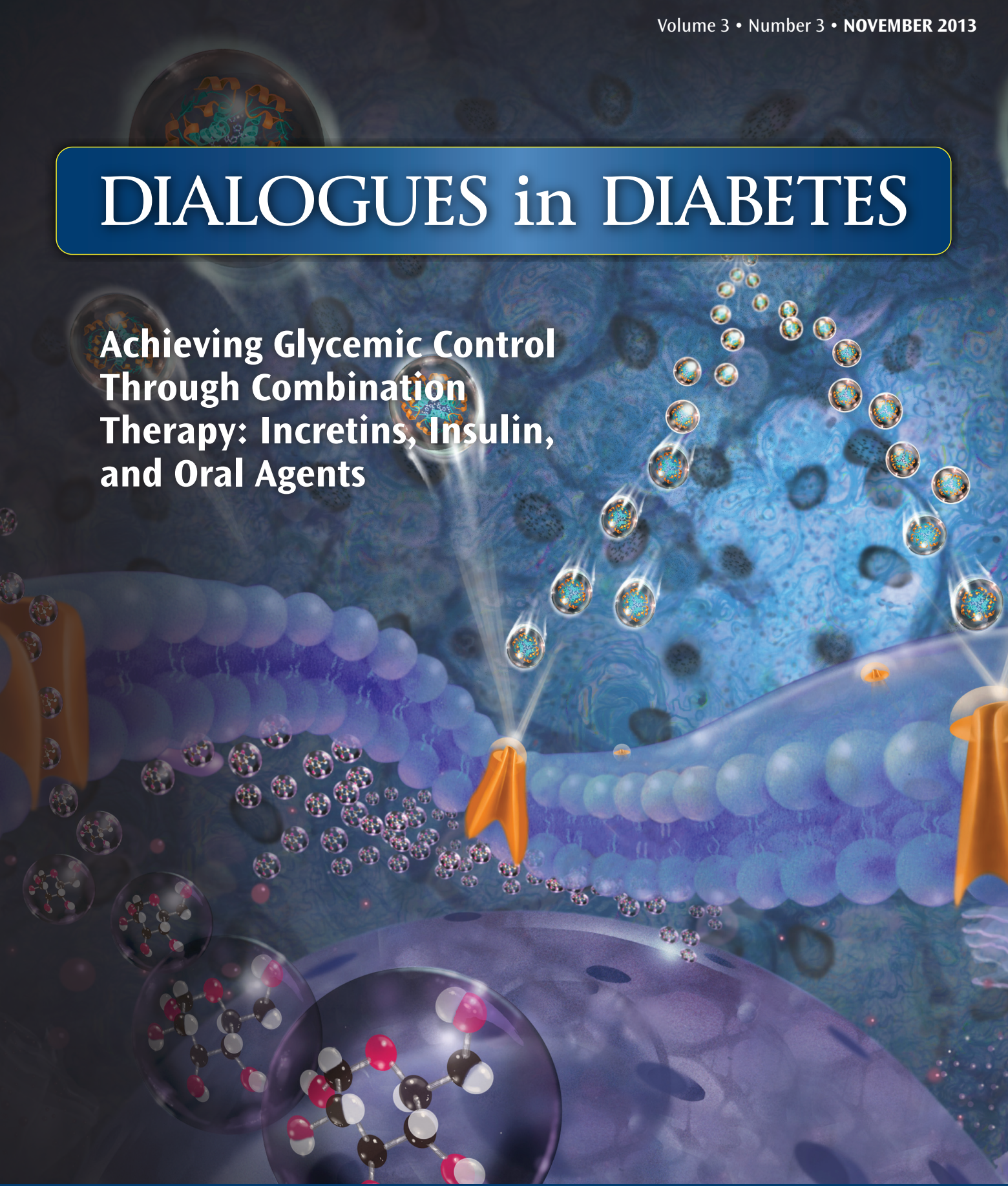
Volume 3 • Number 3 • **NOVEMBER 2013**

DIALOGUES in DIABETES

Achieving Glycemic Control Through Combination Therapy: Incretins, Insulin, and Oral Agents



Supplement to
Endocrinetoday®
CLINICAL NEWS ON DIABETES AND ENDOCRINE DISORDERS
November 2013

VINDICO medical education

DIALOGUES in DIABETES

Featured Articles

EARN **CME** CREDIT

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by genetic heterogenicity with a consistent phenotype that becomes manifested when the disease develops, characterized by impaired insulin secretion, insulin resistance, increased hepatic glucose production due to both increased glycogenolysis and gluconeogenesis, and impaired incretin release. The major incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) increase glucose dependent and first phase insulin secretion and are rapidly deactivated by dipeptidyl peptidase-4 (DPP-4), with GLP-1 suppressing glucagon secretion. The incretins also have a variety of other systemic effects including appetite suppression by a direct effect on the satiety center, delayed gastric emptying, and an increase in beta cell neogenesis with apoptosis inhibition (animal and in vitro). Both GLP-1 and GIP are released from the intestinal cells in response to nutrient intake with GLP-1 being synthesized from proglucagon in the L cells of the small intestine and GIP in the K cells of the proximal intestinal mucosa. These are endogenous incretin hormones whose dual action modulate insulin production and regulate fasting plasma glucose (FPG) and post-prandial glucose (PPG).

This issue will feature a detailed discussion concerning the clinical use of GLP-1 receptor agonists and the DPP-4 inhibitors with the available oral agents to achieve glycemic control. Also featured will be 2 case studies to illustrate the practical and individualized approach to achieving glycemic control, utilizing these incretins agents in combination with insulin. The issue concludes with an expert interview covering some frequently asked and challenging questions that are of concern to practitioners in managing patients with type 2 diabetes.

I trust that this issue will provide some important clinical pearls that providers can utilize in their very challenging task of achieving glycemic control in their patients with this disease.

Vivian Fonseca, MD, FRCP

This continuing medical education activity is sponsored by

VINDICO medical education

This activity is supported by an educational grant from

ADVANCING DIABETES CARE
Bristol-Myers Squibb AstraZeneca

Learning Objectives

At the conclusion of this series, participants should be able to:

- Assess the pathophysiology of hyperglycemia, its role in macrovascular and microvascular diseases, and the role of incretin pathways in type 2 diabetes mellitus.
- Examine the differences in mechanism of action, efficacy, and safety of treatment options that target the incretin pathway.
- Examine approaches to managing the obese patient with type 2 diabetes.
- Incorporate evidence-based guidelines and recommendations into practice when considering the use of incretin-based therapies for type 2 diabetes.
- Utilize GLP-1 agonists and DPP-4 inhibitors in combination with insulin and oral agents to achieve optimal glycemic control.
- Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.

DIALOGUES in DIABETES

Accreditation

Vindico Medical Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

Vindico Medical Education designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material is approved for 1 year from the date of original release, November 1, 2013 to November 1, 2014.

How To Participate in this Activity and Obtain CME Credit

To participate in this CME activity, you must read the objectives and articles, complete the CME posttest, and fill in the evaluation. Provide only one (1) correct answer for each question. A satisfactory score is defined as answering 70% of the posttest questions correctly. Upon receipt of the completed materials, if a satisfactory score on the posttest is achieved, Vindico Medical Education will issue an *AMA PRA Category 1 Credit(s)*™ certificate.

Reviewers

Ronald A. Codario, MD, FACP, FNLA, CCMEP
Carol H. Wysham, MD

Disclosures

In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support, all CME providers are required to disclose to the activity audience the relevant financial relationships of the planners, teachers, and authors involved in the development of CME content. An individual has a relevant financial relationship if he or she has a financial relationship in any amount occurring in the last 12 months with a commercial interest whose products or services are discussed in the CME activity content over which the individual has control.

The authors disclose that they do have significant financial interests in any products or class of products discussed directly or indirectly in this activity, including research support.

Planning Committee and Faculty members report the following relationship(s):

Lawrence Blonde, MD, FACP, FACE
Research Grant Support: To Ochsner for his role as investigator from Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis
Speaker's Bureau: Amylin Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Janssen Pharmaceuticals, Inc., Johnson & Johnson Diabetes Institute, L.L.C., Merck & Co. Inc., Novo Nordisk, Sanofi-Aventis, Santarus, Vivus, Inc.
Consultant: Amylin Pharmaceuticals, Inc., Eisai Inc, GlaxoSmithKline, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk, Pfizer, Sanofi-Aventis, Santarus

Michael H. Davidson, MD, FACC, FACP, FNLA
Consulting Fees: AbbVie, Amgen, AstraZeneca, Daiichi-Sankyo, Esperion, Lipidemx, Merck & Co., Inc
Speakers Bureau: Merck & Co., Inc.
Ownership Interest: Prior to July 2013, ownership interest in Omthera Pharmaceuticals, Inc.

Ralph A. DeFronzo, MD
Consulting Fees: Amylin, Bristol-Myers Squibb, Janssen, Lexicon, Novo Nordisk, Takeda
Contracted Research: Amylin, Bristol-Myers Squibb, Lexicon, Takeda
Speakers Bureau: Amylin, AstraZeneca, Bristol Myers Squibb, Janssen, Novo Nordisk

Vivian A. Fonseca, MD, FRCP
Honoraria for Consulting Fees and Lectures: Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Novo Nordisk, PamLabs, Sanofi-Aventis, Takeda
Research Support (to Tulane): Abbott, Eli Lilly, Endo Barrier, Novo Nordisk, Pan American Laboratories, Rcata, Sanofi-Aventis

W. Timothy Garvey, MD
Consulting Fees: Alkermes, Boehringer-Ingelheim, Daiichi-Sankyo, Eisai, Johnson & Johnson, Liposcience, Novo Nordisk, Vivus
Speakers Bureau: Amylin, Merck, LipoScience
Fees for Non-CME Services Received Directly from Commercial Interest or their Agents: Amylin, Eisai, LipoScience, Merck & Co., Inc., Vivus
Contracted Research: Amylin, Merck & Co., Inc., Weight Watchers
Ownership Interest: ISIS, Lilly, Merck & Co., Inc., Novartis, Pfizer, Vivus

Robert R. Henry, MD
Grant/Research Support: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Sanofi-Aventis
Consultant: Boehringer Ingelheim, Intarcia, Isis, Eli Lilly, Novo Nordisk, Roche/Genentech, Sanofi-Aventis
Advisory Board: Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Elcelyx, Eli Lilly, Intarcia, Johnson & Johnson/Janssen, Merck, Novo Nordisk, Roche/Genentech, Sanofi-Aventis

Anne L. Peters, MD, CDE, FACP
Consulting Fees: Abbott Diabetes Care, BD, BMS/AZ, Boehringer Ingelheim, Janssen, Lilly, Medtronic Minimed, sanofi, Takeda
Speakers Bureau: BMS/AZ, NovoNordisk

Stanley Schwartz, MD, FACP, FACE
Consulting Fees: AstraZeneca, Amylin, Bristol-Myers Squibb, Gerardis Biosystems, Merck & Co., Inc, Takeda
Speaker's Bureau: Abbvie, AstraZeneca, Amylin, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck & Co., Inc., Novo, Nordisk, Santarus, Takeda

Reviewers report the following relationship(s):

Ronald A. Codario, MD, FACP, FNLA, CCMEP
No relevant financial relationships to disclose.

Carol H. Wysham, MD
Consulting Fees: Boehringer Ingelheim, Eli Lilly, Janssen, Sanofi-Aventis
Speaker's Bureau: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Medtronic, Novo Nordisk, Sanofi-Aventis
Contract Research: Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Merck & Co., Inc., Novo Nordisk, Sanofi-Aventis

Vindico Medical Education staff report the following relationship(s):
No relevant financial relationships to disclose.
Signed disclosures are on file at Vindico Medical Education, Office of Medical Affairs and Compliance.

Target Audience

The intended audience for this activity is endocrinologists and other health care professionals involved in the treatment of patients with type 2 diabetes.

Unlabeled and Investigational Usage

The audience is advised that this continuing medical education activity may contain references to unlabeled uses of FDA-approved products or to products not approved by the FDA for use in the United States. The faculty members have been made aware of their obligation to disclose such usage. All activity participants will be informed if any speakers/authors intend to discuss either non-FDA approved or investigational use of products/devices.

Created and published by Vindico Medical Education, 6900 Grove Road, Building 100, Thorofare, NJ 08086-9447. Telephone: 856-994-9400; Fax: 856-384-6680. Printed in the USA.

Using GLP-1 Receptor Agonists in Combination With Oral Agents to Achieve Glycemic Control

Vivian Fonseca, MD, FRCP

Glucagon-like peptide-1 (GLP-1) is a hormone secreted by the gut, usually in response to food intake, which plays an important role in glucose metabolism.[1] GLP-1 stimulates insulin secretion, and suppresses glucagon secretion in a glucose dependent manner – doing so only when the glucose is elevated and not when it is normal or low. Also, GLP-1 indirectly suppresses glucose production in the liver in the postprandial state, through suppression of glucagon. Unfortunately, GLP-1 has a very short half-life of a few minutes and therefore, synthetic GLP-1 receptor agonists that are resistant to degradation have been developed that can be given less frequently by injection.[1] These drugs are currently available for clinical use, alone and in combination with several other medications in the United States and others are in development. This review will focus on the combination of GLP-1 receptor agonists in combination with other oral agents.

The major reasons for the choice of GLP-1 receptor agonists include good efficacy or desire for weight loss; limitations include the cost and adverse effect profile.

Combinations

Because the mechanism of action is unique, GLP-1 receptor agonists can regulate glucose in combination with a number of other medications for diabetes. For example, since they have no direct effect on insulin action, GLP-1 receptor agonists can work well (and perhaps synergistically) in combination with insulin sensitizers. Even though both GLP-1 receptor agonists and sulfonylureas stimulate insulin secretion from the beta cell of the pancreas, they do so by different receptors and pathways and are, therefore, additive in this effect. Similarly, though GLP-1 receptor agonists and metformin both suppress glucose production in the liver, their mechanisms are different and they work well in combination.

The American Diabetes Association and European Association for Study of Diabetes (ADA/EASD) in their recommendations for pharmacological therapy for treatment of diabetes, have included GLP-1 receptor agonists to be used in combination with the wide variety of drugs either as second-line therapy in combination with metformin, or as third-line therapy in combination with 2 other oral agents depending on which ones were previously chosen by the clinician as part of individualized treatment.[2] The major reasons for the choice of GLP-1 receptor agonists cited in the recommendations include good efficacy or desire for weight loss; whereas limitations include the cost and adverse effect profile. In addition, several other clinical trials of GLP-1 receptor agonists, in combination with one or more oral agents, have been done as part of the FDA approval process and most have been published. Some of these trials are discussed in more detail later in this article.

The first GLP-1 receptor agonist to be approved for clinical use was exenatide, which is synthetic exendin-4. Exenatide has been shown to be useful in combination with a sulfonylurea,[3] metformin,[4] as well as a combination of a sulfonylurea and metformin.[5] At the maximum dose of 10 mcg twice-daily, A1C at the end of 6 months decreased by approximately 0.8%, whereas a control group had a small increase. Exenatide significantly reduced A1C in patients with type 2 diabetes unable to achieve adequate glycemic control with maximally effective doses of combined metformin-sulfonylurea therapy.[5] This improvement in glycemic control was associated with no weight gain and was generally well tolerated. In some patients, particularly in combination with metformin, exenatide led to a reduction in body weight. There were some adverse effects with exenatide including nausea and vomiting in about 20% to 30% of people and in about 5% it was severe enough that patients discontinued therapy. There have been occasional reports of pancreatitis associated with the use of GLP-1 receptor agonist therapy and these have been fortunately relatively few.

Other GLP-1 receptor agonists available include a long-acting version of exenatide (exenatide LAR),

and liraglutide, which is an analog of human GLP-1.[6-8] Both are given by subcutaneous injection, but due to different half-lives, liraglutide can be given once-a-day and the exenatide LAR once-a-week. Interestingly, head to head comparisons between these GLP-1 receptor agonists in combination with oral agents have demonstrated that the improvement in glycemia is greatest with liraglutide, although the difference is small.[9]

Some of these studies are interesting as they have combined a hepatic (metformin) and peripheral (thiazolidinedione) insulin sensitizer with a GLP-1 receptor agonists, thus targeting 3 major pathophysiological defects in type 2 diabetes. To determine the efficacy and safety of liraglutide when added to metformin and rosiglitazone in type 2 diabetes, a 26-week, double-blind, placebo-controlled, parallel-group trial randomized 533 subjects to once-daily liraglutide (1.2 mg or 1.8 mg) or placebo in combination with metformin (1 g twice-daily) and rosiglitazone (4 mg twice-daily).[10] Mean A1C values decreased significantly more in the liraglutide groups vs. placebo (mean ± SE -1.5 ± 0.1% for both 1.2 mg and 1.8 mg liraglutide and -0.5 ± 0.1% for placebo). Fasting plasma glucose, body weight, and blood pressure also decreased significantly. Minor hypoglycemia occurred more frequently with liraglutide, but there was no major hypoglycemia. Gastrointestinal adverse events were more common with liraglutide, but most occurred early and were transient.

The concept of adding a once-weekly injection to oral agents may be more acceptable to patients than daily insulin when oral agents fail. In a randomized, placebo-controlled phase 2 study, exenatide LAR (0.8 mg or 2.0 mg) was administered subcutaneously once-weekly for 15 weeks to subjects with type 2 diabetes suboptimally controlled with metformin and/or diet and exercise (mean A1C 8.5%).[11] Exenatide LAR reduced mean A1C by up to -1.7% compared with +0.4% with placebo. Subjects receiving 2.0 mg exenatide LAR had body weight reductions of a mean of 3.8 kg, whereas body weight was unchanged with both placebo and the 0.8 mg dose. Mild nausea was the most frequent adverse event.

Short-acting and Long-acting Analogs

Other agents in development include short-acting and long-acting analogs, such as lixisenatide[12] and albiglutide,[13] respectively. In addition, they have other differing effects on glucose metabolism. Exenatide and lixisenatide have a more powerful effect on postprandial glucose whereas liraglutide and exenatide LAR lower fasting glucose to a greater degree. The effect of exenatide and lixisenatide on gastric emptying has been studied and shown to be quite marked, whereas liraglutide has less of an effect on stomach emptying. In all combination trials, there is a reduction in body weight. However, hypoglycemia only occurs in combination with a sulfonylurea. An interesting combination is GLP-1 receptor agonists and pioglitazone. Since pioglitazone is a drug known to cause weight gain, the beneficial effect of the GLP-1 receptor agonist leads to either a small degree of weight loss or is weight neutral, which is an advantage in clinical practice.

The combination of a dipeptidyl peptidase-4 (DPP-4) inhibitor and a GLP-1 receptor agonist for enhanced glycemic control has not been studied. On a theoretical basis, the rationale for such a combination is weak, since GLP-1 receptor agonists have been designed to be resistant to the effect of the enzyme DPP-4. In addition, some of the newer agents, such as canagliflozin have not been studied in combination with a GLP-1 receptor agonist.

Summary

GLP-1 receptor agonists have been tested in clinical trials with a wide variety of oral agents, both as 2 and 3 drug therapies. Such combinations offer several theoretical and clinical advantages with synergies in addressing multiple pathophysiological defects translating into clinically meaningful reductions in glucose. In addition, weight loss and low rates of hypoglycemia in the context of improving control are very important to patients. Tolerability may be a problem in some patients, though nausea and vomiting is often transient.[14] Outcome studies are ongoing and will provide data on long-term safety.

References

1. Ahren B, et al. *Horm Metab Res.* 2004; 36(11-12):867-876.
2. Inzucchi SE, et al. *Diabetes Care.* 2012; 35(6):1364-1379.
3. Buse JB, et al. *Diabetes Care.* 2004; 27(11):2628-2635.
4. DeFronzo RA, et al. *Diabetes Care.* 2005; 28(5):1092-1100.
5. Fineman MS, et al. *Diabetes Care.* 2003; 26(8):2370-2377.
6. Mudaliar S, et al. *Diabetologia.* 2012; 55(7):1865-1868.
7. Russell-Jones D, et al. *Diabetologia.* 2009; 52(10):2046-2055.
8. Marre M, et al. *Diabet Med.* 2009; 26(3):268-278.
9. Buse JB, et al. *Lancet.* 2009;374(9683): 39-47.
10. Zinman B, et al. *Diabetes Care.* 2009; 32(7):1224-1230.
11. Kim D, et al. *Diabetes Care.* 2007; 30(6):1487-1493.
12. Ratner RE, et al. *Diabet Med.* 2010; 27(9):1024-1032.
13. Rosenstock J, et al. *Diabetes Care.* 2009; 32(10):1880-1886.
14. Aroda VR, et al. *Diabetes Metab Res Rev.* 2011;27(6):528-542.

Full references are available at www.healio.com/endocrinology/education-lab.

Using DPP-4 Inhibitors in Combination Oral Agents to Achieve Glycemic Control

Stanley Schwartz, MD, FRCP, FACE

We are in the midst of an epidemic of obesity and diabetes. Hyperglycemia[1-3] by spikes or in a continuous mode leads to both acute and chronic toxicity, with subsequent microvascular and macrovascular complications. Data from the UK Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (ECCT/EDIC) trials, indicated that control of glycohemoglobin to a goal of 7.0% resulted in microvascular complication reduction, and even 10 years following the end of both studies could demonstrate reduced macrovascular complications, while reducing mortality as well.[4-12] The confusion occurred when, several years ago, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) trials in patients with longer duration diabetes, older, and many with cardiovascular comorbidities, showed no benefit in intensive care to a goal of 6.0%, and the ACCORD trial actually showed increased mortality.

These results were likely because there was an overuse of sulfonylureas and insulin such that in the ACCORD trial there was an average weight gain of 6 lbs, and 10% of the population gained more than 20 lbs. All studies were able to show a direct correlation of hypoglycemia (Table 1), specifically with increased mortality and QT prolongation.

There is clearly an increased mortality with sulfonylurea use, since sulfonylureas block ischemic preconditioning. Moreover, the fear of hypoglycemia leads to inadequate control, increases the risk of dementia, and causes undue worry for friends, spouse, and coworkers. In addition, sulfonylureas can cause increased beta-cell apoptosis, so they may work for 1 year, but over the next 2 to 3 years they lose effectiveness, requiring more medications to achieve glycemic goals.

Type 2 diabetes is a strongly genetic disease driving insulin resistance and beta-cell failure. In this current environment with overeating and reduced exercise, obesity results, and this carries with it the insulin resistance phenotype which is associated with atherosclerotic risk, hypertension, hyperlipidemia, endothelial dysfunction, polycystic ovarian syndrome (PCOS), and erectile dysfunction, enhancing the risk for macrovascular complications.

However, there are multiple causes of hyperglycemia in type 2 diabetes,[13,14] including abnormal beta cell function, reduced insulin secretion, reduced incretin effect, inappropriate glucagon secretion, lack of glucagon suppression, increased insulin resistance, accelerated gastric emptying, impaired renal glucose clearance, and centrally controlled mechanisms which result in increased sympathetic tone.

Increased glucagon secretion can be suppressed with incretins and

Table 1. Consequences of Hypoglycemia

Prolonged QT-intervals • **Can be of pronged duration** • **Greater with higher catecholamine levels**
Associated with Angina **Ischemic EKG changes**
Associated with Arrhythmias
Associated with Sudden Death
Increased Variabilty • **Increases inflammation, ICU mortality**

Studies were able to show a direct correlation of hypoglycemia with increased mortality and QT prolongation.

Source: Modified from Moheet A, et al. *Curr Atheroscler Rep.* 2013;15(9)351.

pramlintide, alpha glucosidase inhibitors delay gut glucose absorption, while thiazolidinediones and metformin decrease insulin resistance. Pharmacologic levels of incretin suppress appetite at the hypothalamic centers for appetite, while bromocriptine in a quick-release formulation restores a morning spike in dopamine in the suprachiasmic nucleus, reducing peripheral insulin resistance and decreasing sympathetic tone.

The sodium glucose co-transporter 2 (SGLT2) inhibitors[15,16] reduce glucose reabsorption in the kidney, resulting in increased glucose excretion in the urine.

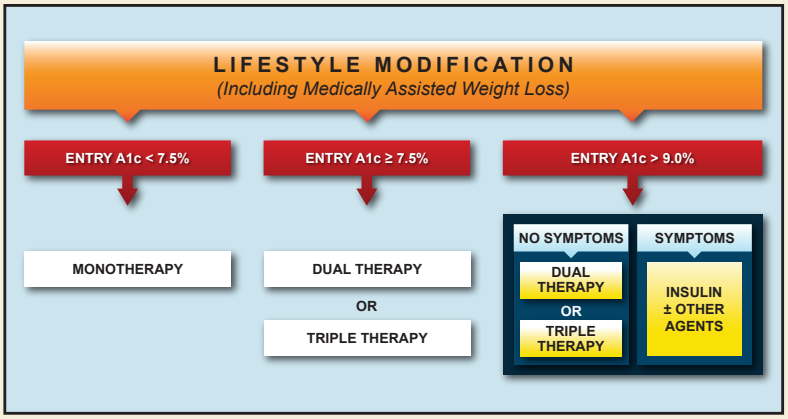
The AACE guidelines, which were updated in 2013, recognize that we should be using sulfonylureas last, if at all, and also recognizes that we should be using multiple combination therapies early in the course of the disease. If HbA1C is from 6.5% to 7.5%, one drug, along with diet and exercise is sufficient, if HbA1C is from 7.5% to 9.0%, dual therapy with diet and exercise is suggested; and if they are over 9.0%, we recommend a triple therapy with diet and exercise (Figure 1).

The AACE guidelines also recognize that there are first-tier drugs including metformin, pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, which drop glycohemoglobin from 1% to 2% in monotherapy. We have second-tier agents that drop glycohemoglobin from 0.5% to 1%; these include the SGLT2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, colesevelam, alpha-glucosidase inhibitors, and bromocriptine quick release.

The AACE guidelines also note that if a patient has a glycohemoglobin of over 9% and is symptomatic, that insulin is recommended.

Metformin is still felt to be the first-line oral agent, as it drops glycohemoglobin from 1% to 2%; with no hypoglycemia used alone or in combination with other drugs including

Figure 1. AACE/ACE: First-line Therapy Recommendations Based on A1C at Diagnosis



Multiple combination therapies should be used early in the course of the disease.
(See page 17 to view the entire algorithm.)

Source: AACE Comprehensive Diabetes Management Algorithm. *Endocr. Pract.* 2013;19:327-336.

DPP-4 inhibitors as long as clinicians are not using them with sulfonylureas or insulin. They have an advantageous lipid profile, showing cardiovascular risk reduction in UKPDS obese subgroup.

Pioglitazone, the most accepted thiazolidinedione at the present time, improves insulin resistance and beta cell function, reduces steatohepatitis, has a benefit on blood pressure reduction and microalbumin, improves endothelial dysfunction with an advantageous lipid profile, and can be effective in patients with renal insufficiency causing no hypoglycemia used as monotherapy. Pioglitazone has a potential to delay or prevent diabetes, and in the PROactive trial had reduction in composite endpoint of heart attack, stroke, and death of 16%, and reduced risk of a second MI, with the best reduction in the risk of secondary stroke of 47% of any drug available.

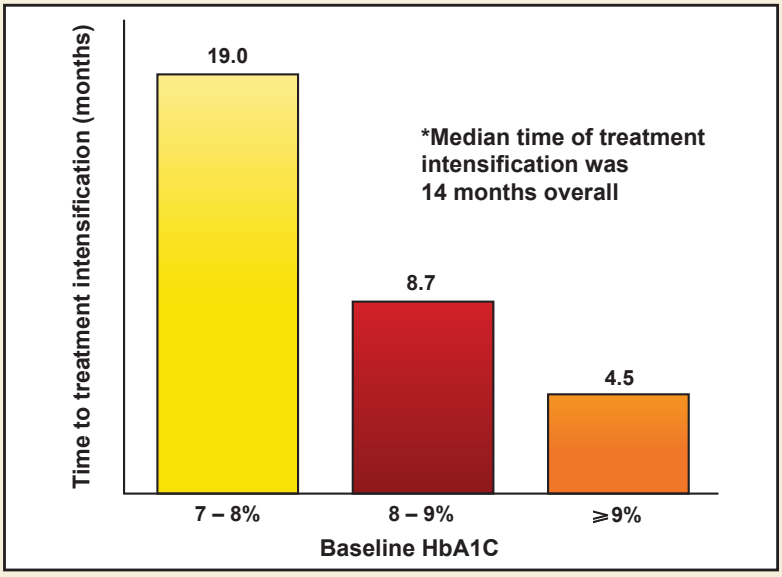
The recently released SGLT2 inhibitor, canagliflozin, has remarkable benefits for combining reduction in glycohemoglobin from 0.5% to 0.7%, reduction in weight from 3% to 4% over 6 months, and reduction in blood pressure and is effective over mono-, dual- and triple-therapy in combination with insulin, while not causing hypoglycemia if used without sulfonylureas and insulin. Though volume contraction, urinary tract infection, and genital yeast infections may be an issue, the risk can be reduced by encouraging patients to drink lots of fluids and maintain fastidious hygiene.

Bromocriptine QR drops glycohemoglobin from 0.5% to 1.0%, and as long as one titrates slowly to avoid GI upset and hypotension, it seems to be very effective in patients with higher triglycerides and hypertension and has clear CV safety and potential for reducing adverse CV outcomes due to its effecting reduced sympathetic tone.

There are second-tier agents that drop glycohemoglobin; these include SGLT2, DDP-4, and alpha-glucosidase inhibitors, colesevelam, and bromocriptine quick release.

Colesevelam has similar glycohemoglobin responses without undue adverse effects, and has the additional

Figure 2. Treatment Intensification



*Evaluation factors associated with treatment intensification in patients with type 2 diabetes who failed metformin monotherapy.

Source: Modified from Fu AZ, et al. *Diabetes Obes Metab*. 2011;13:765–769.

benefit of reducing low-density lipoprotein cholesterol (LDL-C).

Both the ADA/EASD and AACE guidelines recognize the importance of incretin therapy, (GLP-1 receptor agonists and DPP-4 inhibitors). The background in this regard is that the genetically predisposed beta-cell has reduced function over time, including reduced incretin effect.

DDP-4 inhibitors have proved to be remarkable additions because of their efficacy, safety, tolerability, and additional benefit in combination with other agents.

The incretin effect was discovered more than 30 years ago, where it was noticed that glucose administered by mouth increases insulin secretion 4 times greater than glucose administered intravenously, and that this incretin effect was reduced markedly in patients with diabetes. Two predominant incretins were discovered, GLP-1 and GIP.

However, though it is secreted to a lesser degree in patients with type 2 diabetes, GLP-1 resistance has also been demonstrated in some studies. However, this can be overcome by pharmacologic increases in its concentration.

GLP-1 increases both first-phase and second-phase insulin release. When GLP-1 is infused, it can normalize glucose levels in patients with type 2 diabetes.[17,18]

In patients with stress diabetes (eg, severe illness, surgery, steroid use, transplantations), incretins have proved very valuable in overcoming and treating hyperglycemia due to both corticosteroids and calmodulin inhibitors.

Moreover, GLP-1 has actions that extend beyond the pancreas, including suppression of appetite, slowing gastric emptying, increasing sodium excretion, reducing production of glucose at the liver, while having a modest effect on increasing insulin sensitivity at the muscle, increasing insulin synthesis, and decreasing beta cell apoptosis.

Of fascinating import is that there are GLP-1 receptors in the heart, and they result in multiple potential benefits including reductions in systolic and diastolic blood pressure, improved endothelial dysfunction, and enhancing myocardial contractility.

Thus, there is a logic for their benefit on reducing adverse cardiovascular outcomes in patients with type 2 diabetes, but long-term prospective studies are actually being done now to see if this can be demonstrated.

DPP-4 inhibitors, have proven to be remarkable additions to our armamentarium because of their efficacy, safety, tolerability, as well as their additional benefit in combination with other agents, reducing glycohemoglobin on the order of 0.5% to 0.8% in monotherapy.[19-22]

The drugs currently available in the United States are sitagliptin, saxagliptin, linagliptin, and alogliptin which are all once-a-day dosing. Linagliptin is safe at all levels of eGFR, including renal insufficiency, requiring no dose adjustments. The DPP-4 inhibitors are weight-neutral with no hypoglycemia in the absence of concomitant sulfonylurea, glinide, and insulin therapy. Two recent studies with the use of saxagliptin and alogliptin have shed some light on the cardiovascular effects of these agents. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI) trial, demonstrated that DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Among patients with type 2 diabetes who had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.

We like to think about the use of incretins, and particularly DPP-4 inhibitors, across the continuum of the natural history of diabetes.

When using incretins in combination therapy, there are some "generic principles" to understand. We know that there is significant clinical inertia in advancing therapy in patients with type 2 diabetes, such that in patients who are on either metformin or sulfonylurea therapy, the time to add a second agent was 27 and 35 months, respectively, before physicians changed therapy (Figure 2).

Combination therapy of DPP-4 inhibitor with metformin is particularly effective with less hypoglycemia and with no rise in weight as is seen with sulfonylurea use.

SGLT2 inhibitors with incretins can result in a remarkable improvement in glycemic control, with an additional weight reduction of approximately 3.2% to 3.9% of body weight. So, the combination of a DPP-4 inhibitor with an SGLT2 inhibitor can result in an equivalent drop in glycohemoglobin of a GLP-1 receptor agonist, with similar weight reduction, without the issues of using an injectable agent, and without GI upset risk that can occur with GLP-1 receptor agonist therapy.

The principles of combination therapy of DPP-4 with other agents have been reviewed, but there are clear specific benefits surrounding fixed-dosed combination therapy of DPP-4 inhibitors with other agents that include improved compliance and reduced cost.

Summary

Patients with diabetes need to be treated aggressively because there is an epidemic that increases the risk for adverse outcomes. We can reduce adverse outcomes by glycemic control, especially if we do so without hypoglycemia and weight gain. The oral and injectable incretin agents are efficacious, reduce the risk of weight gain and hypoglycemia, and have a potential benefit on cardiovascular outcomes. The key is to pick the right drug for the right patient and the right patient for the right drug.

References

1. American Diabetes Association. At: http://www.diabetes.org/diabetes-statistics/complications.jsp.
2. Brownlee M. Diabetes mellitus: theory and practice. Elsevier Science Publishing Co., Inc; 1990:279-291.
3. Ceriello A. *Diabetes*. 2005;54:1-7.
4. Meinert CL. *Diabetes.* 1970;19(suppl): 789-830.
5. Goldner MG. *JAMA.* 1971;218(9):1400-1410.
6. UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:854-865.
7. Holman RR. *N Engl J Med.* 2008; 359(15):1577-1589.
8. DCCT Research Group. *N Engl J Med.* 1993;329;977-986.
9. Nathan DM, et al. *N Engl J Med.* 2005; 353:2643-2653.
10. Gerstein HC, et al. *N Engl J Med.* 2008; 358:2545-2559.
11. Patel A, et al. *N Engl J Med.* 2008; 358: 2560-2572.
12. Duckworth W, et al. *N Engl J Med.* 2009; 360(2):129-139.
13. Inzucchi SE, et al. *Diabetes Care.* 2012; 35(6):1364-1379.
14. DeFronzo RA. *Am J Med.* 2010;123(3 suppl):s38-s48.
15. List JF, et al. *Diabetes Care.* 2009:32:650-657.
16. Wilding JP, et al. *Diabetes Care.* 2009; 32:1656-1662.
16. Rachman M et al. *Diabetologia.* 1997; 40:205-211.
18. Nauck MA et al. *Diabetologia.* 1993; 36:741–744.
19. Rosenstock J et al. *Curr Opin Endocrinol Diabetes Obes.* 2007;14:98-107.
20. Nathan DM, et al. *Diabetes Care.* 2008; 31:193-203.
21. Herman GA et al. *J Clin Endocrin Metab.* 2006;91:4612-4619.
22. Raz I et al. Diabetologia. 2006;49:2564-2571.

Full references are available at www.healio.com/endocrinology/education-lab.

Dialogues in Diabetes Case Discussions

W. Timothy Garvey, MD

Case 1

A 63-year-old hypertensive female with type 2 diabetes for 10 years who is currently taking rosuvastatin 10 mg daily, glimepiride 4 mg once-daily, metformin 1,000 mg twice-daily, saxagliptin 5 mg daily, olmesartan 40 mg once-daily, and ASA 325 mg daily. Her body mass index (BMI) is 25 kg/m^2, blood pressure (BP) is 132/80 mm Hg bilaterally, waist circumference (WC) is 35 inches, and she has no pretibial edema. She has gained 3 lbs over the past year and tries to follow a 1,500 calorie American Diabetes Association (ADA) diet. She works as a medical receptionist, is a non-smoker, does not exercise, and occasionally self monitors her blood glucose. Her A1C one year ago was 7.9%. She presents with the following data:

LDL-C: 117 mg/dL

HDL-C: 38 mg/dL

Triglycerides: 246 mg/dL

Non-HDL-C: 166 mg/dL

Total cholesterol: 204 mg/dL

A1C: 8.4%

Fasting glucose: 148 mg/dL

eGFR: 91 mL/min/1.73 m^2

Urine microalbumin/creatinine ratio: normal

Urine protein: negative

Discussion

This patient presents with a common problem seen in managing patients with type 2 diabetes mellitus (T2DM), progressive increases in A1C. She is currently on optimum doses of effective oral agents. Before making a decision on diabetes therapy, it is important to first assess that the patient is actually compliant to the prescribed medications and to assure that there is not some dietary indiscretion (eg, excessive consumptions of sodas) that could be exacerbating hyperglycemia. In deciding on changes to therapy, weight gain, and obesity are currently not major issues, although she does meet all 5 criteria for the metabolic syndrome. The WC of 35 inches does indicate relative accumulation of abdominal fat in this patient with a BMI of 25 kg/m^2. The HbA1c is not at target and intensification of diabetes treatment is indicated. The current combination of a dipeptidyl peptidase-4 (DPP-4) inhibitor (saxagliptin) and metformin are important to maintain, since metformin may augment glucagon-like peptide-1 (GLP-1) receptor agonists secretion by the L-cells, while the DPP-4 inhibitor improves beta-cell function and inhibits glucagon secretion.[1] In terms of cardiovascular safety, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI) trial, demonstrated that DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased.[2] Among patients with type 2 diabetes who had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin, as compared with placebo.[3]

The addition of a sodium glucose co-transporter 2 (SGLT2) inhibitor may result in mild weight loss and A1C reduction. However, her dyslipidemia could be adversely affected since these agents can increase LDL-C and non-HDL-C.[4]

Current American Association of Clinical Endocrinologists (AACE), ADA, and European Association for the Study of Diabetes (EASD)[5] recommendations would indicate that insulin therapy should be the next therapeutic choice to enhance glycemic control. With the addition of insulin, strong consideration should be given to discontinuing the glimepiride to decrease risk of hypoglycemia. Not to be overlooked is the necessity of referral to a certified diabetes educator for a refresher course on meal and portion selection as well as encouraging her to pursue a structured exercise program.

There are several possible methods of initiating insulin therapy in patients presenting in this manner, including a long-acting insulin analog, bedtime NPH, mixed insulin preparations at the largest meal of the day, or even short-acting insulin prior to each meal.

Initiating insulin treatment by adding basal insulin glargine once-daily can be safer and more effective than beginning twice-daily injections of 70/30 insulin NPH/regular mix while discontinuing oral agents in patients with uncontrolled T2DM.[6] From a practical point of view, long-acting insulin analog (glargine or detemir) would be a prudent choice in this patient. Initial recommended doses for patients are 10 units once-daily (or 0.1 to 0.2 units/kg).[7] The long-acting insulin dose can be titrated upward, if necessary, by 5 units once-weekly until the prebreakfast glucose is less than 100 mg/dL. By improving glycemic control and instituting long-acting basal insulin in this patient, triglyceride reduction can often be achieved by enhancing lipoprotein

lipase activity reducing insulin resistance due to hyperglycemia, and attenuating hepatic gluconeogenesis. In addition, lower pre-meal glucose levels usually result in lower postprandial glucose, and both contribute to the reduction in A1C. Thus, the addition and up-titration of a long-acting insulin analog, with discontinuation of the glimepiride, and an RD referral for a diet and exercise program, represent a reasonable approach to better glycemic control in this patient. Since LDL-C is not at target, it would also be appropriate to increase rosuvastatin to 20 mg/day.

Case 2

A 59-year-old male, non-smoker, with type 2 diabetes and hypertension for 13 years. He admits being non-compliant at times with his diet and has gained 14 lbs over the past year, complaining that he is "always hungry". In addition, his A1C has risen from 6.5% to its current level of 8.0%. His BP is 142/96 mm/Hg, BMI is 28 kg/m^2, WC is 40 inches, and there is no pre-tibial edema. He is worried about his weight gain and increasing glycemia, since his father died at age 72 due to complications from diabetes. His medications include insulin glargine 20 units daily, glipizide XL 20 mg daily, metformin 1,000 mg twice-daily, pioglitazone 30 mg once-daily, pitavastatin 4 mg daily, losartan 100 mg daily, and ASA 325 mg daily. He presents with the following data:

LDL-C: 112 mg/dL

HDL-C: 42 mg/dL

Triglycerides: 254 mg/dL

Non-HDL-C: 172 mg/dL

Total cholesterol: 204 mg/dL

A1C: 8.0%

eGFR: 89 mL/min/1.73 m^2

Fasting blood glucose: 108 mg/dL

Urine microalbumin/creatinine ratio: normal

Urine protein: negative

Discussion

This obese, hypertensive male with type 2 diabetes and metabolic syndrome is at high risk for a cardiovascular disease event, and his glycemia, LDL-C, and blood pressure are not at target. A weight loss program involving lifestyle intervention and consideration of a weight loss medicine to blunt appetite would be therapeutically beneficial. Regarding glycemic control, consistent with recent AACE as well as ADA and EASD guidelines,[8] a prudent choice in this patient would be the addition of a GLP-1 receptor agonist, which would also help address his persistent hunger, reduce postprandial lipemia, lower blood pressure, promote weight loss, and improve glycemic control. At the same time, the sulfonylurea could be decreased to reduce polypharmacy since its bioactivity is likely diminished after the long period of administration. Twice-daily exenatide in patients with T2DM with a starting A1C of 8.0% to 8.2% can achieve weight losses of 4 to 8 lbs over the first 6 to 12 months with a drop in A1C of 1.0 to 1.2%.[8] Longer acting GLP-1 receptor agonist therapy with either liraglutide or once-weekly exenatide will also provide 24-hour glycemic control improving both fasting and postprandial plasma glucose. In a head-to-head 24-week study comparing twice-daily exenatide vs. exenatide once-weekly, greater weight loss and A1C reductions were achieved with the longer acting agent.[9] In addition, a direct comparison of liraglutide vs. twice-daily exenatide demonstrated a 0.33% greater decrease in A1C with liraglutide,[10] and a one-year study demonstrated a decrease in A1C of 0.2% with liraglutide vs. once-weekly exenatide LAR.[11] In addition GLP-1 receptor agonist therapy can be beneficial in reducing postprandial hyperlipidemia and promote vasodilatation which can decrease blood pressure.[12] Finally, the use of a long-acting insulin to restrain hepatic glucose production and lower fasting glucose, together with a GLP-1 receptor agonist which increases insulin secretion with reductions in postprandial glucose, can be a very effective combination. Current FDA approved combinations are glargine insulin with exenatide and detemir insulin with liraglutide, while exenatide once-weekly has not yet received formal FDA approval for concomitant use with insulin.[13] Pioglitazone, although beneficial in reducing triglycerides, A1C, free fatty acids and LDL particle number, can cause fluid retention, particularly when used with insulin. The clinician should be cognizant of fluid retention, as a potential cause for weight gain with this combination.

References

1. Deacon CF. *Diabetes Obes. Metab*. 2011: 13(1):7-18.
2. Scirica BM, et al. *N Engl J Med.* 2013; 369(14):1317-1326.
3. White WB, et al. *N Engl J Med*. 2013; 369(14):1327-1335.
4. Guthrie RM. *Postgrad Med.* 2013; 25(3):21-32.
5. Inzucchi SE, et al. *Diabetes Care.* 2012; 35(6):1364-1379.
6. Janka HU, et al. *Diabetes Care.* 2005; 28(2):254-259.
7. Swinnen S, et al. *Cochrane Database Syst Rev*. 2011;7:CD006383.
8. Aroda VR, et al. *Clin Ther.* 2012; 34(6):1247-1258.
9. Blevins T, et al. *J Clin Endocrinol Metab.* 2011;96(5):1301-1310.
10. Buse JB. et al. *Lancet.* 2009: 374 (9683):39-47.
11. Buse JB, et al. *Lancet*. 2013; 381 (9861):117-124.
12. Farr S, et al. *Curr Opin Lipidol*. 2012; 23(1):56-61.
13. Russell-Jones D, et al. *Clin Endocrinol*. 2012;77(4):489-499.

Full references are available at www.healio.com/endocrinology/education-lab.

Expert Interview with Anne L. Peters, MD, CDE, FACP

For a patient with an A1C of 7.9% that fails to respond to initial metformin therapy, how do you make a decision on the next course of treatment, and what drugs do you personally use?

Anne L. Peters, MD, CDE, FACP: In this era of individualized patient care, the first thing I do is actually talk with the patient about what their goals are and what point they are at in terms of understanding the disease. There are some patients who really want to lose weight and get their A1C well below 7%, for these patients I might start a glucagon-like peptide-1 (GLP-1) receptor agonist because you get a good A1C reduction along with weight loss, but it is an injection, and the patient needs to be interested in an injectable kind of therapy.

> There are different choices that will get you to a better AIC; some differ in terms of adverse effects and all differ in terms of cost.

However, I personally take care of many patients who have very little money and they want to get their A1C down but they need to do it in the most cost-effective way possible, so these are patients where the next choice would most likely be a sulfonylurea agent. We all know the advantages and disadvantages of that. So, there would be a subset where cost would be the most important part.

A dipeptidyl peptidase-4 (DPP-4) inhibitor is also another choice. For instance, if there is a patient who is coming down from an A1C of 9% and they have come to this point and still seem to be working on lifestyle, etc, a DPP-4 inhibitor might be a reasonable choice because it would help the patient get to around 7% without causing hypoglycemia or weight gain.

Another possibility to be considered is basal insulin, although I tend not to use basal insulin because I would rather try non-insulin therapies because of the complexity that insulin adds.

Lastly, we now have the sodium glucose co-transporter 2 (SGLT2) inhibitors, which are also a possibility at this stage, and again a discussion with the patient concerning what they are most interested in doing in terms of lifestyle, their readiness to give an injection, and/or their interest in trying a new drug versus some of the older agents would be appropriate.

So, I would have a discussion with the patient because there are many different choices that will get you to a better A1C, but some of them do differ in terms of their adverse effects, and they all differ in terms of their costs.

How does exenatide once-weekly compare with liraglutide once-daily for GI-related adverse effects for weight loss, glycemic control, and appetite suppression?

Dr. Peters: There are several things. If you look at the clinical trials where they compare these drugs, you get several gastrointestinal (GI) adverse effects with exenatide once-weekly compared to liraglutide once-daily. But liraglutide tends to give you a greater reduction in A1C and greater weight loss. But in an individual patient, obviously there is going to be variability.

I offer most patients the option because there are some patients where once-a-week therapy is a godsend versus other patients where taking something daily is not an issue.

If I have a patient on liraglutide who is getting a lot of GI adverse effects, I might try them on exenatide once-weekly just to see if I can mitigate some of those GI adverse effects, because unfortunately you cannot predict whether they are going to experience GI adverse effects or not. But again, you can look at the clinical trial data and then you look at your own patient and make some assessment of what is appropriate.

There are 2 issues with exenatide once-weekly: First, it may take several weeks for the appetite suppression effect to kick in; and secondly, the difficulty that some patients have with the device itself, such as mixing the amount of fluid being injected. Have you seen those as challenges or problems? And, if so, how do you help patients overcome those challenges?

Dr. Peters: Well, I do not find them to be a problem because I have a very good teaching protocol. I like using exenatide once-weekly because I know how to teach people how to use it. And once you have taught them, they can manage it if you give them sound information. I think the bigger issue comes from providers who do diabetes care all the time but they do not routinely teach the process, so then it becomes more of a barrier.

Also, you do get these little lumps at the site where exenatide once-weekly is injected. I tend to tell patients that this might happen so they are not surprised. And, I also tell patients that there may be a delay before they actually see the clinical benefits of the drug.

I personally can get past those barriers because of my own familiarity, but I think it is a barrier when providers are not familiar to it, and they do not warn patients of how the drug is going to act. Once there are better devices for once-weekly compounds we are going to do better in terms of giving these drugs.

Where do you personally see the SGLT2 inhibitors being best utilized in treating patients with type 2 diabetes? And also, where do you feel they will be least effective?

Dr. Peters: I did not do any of the research with SGLT2 inhibitors, so my real experience is both from reading the literature as well as using it in a smaller number of patients. I think one of the most effective things about SGLT2 inhibitors is that you can use it in patients in any part of the pathway. You can use it in patients as monotherapy; you can use it in patients on combination therapies; and you can use it in patients on insulin because it is basically a treatment that has a different mechanism of action than anything else.

The place you cannot use SGLT2 inhibitors is in patients who have renal insufficiency. If the patient's estimated glomerular filtration rate (eGFR) is less than 45, or particularly, less than 30, you are not supposed to use the drug. So, the renal dysfunction component is something that is quite significant in terms of guiding its use.

But for people with normal renal function or near-normal renal function, I think in almost any part of the disease cycle you can use these agents.

In my own practice, I have been using SGLT2 inhibitors as sort of third-line or fourth-line therapy because it is new. I have been using it in patients who are already on other agents, such as metformin, GLP-1 receptor agonists, or basal insulin and I have added it in part. Some of these patients have wanted to get off of insulin because of the weight gain quality to it, and by adding in an SGLT2 inhibitor they have been able to taper off of the insulin.

I think that there is a lot of utility, but I think we are new to this class of drugs, so there is a lot we need to explore in terms of actual clinical use. And I do not think that SGLT2 inhibitors will be widely used as monotherapy just because metformin is such a good monotherapy drug, but clearly they would work as monotherapy if given to a patient that way.

One of the issues with the SGLT2 inhibitors is that they can raise the non-HDL-C, and also raise the LDL-C. How do you feel about using these drugs in patients with cardiovascular disease or patients with dyslipidemia? Is this a relative contraindication, or a concern for you?

Dr. Peters: Yes. Obviously I do not like raising the low-density lipoprotein cholesterol (LDL-C); it is not something we actually want to do. However, I do not know how it is going to translate to cardiovascular outcomes because I think the absolute change in LDL-C is relatively small. But that is one of the things that we need to observe in our patients after we have started them on a drug and make sure that their LDL stay on target. Therefore, it is not a preferred effect and we need to make sure it does not have any clinical consequences.

I think when you first use SGLT2 inhibitors it is a bit like starting a diuretic, so you need to make sure that patients are aware of the fact that there could be some degree of volume depletion and that they need to make sure they are hydrated.

There are drugs that we need to watch over carefully because they are brand new. Also, there is the concern that women in particular have an increased risk of vaginal fungal infections, and for women who have type 2 diabetes, they may have a fairly significant issue with an additional complication.

With the onset of the long-acting insulin analogs, such as glargine, insulin detemir, and GLP-1 receptor agonists, the use of the insulin mixes seems to have been decreasing. Where do you personally see the insulin mixes fitting in with treating patients with type 2 diabetes, and who are the ideal patients that we should be targeting for mixes?

Dr. Peters: As an endocrinologist, we do not like mixes because we like to be able to adjust doses. But I think that mixed insulins are really helpful in patients. I think that if a provider gets good results on premixed insulin and can teach and monitor it, that patients then get better. If a provider's comfortable with it and they get to target, then I think it is great, especially without hypoglycemia. And there are a lot of studies on premixed insulin that show if titrated appropriately, you can get patients to target.

One of the most effective things about SGLT2 inhibitors is that you can use it in patients in any part of the pathway.

So, I would not throw them out as an insulin, but I have never felt that they should be a first choice. But in a patient where other options for mixing insulin is too complicated and difficult, then I would say they still have a role, but it really depends on the provider who is

using it. If a patient is using it effectively, then they should keep using it.

Please compare the DPP-4 inhibitors with the GLP-1 receptor agonists for both postprandial and A1C glycemic control when added to metformin.

Dr. Peters: The overall A1C reduction is greater with GLP-1 receptor agonists than with DPP-4 inhibitors. DPP-4 inhibitors primarily affect postprandial blood sugar levels, so they do not affect the fasting to a huge extent. And you will see much more of a benefit postprandially.

The GLP-1 receptor agonists will affect both fasting and postprandial values. If you are looking at shorter-acting exenatide you get more of a postprandial effect; if you are looking at longer-acting exenatide once-weekly or liraglutide you will get a nice fasting effect with some reduction in postprandials but relative to the fasting, it is not quite as much of a change as the change in the fasting.

For the patient who is gaining weight on metformin, you can either add in a DPP-4 inhibitor or a GLP-1 receptor agonist.

Discuss the approach to the obese patient that continues to gain weight with type 2 diabetes on metformin. What drugs seem to work best, and are these drugs additive to metformin or synergistic?

Dr. Peters: Everything is additive, because once you are not succeeding with one, you want to add another. But they do act in synergy with the metformin because they are all different mechanisms of action. But the best for weight loss is a GLP-1 receptor agonist, although I would argue that the best for weight loss is also continued work in either a group setting or with an individual dietitian to really have the patients work on their lifestyle, because I think it takes really hard work to lose weight, and you can not just expect a drug to do it for you.

I am one of the Principal Investigators for the Look AHEAD trial and I know how hard it was to get our patients to lose weight, and yet if engaged, we could get them to lose weight. So, I think it is multifactorial. I think adding in a GLP-1 receptor agonist is great if you are looking for weight loss, but again, continued encouragement on lifestyle is also very useful.

In the patient that is taking metformin and insulin, and continuing to gain weight, what agents do you normally use to try and attenuate the weight gain? And where do you see the role of pramlintide? Is there any role currently for the type 2 diabetic or are we all using GLP-1 receptor agonists?

Dr. Peters: For the patient who is gaining weight on metformin, you can either add in a DPP-4 inhibitor or a GLP-1 receptor agonist. Most of the time, I want more. I really want to see some weight loss and I will add in a GLP-1 receptor agonist. But I do not believe that exenatide once-weekly is approved yet for use with insulin and I believe that liraglutide is not approved yet for use with prandial insulin. So, if you want to go by the guidelines, in those patients with prandial insulin you are suppose to add in pramlintide.

Now, off-label, what I do is add in a GLP-1 receptor agonist. But I do think pramlintide has a role, given that some of my patients like it because it reminds them that they are working on their diet, because it is something they have to take before each meal when they think about it, and there is a more conscious quality to it.

And I have also had patients who have either had pancreatitis or been afraid of using a GLP-1 receptor agonist for various reasons when they have gone on pramlintide, and also a couple that just did not tolerate it.

Therefore, I do not use it as a first injectable for satiety, but I will use it in patients where they might fall out of the ability to use a GLP-1 receptor agonist. It still works – it is just more labor intensive than using these once-a-day or once-a-week drugs.

Discuss your approach to initiating insulin therapy in the uncontrolled type 2 diabetic who has not been controlled on oral agents, but is using them to their maximum. How do you approach that patient? Do you use any formulas? How do you begin insulin therapy in your own personal practice?

Dr. Peters: I almost always use glargine if I can. In my lower-income population, I use NPH, and I use it always at bedtime. So, whether it is NPH or glargine, I start it at bedtime, and I always start with 10 units, and I do that because it is simple and I do not have to do math. And if a patient's blood sugar is at 350 and they are symptomatic, I might start with 16 units. But in general I will start with either 10 or 16 units at bedtime.

And then, depending on the patient, I will have them increase the dose by either 1 unit or 2 units every day until their fasting blood sugar is below 150. I do not have a hard-and-fast rule for who I start increasing at 1 unit a day and who I start at 2 units a day. But sometimes, my patients are new on insulin and are slightly nervous, so I have them either text me or e-mail me, or even call every 3 days for the first 2 weeks, and then I will do the

dose adjustings just to make sure that they are feeling comfortable.

So, it really depends on the patients if I start immediately with self-adjustment, or I go through some sort of hand-holding phase. But whatever I do, I will increase the dose until I get their fasting down, or until they reach a dose of about 50 units. And once they are at 50 units, then I am sure they are going to need prandial insulin, and then I will have them do some testing to see where their high is. If they are highest most after lunch or dinner, I will start with prandial insulin on their biggest meal in terms of carbohydrate consumption.

But the only other caveat is that if my other patients on NPH develop hypoglycemia at night and/or they prove to be patients who can not remember to give a shot at night, I will switch them to glargine.

A patient is maxed out on oral agents, including a DPP-4 inhibitor. Would there be any situations where you would prefer to stop the DPP-4 inhibitor and switch to a GLP-1 receptor agonist, or would you just assume that since the patient is not really well-controlled on this regimen, that they really must go on some type of long-acting insulin, or at least some type of insulin therapy? How do you approach that kind of patient?

Dr. Peters: I would prefer to give patients a GLP-1 receptor agonist, and a lot of that concern is about hypoglycemia because I think you may have less hypoglycemia on a GLP-1 receptor agonist. I mostly go to a GLP-1 receptor agonist in an overweight patient. If they are lean, I am not going to do that. But anyone whose BMI is >25 kg/m^2, I will go to a GLP-1 receptor agonist; and then, if that does not work, I will add insulin.

I do not think the order in which you administer the drugs matters so much. I think that you just keep on top of the patient and keep adding the drugs according to the patient and their preferences to reach their target. So, you can start one first or the other and still get to the same target.

Do you find that the duration that a patient has had type 2 diabetes can influence your decision to starting a GLP-1 receptor agonist, particularly if that patient has had type 2 diabetes for over 12 to 15 years? Would the patient be less responsive in your experience?

Dr. Peters: No. And in the clinical trials, duration of diabetes did not seem to predict response.

I think that we do not really know what people's beta cells are doing, so arguably, the patient who has had the disease for a longer period of time will have fewer beta cells to respond. But I think our understanding of beta-cell physiology in type 2 diabetes is rudimentary because we really cannot image beta cells and know what is going on.

Therefore, I would argue that it is about the patient, and I always tell patients that their body is going to tell me if the drug is going to work. And there is always a percent who just do not respond to any given drug except for insulin.

I say to patients, "Let's give this a try and I will see if it works, and let's see how your body responds" rather than trying to predict in advance who will respond ... eventually you may have the ability to measure some blood tests and look for responders, but right now it is really kind of a guess.

What practical guidelines, or perhaps even formulas, can you give to intensify insulin therapy in patients taking oral insulin or oral agents and a GLP-1 receptor agonist, but are still not controlled with insulin therapy added to that? Does the A1C impact your decision? How do you go about titrating your insulin therapy in those patients?

Dr. Peters: I would say that one should start insulin sooner rather than later. So, if I have a 45-year-old patient who has a really long life expectancy, where hypoglycemia is not a huge concern because they do not have complications, I will put them on insulin. I think that it is better to start sooner and not wait until the A1C is 8% or 9%, and I think that happens too often with insulin.

I would argue that we should start insulin in the low 7's, you just start basal insulin and keep them on metformin and GLP-1 receptor agonists and then basal insulin. I would titrate up to basal insulin and make sure I do that appropriately to get their fasting down to around 100 mg/dL. And then I would see how they do.

I think metformin, GLP-1 receptor agonists, and basal insulin are a great combination. And then, if the patient does not do well with that and their blood sugars start to creep up you could add an SGLT2 inhibitor into that mix; or, you can add in meal-time insulin or rapid-acting insulin before the biggest meal. There is an occasional patient who will respond to nateglinide or repaglinide before a big meal just to get that blood sugar down. But when you start getting to the point where they need prandial insulin, it becomes much more complicated for the patient, and that is

I think our understanding of beta-cell physiology in type 2 diabetes is rudimentary because we cannot image beta cells and know what is going on.

where I try to be as creative as I can to work with the patient to get that down; and then, obviously, if they can work on meal composition.

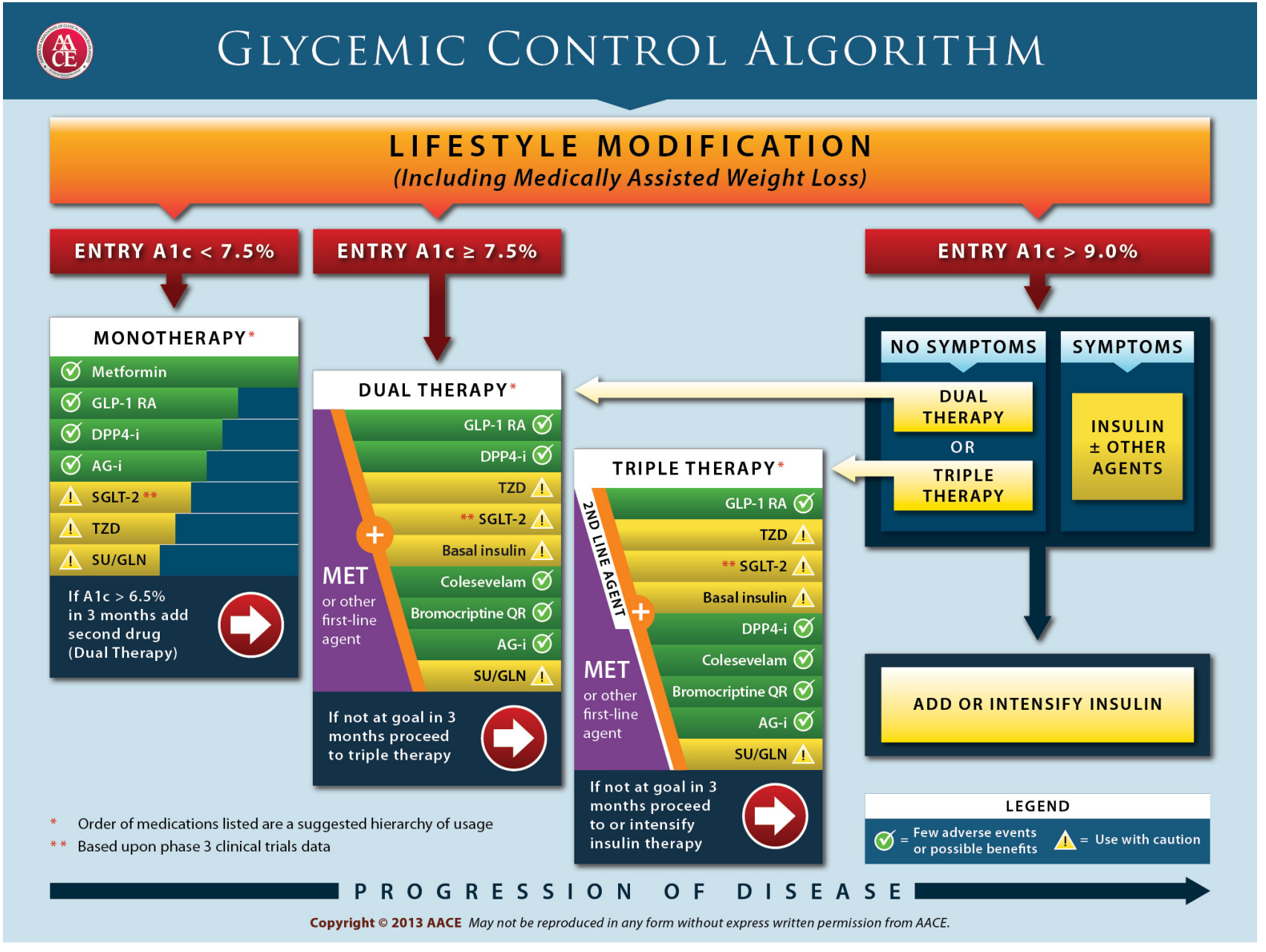
Everybody who I see at 10 am in the morning, always has a blood sugar of 300 mg/dL, because everybody loves to eat cereal. If you talk with the patient about their diet and talk about cereal and the postprandial glycemic response, you can really get people to modify what they eat, and actually will help a lot.

You mentioned the Look AHEAD trial. Were you surprised that there was no significant reduction in cardiovascular risk in those patients?

Dr. Peters: I do not think I was surprised. It took 10 years in the SOS trial from the bariatric surgery, which was not a randomized trial, to show benefit in terms of cardiovascular risk.

Once you have established vascular disease, and most of these patients with diabetes by definition do, even if it is not overt, it is really hard to regress it. But I think that it's not a simple fix, but I think patients with diabetes do better in all sorts of domains through weight loss and exercise. I just think it is not as easy to show in a population.

And, you know, we do analyze Look AHEAD based on if you lost weight and what your outcomes were. We did it by treatment arm. So, it may be that if you actually look at those who did lose weight, perhaps they actually did do better. But that needs to be looked at subsequently. But the primary outcome was not positive; it is still not clear to me what the data, once it is analyzed differently, will show us.



Reprinted with permission from American Association of Clinical Endocrinologists. Garber AJ, et al. AACE Comprehensive Diabetes Management Algorithm. *Endocr. Pract.* 2013;19:327-336.

CME Posttest

CME Instructions

1. Review the activity learning objectives stated on the front cover.
2. Read the articles, including the tables and illustrative materials.
3. Proceed to the CME Registration Form. Type or print your name, address, and date of birth in the spaces provided.
4. Answer each test question by circling the letter corresponding to the correct answer or by entering it in the space provided on the Registration Form. Be sure to retain a copy of your answers for your records.
5. Complete the evaluation portion of the CME Registration Form. CME Registration Forms will be returned to you if the evaluation is not completed.
6. CME Registration Forms will not be accepted after the expiration date. Return the CME Registration Form before the test expires to:

   Vindico Medical Education
   PO Box 36
   Thorofare, NJ 08086-0036
   Or Fax to: 856-384-6680

7. The CME test will also be available online (within 1 month of mailing date) at:

   www.healio.com/endocrinology/education-lab

1. Glucagon-like peptide-1 (GLP-1):
A. has a half life of over 60 minutes in the body.
B. stimulates glucagon release.
C. suppresses glucagon release.
D. is secreted by the pancreatic beta cells.

2. Which of the following oral agent class has NOT been approved for use with GLP-1 receptor agonists?
A. DPP-4 inhibitors
B. Metformin
C. Thiazolidinediones
D. Sulfonylureas

3. When used with a GLP-1 receptor agonist, which of the following oral agents can result in enhanced weight loss?
A. Glimepiride
B. Pioglitazone
C. Metformin
D. Repaglinide

4. Which of the following has NOT been associated with GLP-1 receptor agonist therapy?
A. Peripheral vasodilatation
B. Reduction in post prandial lipemia
C. Peripheral vasoconstriction
D. Improved myocardial contractility

5. Exenatide once weekly:
A. has been FDA approved for use with insulin detemir.
B. causes less nausea than short-acting exenatide twice-daily.
C. has an immediate effect on appetite suppression.
D. causes greater gastrointestinal adverse effects than liraglutide.

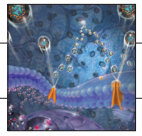
6. SGLT2 inhibitors should not be used in patients:
A. taking sulfonylureas.
B. taking metformin.
C. with eGFR less than 30 mL/min/1.73 m^2.
D. taking insulin.

7. The SAVOR-TIMI trial demonstrated no increase in ischemic cardiac events with what DPP-4 inhibitor?
A. Linagliptin
B. Alogliptin
C. Sitagliptin
D. Saxagliptin

8. A 64-year-old white male is concerned because his A1C has continued to climb over the past year from 7.0% to 8.0%. He complains that he is always hungry. He currently takes glimepiride 4 mg daily, metformin 1,000 BID. What would be the best drug to choose to reduce his A1C and enhance satiety?
A. DPP-4 inhibitor
B. SGLT2 inhibitor
C. Insulin glargine
D. GLP-1 receptor agonist

9. DPP-4 inhibitors are FDA approved for use with all of the following EXCEPT:
A. GLP-1 receptor agonists
B. Long-acting insulin analogs
C. SGLT2 inhibitors
D. Sulfonylureas

10. Which of the following DPP-4 inhibitors does not require dose reductions in patients with renal insufficiency?
A. Alogliptin
B. Linagliptin
C. Sitagliptin
D. Saxagliptin



CME Registration Form

Questions about CME? Call us at 856-994-9400 ext. 504, Fax 856-384-6680

DIALOGUES in DIABETES

Volume 3 • Number 3

POSTTEST

1	2	3	4	5	6	7	8	9	10

***Time spent on this activity: Hours ☐ Minutes ☐**
(reading articles and completing the learning assessment and evaluation)
This information MUST be completed in order for the quiz to be scored.

Release date: November 1, 2013
Expiration date: November 1, 2014

PRINT OR TYPE

Last Name First Name Degree

Mailing Address

City State Zip Code

Date of Birth (used for tracking credits ONLY)

Phone Number FAX Number E-mail

Degree: *Please select one*

❑ MD ❑ PA
❑ PhD ❑ NP
❑ DO ❑ Other_____

Specialty: *Please select one*

❑ Primary Care ❑ Diabetes
❑ Endocrinology ❑ Obesity
❑ Other_____

EVALUATION (must be completed for your CME Quiz to be scored)

Please circle answers neatly and write legibly.

1. The content covered was useful and relevant to my practice. Yes No
2. The activity was presented objectively and was free of commercial bias. Yes No
   [Please use the additional comments field below to provide further information.]
   Additional comments regarding bias: _____
3. Based on the information I learned during this activity, I feel more confident in treating patients within my practice. Yes No
4. Knowledge acquired from this activity will be utilized to improve outcomes in my patients. Yes No
5. Future activities concerning this subject matter are necessary. Yes No

6. I plan to make the following changes to my practice:

Y = Yes N = No 2 = I Already Do This in My Practice 1 = Not Applicable

Examine more closely the differences, efficacy, and safety of treatment options that target incretin pathway.	Y N 2 1
Assess the pathophysiology of incretin pathways in type 2 diabetes mellitus.	Y N 2 1
Examine approaches to managing the obese patient with type 2 diabetes.	Y N 2 1
Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.	Y N 2 1

Other - *Please explain:*

7. These are the barriers I face in my current practice setting that may impact patient outcomes:

Lack of evidence-based guidelines	Yes No
Lack of applicable guidelines for my current practice/patients	Yes No
Lack of time	Yes No
Organizational/institutional	Yes No
Insurance/financial	Yes No
Patient adherence/compliance	Yes No
Treatment-related adverse events	Yes No

Other - *Please explain:*

8. This activity supported achievement of each of the learning objectives. Yes No

Please explain:

9. I see the following number of patients per week with type 2 diabetes mellitus:

A. <10
B. 10 to 25
C. 26 to 50
D. >50

10. Please list CE/CME topics that would be of value to you.

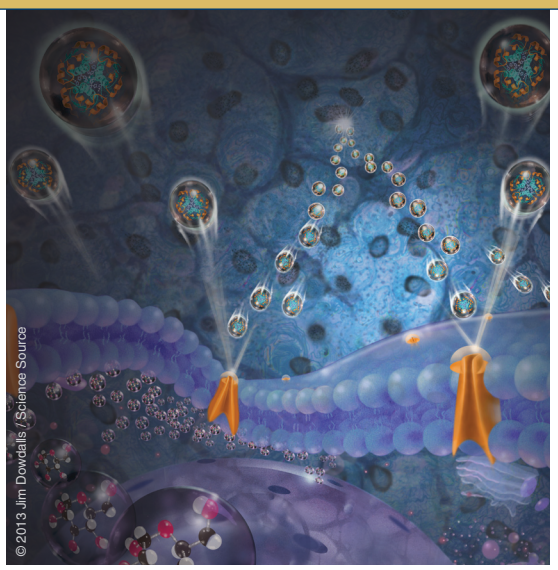
CME ACTIVITY REQUEST

❑ Yes, I would like the opportunity to earn CME credits through activities sponsored by Vindico Medical Education.

***Required Field**

OFFICE USE ONLY
Enduring material: Other
November 2013 ET-J26C

DIALOGUES in DIABETES



VINDICO
medical education

6900 Grove Road, Bldg 100, Thorofare, NJ 08086 USA
phone: 856-994-9400 • fax: 856-384-6680 • VindicoMedEd.com