (CI) of the A1C difference between treatments was less than 0.3%. As shown in the graph, mean A1C reductions from baseline at week 18 were 0.52% with saxagliptin and 0.62% with sitagliptin. The between-group difference was 0.09% and the 95% CI was -0.01 to 0.20%. Therefore, saxagliptin met the criterion for noninferiority to sitagliptin.

The table shows that the incidence of AEs was similar in the saxagliptin and sitagliptin groups and that the pattern of AEs was similar to that seen in other studies of DPP-4 inhibitors. Collectively, the most commonly reported AEs were minor infections involving the respiratory system and urinary tract. The incidence of minor hypoglycemia was about 3% in each group. The incidence of major hypoglycemia was 0% with saxagliptin and 0.2% with sitagliptin.

Case 2: Patient Profile

- Allen, a 62-year-old white male
- Married with 2 adult children
- Computer specialist in manufacturing company
- Height, 70 in; weight, 212 lb; BMI, 30.4 kg/m²
- Stable weight over past year
- Says he does not have time for/interest in physical activity
- 2-year history of type 2 diabetes
- No diabetes-associated complications, normal renal function
- Says he would like to avoid an injectable therapy

This case describes a patient who is an appropriate candidate for treatment with a DPP-4 inhibitor.

Allen is a 62-year-old white male who comes to the clinic for a routine physical examination for work. He is married and has 2 adult children. He works full-time as a computer specialist in a manufacturing company.

Allen is 70 inches tall, weighs 212 pounds, and has a BMI of 30.4 kg/m². His weight has been stable over the past year. He says that while his wife prepares balanced meals that are consistent with his food plan, he often makes unwise food choices when he goes out for lunch during the work week. He also says that by the time he gets home from work he lacks the energy and motivation to exercise, and that his weekends are filled with errands and family visits.

Allen was diagnosed with type 2 diabetes 2 years ago. Currently he has no known diabetes complications. Testing last year revealed normal renal function. Aside from mild seasonal allergic rhinitis, he has no other health issues.

Allen says that he would like to avoid using an injectable therapy, if possible.

Case 2: Current Regimen, Blood Pressure, and Laboratory Values

- Metformin 500 mg twice daily
- Glimepiride 8 mg once daily

Parameter	Allen's Value	ADA Recommendation
A1C, %	7.8	<7.0
FPG, mg/dL	162	70–130
PPG, mg/dL	231	<180
SBP/DBP, mmHg	135/82	<130/80
LDL-C, mg/dL	81	<100*
HDL-C, mg/dL	37	>40 [†]
Triglycerides, mg/dL	101	<150

Green type = meets ADA goal; red type = does not meet ADA goal.

*Goal for individuals without overt cardiovascular disease (CVD). Goal is <70 mg/dL in individuals with overt CVD.

[†]Goal in men. Goal is >50 mg/dL in women.

American Diabetes Association. *Diabetes Care*. 2011;34(Suppl 1):S11–S61.

Allen's current pharmacologic regimen is metformin 500 mg twice daily and glimepiride 8 mg once daily. Both agents are well tolerated.

As the table shows, Allen's blood glucose levels, blood pressure, and HDL-C level do not meet ADA targets for these values.

His A1C is 7.8%, his FPG is 162 mg/dL, and his PPG is 231 mg/dL. Thus, his A1C level exceeds the ADA target by 0.8%, his FPG exceeds the high end of the recommended range by 32 mg/dL, and his PPG exceeds the ADA target by 51 mg/dL.

Allen's blood pressure is 135/82, and thus it is slightly above the ADA target of <130/80. Given his current BP level, a 3-month trial of lifestyle therapy an option for him.

Allen's LDL-C and triglyceride levels are at goal. At 37 mg/dL, his HDL-C level is slightly below the recommended level of ≥40 mg/dL for men. However, since he is over the age of 40 and has obesity, Allen should begin statin therapy at this point, regardless of his lipid levels.

Case 2: Considerations in Selecting a Treatment Regimen

- Allen's A1C, FPG, and PPG are not at goal
- He has obesity, borderline hypertension, and low HDL-C
- He is already receiving maximum recommended glimepiride dose (8 mg once daily)

Treatment	Considerations
Increase MET dose from 1000 mg/d to MED (2000 mg/d)	Unlikely to have sufficient effect on BG values; better to add agent with complementary MoA
Add a TZD	Might bring BG values to goal, but could result in further weight gain
Add a GLP-1 agonist	Would probably reduce BG levels sufficiently and have beneficial effects on weight, BP, and lipids, but would need to be administered by injection
Add a DPP-4 inhibitor	Would probably bring BG values to goal and would not increase weight
Add a statin	Combined with lifestyle modification, would bring HDL-C to goal

MED = maximum effective dose;
MoA = mechanism of action.

Nathan DM, et al. *Diabetes Care*. 2009;32:193–203.

In determining the optimal treatment regimen for Allen, several considerations are important. His A1C, FPG, and PPG are not at goal. Additionally, he has obesity, borderline hypertension, and low HDL-C. He is already receiving the maximum recommended glimepiride dose of 8 mg once daily. Allen tolerates glimepiride well, so it seems advisable to keep it as part of his regimen, at least for the immediate future.

There are several treatment options for Allen. His metformin dose could be increased from 1000 mg/day to the maximum effective dose of 2000 mg/day, but this increase would be unlikely to have a sufficient effect on Allen's BG values. A better option would be to add an agent with a complementary mechanism of action. Adding a TZD to Allen's regimen might bring his BG values to goal, but could also result in additional weight gain. Adding a GLP-1 agonist would probably reduce Allen's blood glucose levels sufficiently and would have beneficial effects on weight, blood pressure, and lipids, but a GLP-1 agonist would need to be administered by injection. In the short term, it would be better to try to bring Allen to goal using oral medication.

Considering his overall situation, adding a DPP-4 inhibitor appears to be the best option for Allen. It would probably bring his BG values to goal and would not increase his weight. As already mentioned, Allen should also begin statin therapy since he is over 40 and has hypertension. When used in conjunction with MNT, statin therapy should bring his HDL-C level to goal.

To help him make more appropriate food choices, especially when he eats away from home, the health care provider refers Allen to a registered dietitian for MNT. The health care provider also discusses the ADA recommendation that people with diabetes perform at least 150 minutes per week of moderate-intensity physical activity. Allen says that the most realistic way for him to accomplish this is to start taking his lunch to work and then to walk briskly for 30 minutes around his office park.

Case 2: Treatment Regimen and Three-Month Results

- Metformin 500 mg twice daily, **glimepiride 4 mg** once daily, and **sitagliptin 100 mg** once daily
- Pravastatin 40 mg once daily
- Weight reduction: 13 pounds

Parameter	Allen's Value	ADA Recommendation
A1C, %	6.9	<7.0
FPG, mg/dL	127	70–130
PPG, mg/dL	186	<180
SBP/DBP, mmHg	126/75	<130/80
LDL-C, mg/dL	74	<100*
HDL-C, mg/dL	44	>40†
Triglycerides, mg/dL	96	<150

Green type = meets ADA goal; red type = does not meet ADA goal.

*Goal for individuals without overt cardiovascular disease (CVD). Goal is <70 mg/dL in individuals with overt CVD.

†Goal in women. Goal is >40 mg/dL in men.

American Diabetes Association. *Diabetes Care*. 2011;34(Suppl 1):S11–S61.

Allen's new glucose-lowering regimen includes metformin 500 mg twice daily, glimepiride 4 mg once daily, and sitagliptin 100 mg once daily. Note that Allen's former dose of glimepiride was reduced by 50%, a recommended approach for reducing the risk of hypoglycemia when a sulfonylurea is administered with a DPP-4 inhibitor or a GLP-1 agonist. Allen also began statin therapy, taking pravastatin at a dose of 40 mg once daily.

Thanks to what he learned about food choices in his MNT program and his lunch-hour walks, Allen lost 13 pounds over a 3-month period. He also experienced marked improvements in his BG values, blood pressure, and lipid levels. In the table, values that are at goal are shown in green and the single value that is still above goal is shown in red. Over the 3 months, Allen's A1C decreased by 0.9%, falling from 7.8% to 6.9%. His FPG decreased by 35 mg/dL, falling from 162 to 127 mg/dL. Thus, both his A1C and FPG are now at goal. His PPG decreased by 45 mg/dL, falling from 231 to 186 mg/dL. Therefore, it remains only slightly above goal. With lifestyle modifications and weight loss, Allen's BP decreased from 135/82 to 126/78, and is thus at goal. All of his lipid values improved as a result of lifestyle modification and statin therapy, and his HDL-C level and other levels are now at goal.

Given the excellent progress he has made and the fact that all values are at or approaching goal, Allen will continue his current regimen for 3 more months. Eventual modifications to his glucose-lowering regimen might include replacing the sulfonylurea with a TZD and substituting a GLP-1 agonist for the DPP-4 inhibitor.

Checkpoint 3

A factor when considering a DPP-4 inhibitor for a patient with diabetes is that _____.

- a. the dose must be titrated upward over a 1-month period
- b. A1C reductions are generally greater than those seen with a GLP-1 agonist
- c. patients are likely to lose a moderate amount of weight during treatment
- d. overall, the DPP-4 inhibitors are very well tolerated

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Answer to Checkpoint 3

The correct answer is **d**.

A factor when considering a DPP-4 inhibitor for a patient with diabetes is that overall, the DPP-4 inhibitors are very well tolerated.

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Comparative Trial: Liraglutide vs Sitagliptin

52-Week (26 wks + 26-wk extension), Randomized, Open-Label, Phase 3 Trial, N = 665
Patients Also Received Metformin

Variable	Liraglutide 1.2 mg n = 225	Liraglutide 1.8 mg n = 221	Sitagliptin n = 219
Mean Baseline A1C, %	8.4	8.4	8.5
Mean Baseline FPG, mg/dL	182	178	180
Mean A1C ↓, %	1.3*	1.5*	0.9
Mean FPG ↓, mg/dL	31*	37*	10.6
A1C <7%, %	50*	63*	27
Weight ↓, kg	2.8*	3.7*	1.2
Nausea, %	22	28	6
Minor hypoglycemia [†]	0.14	0.15	0.14
Major hypoglycemia, %	0.4	0	0

*P < 0.0001 vs sitagliptin

[†]Episodes per patient per year.

Pratley R, et al. *Int J Clin Pract.* 2011;65:397–407. Pratley R, et al. *Lancet.* 2010;375:1447–1456.

Several clinical trials comparing the efficacy and safety of a GLP-1 agonist and a DPP-4 inhibitor have been conducted. Pratley and colleagues conducted a 52-week open-label study, consisting of an initial 26-week study period and a 26-week extension. Patients were randomized to receive liraglutide at a dose of 1.2 or 1.8 mg/day or sitagliptin 100 mg/day, all in combination with metformin. Mean baseline A1C values ranged from 8.4% to 8.5% and mean baseline FPG levels ranged from 178 to 182 mg/dL.

At study end point, patients in both liraglutide groups had significantly greater A1C reductions from baseline than patients in the sitagliptin group, and significantly higher proportions of patients in the 2 liraglutide groups had an A1C of <7%. Weight reduction from baseline was also significantly greater for both liraglutide doses compared to sitagliptin. The incidence of nausea was 22% with liraglutide 1.2 mg/day, 28% with liraglutide 1.8 mg/day, and 6% with sitagliptin. Consistent with the pattern seen in other studies, the frequency of nausea in liraglutide-treated patients declined after the first 3 weeks of treatment and remained low for the rest of the study. Rates of minor hypoglycemia were very low in all groups, ranging from 0.14 to 0.15 episodes per patient per year. Only one patient, in the liraglutide 1.2 mg/day group, experienced major hypoglycemia.

Comparative Trial: ExQW vs Sitagliptin

DURATION-2: 26-Week, Randomized, Open-Label, Phase 3 Trial, N = 514
Patients Also Received Metformin*

Variable	ExQW 2 mg n = 160	Sitagliptin 100 mg n = 166	P-Value for Comparison
Mean Baseline A1C, %	8.6	8.5	NS
Mean Baseline FPG, mg/dL	166	164	164
Mean A1C ↓, %	1.5	0.9	<0.0001
Mean FPG ↓, mg/dL	32	16	0.0038
A1C <7%, %	59	30	<0.0001
Weight ↓, kg	2.3	0.8	<0.0002
Nausea, %	24	10	NR
Minor hypoglycemia [†]	1.2	3.0	NS
Major hypoglycemia, %	0	0	NS

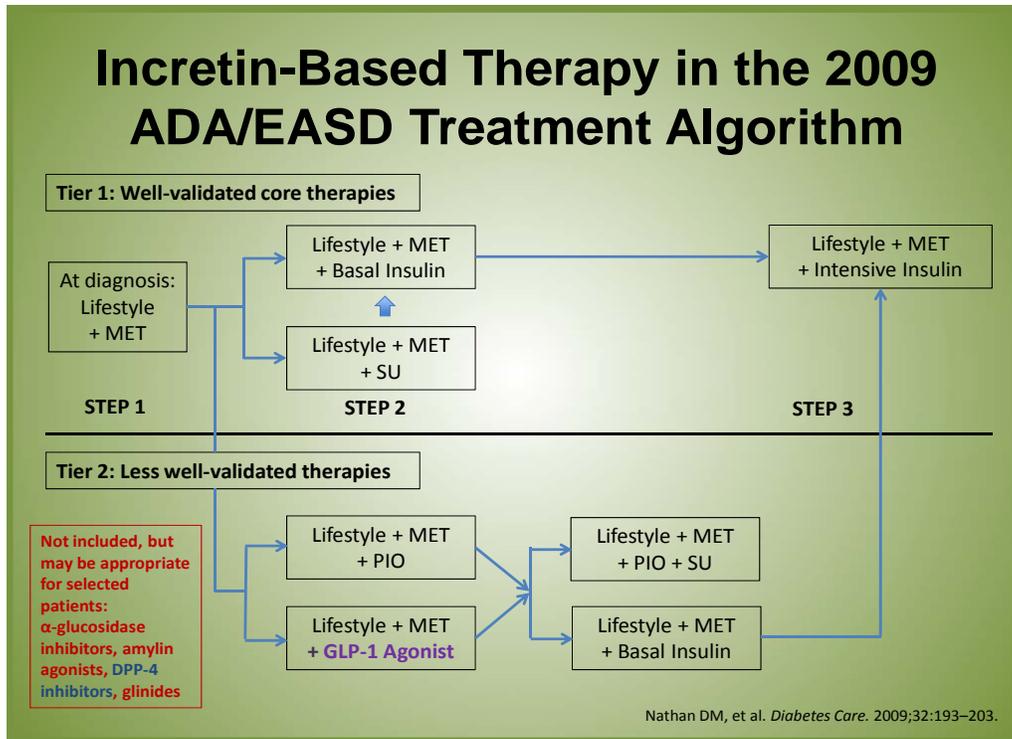
*Study also had pioglitazone arm; data not reported here;
[†]Episodes per patient per year.

Bergenstal RM, et al. *Lancet*. 2010;376:431–439.

Bergenstal and associates conducted the DURATION-2 trial, a 26-week, double-blind, double-dummy study in which patients were randomized to receive ExQW 2 mg once weekly, sitagliptin 100 mg/day, or pioglitazone 45 mg/day in combination with metformin. Pioglitazone data are not reported here. Baseline A1C and FPG values were similar in the ExQW and sitagliptin groups.

Overall, the major findings of this study were similar to those of the 52-week comparative study with liraglutide and sitagliptin. ExQW was associated with significantly greater A1C and FPG reductions at end point than sitagliptin, and weight reduction was also significantly greater with ExQW. A1C reductions from baseline were 1.5% with ExQW compared to 0.9% with sitagliptin, and a significantly higher percentage of patients in the ExQW group than in the sitagliptin group attained an A1C of <7%. The incidence of nausea was 24% in the ExQW group and 10% in the sitagliptin group. No major episodes of hypoglycemia were reported, and the incidence of minor hypoglycemia was 1.2% in the ExQW group and 3.0% in the sitagliptin group.

Incretin-Based Therapy in the 2009 ADA/EASD Treatment Algorithm

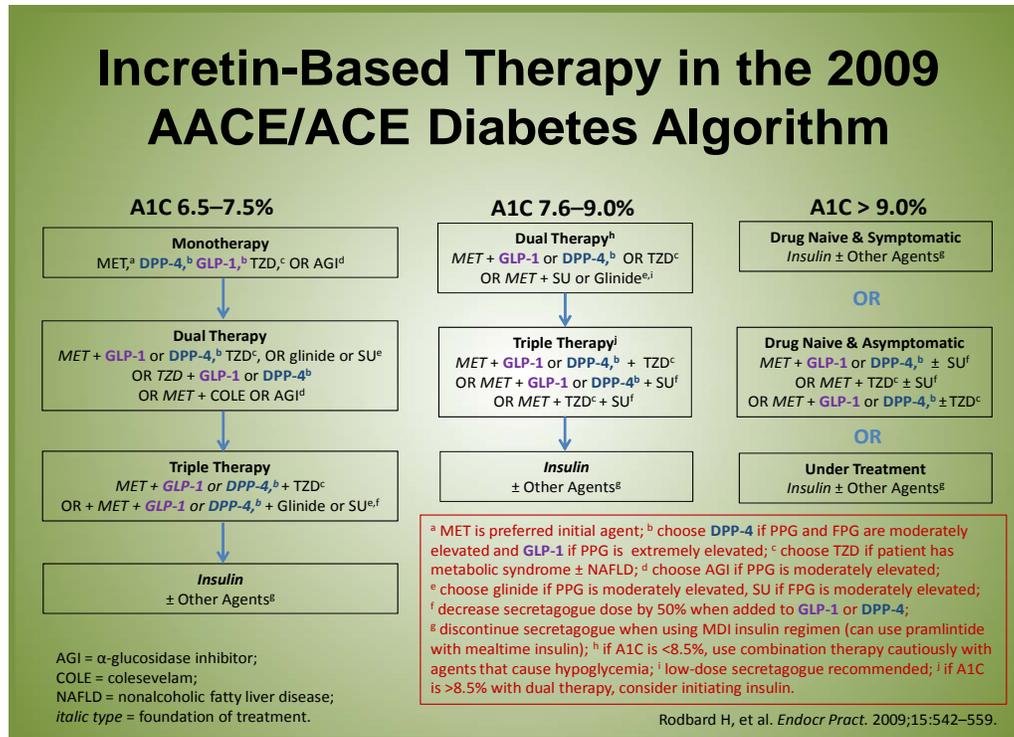


The most recent ADA/EASD treatment algorithm was developed during the latter part of 2008 and published in its definitive form in January 2009. Thus, it was prepared when ExBID was the only FDA-approved GLP-1 agonist, sitagliptin was the only approved DPP-4 inhibitor, and limited data were available for these classes of glucose-lowering drugs. The algorithm includes the GLP-1 agonists as a tier 2, step 1 therapy to be used with lifestyle modification and metformin. This placement indicates that the algorithm’s developers considered the GLP-1 agonist class, and specifically ExBID, to be a therapy for which limited data were available but which appeared to be a beneficial treatment for specific subgroups of patients. According to the text that accompanies the algorithm, GLP-1 agonist therapy may be appropriate when weight loss is a major consideration and the A1C is <8.0%. The text notes that a GLP-1 agonist can also be considered when hypoglycemia is particularly undesirable, such as in patients with hazardous jobs.

The DPP-4 inhibitors, like the α -glucosidase inhibitors, amylin agonists, and glinides, are not included in the algorithm. However, the text notes that these agents may be appropriate choices for selected patients.

Given the large body of data, including long-term data, that now supports the efficacy of the GLP-1 agonists and the DPP-4 inhibitors, it appears likely that these classes of glucose-lowering drugs will figure more prominently in the next version of the ADA/EASD treatment algorithm.

Incretin-Based Therapy in the 2009 AACE/ACE Diabetes Algorithm



The AACE/ACE Diabetes Algorithm for Glycemic Control was published in September 2009, eight months after publication of the definitive version of the ADA/EASD algorithm. In the period between the publication of the 2 algorithms, the FDA approved saxagliptin and the results of many randomized, controlled trials of incretin-based therapy were reported in preliminary or final form. Not surprisingly, therefore, incretin-based therapies play a more important role in the AACE/ACE algorithm than in the ADA/EASD algorithm.

As shown in the slide, the DPP-4 inhibitors and GLP-1 agonists occupy the same positions in the algorithm, and are recommended as monotherapy and as components of dual- and triple-therapy regimens. With metformin, they are considered foundations of treatment for patients who have an A1C of 6.5 to 7.5% and require triple therapy.

According to the authors of the algorithm, the major difference between the agents is that a DPP-4 inhibitor is recommended for patients with moderate FPG and PPG elevations, while a GLP-1 agonist is recommended for patients with extremely elevated PPG levels. (Unfortunately, the algorithm does not assign quantitative ranges for these degrees of PPG elevation.)

For many of the patients who require monotherapy, the authors consider a DPP-4 inhibitor to be preferable to a GLP-1 agonist because it is administered orally and has excellent tolerability, with a very low risk of nausea. For many of the patients who require combination therapy, on the other hand, the authors consider a GLP-1 agonist to be preferable to a DPP-4 inhibitor because of its somewhat greater effectiveness in reducing PPG excursions relative to a DPP-4 inhibitor and because about 30% of treated patients are likely to experience considerable weight loss during treatment. The algorithm recommends that if an insulin secretagogue is going to be added to a GLP-1 agonist or a DPP-4 inhibitor, the usual dose of the secretagogue should be reduced by 50%.

AACE/ACE Algorithm: Appraisal of Incretin-Based Therapies

[The algorithm] “favors the use of GLP-1 agonists and DPP-4 inhibitors with higher priority [than sulfonylureas] because of their effectiveness and overall safety profiles. In view of the millions of patients who have benefited from the use of these agents and their excellent performance in a wide range of clinical studies, in combination with the growing literature indicating the serious risks of hypoglycemia, these agents are increasingly preferred for most patients in place of sulfonylureas and glinides.”

Rodbard H, et al. *Endocr Pract.* 2009;15:542–559.

In the text that accompanies the 2009 AACE/ACE algorithm, the authors explain why incretin-based therapies have largely supplanted the insulin secretagogues, and especially the sulfonylureas, in the treatment of type 2 diabetes.

They note that the algorithm “favors the use of GLP-1 agonists and DPP-4 inhibitors with higher priority [than sulfonylureas] because of their effectiveness and overall safety profiles. In view of the millions of patients who have benefited from the use of these agents and their excellent performance in a wide range of clinical studies, in combination with the growing literature indicating the serious risks of hypoglycemia, these agents are increasingly preferred for most patients in place of sulfonylureas and glinides.”

They go on to explain that the algorithm “moves sulfonylureas to a lower priority because of the associated risks of hypoglycemia, weight gain, and the failure of these agents to provide improved glycemic control after use for a relatively short period (1 to 2 years in typical patients).”

The commentary also notes that the algorithm “includes TZDs as ‘well-validated’ effective agents with demonstrated extended durability of action, but with a lower priority for many patients in light of their potential adverse effects, especially when TZDs are used in combination with sulfonylureas or insulin, and the recent confirmation of previous reports of a significant increase in bone fractures associated with their use in men and women.”

AACE/ACE Algorithm: Appraisal of Incretin-Based Therapies

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- Incretin-based therapies increase plasma GLP-1 levels, resulting in enhanced insulin secretion, as well as reduced glucagon secretion and postprandial hyperglycemia
- Monotherapy with an incretin-based therapy can improve A1C levels in selected patients with newly diagnosed type 2 diabetes. In phase 3 clinical trials, A1C reductions from baseline ranged from 0.7% to 1.5% with a GLP-1 agonist and from 0.4% to 0.8% with a DPP-4 inhibitor
- Incorporation of an incretin-based therapy into dual- and triple-agent regimens can increase the proportion of patients who achieve the ADA A1C target of <7%. In phase 3 clinical trials, proportions of patients who reached this target ranged from 25% to 60% with a GLP-1 agonist and from 11% to 63% with a DPP-4 inhibitor