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# Current antihyperglycemic treatment strategies for patients with type 2 diabetes mellitus

## ■ ABSTRACT

The current epidemics of excessive weight and type 2 diabetes mellitus (T2DM) cause significant morbidity and mortality. T2DM frequently coexists with excess weight as well as hypertension and dyslipidemia, placing a significant percentage of the population at an elevated risk of cardiovascular disease. Maintaining effective glycemic control is linked with a diminished risk of developing microvascular complications, and recent studies have shown it may also reduce overall macrovascular complications. Reduction of associated risk factors, including those related to excessive weight, high blood pressure, and dyslipidemia, are also necessary to meaningfully decrease cardiovascular risk. Agents that can improve glycemia with weight neutrality or weight loss could offer additional benefit to overweight patients with T2DM. Although the major pathophysiologic defects in T2DM are recognized to be beta-cell dysfunction and peripheral insulin resistance, derangements in the incretin system may contribute as well. Antidiabetes agents targeting this system include dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Both classes have been shown to significantly reduce hyperglycemia. GLP-1 receptor agonists also promote significant weight loss and have potentially beneficial effects on cardiovascular risk markers.

## ■ KEY POINTS

Up to 65% of deaths among people with diabetes are caused by cardiovascular disease.

Glycemic control can delay or slow the progression of microvascular complications.

In addition to hyperglycemia, comprehensive diabetes therapy must target cardiovascular disease-related risk factors, including excess weight/obesity, elevated blood pressure, and abnormal lipid concentrations.

Diminished incretin hormonal activity contributes to the pathophysiology of diabetes.

Data from the Centers for Disease Control and Prevention indicate that almost 24 million Americans, or 7.8% of the population, have diabetes; 90% to 95% of these have type 2 diabetes mellitus (T2DM).<sup>1</sup> Diabetes and excessive weight often coexist. An analysis of data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) showed that among individuals with diabetes, 85% were overweight or obese and 55% were obese.<sup>2</sup>

Gaps remain in the management of T2DM between the goals for clinical parameters of care (eg, control of glucose, blood pressure [BP], and lipids) and actual clinical practice.<sup>3</sup> NHANES data reveal that glycemic control improved from a mean glycosylated hemoglobin A1c (HbA1c) of 7.82% in 1999–2000 to 7.18% in 2003–2004.<sup>4</sup> Hazard models based on the United Kingdom Prospective Diabetes Study (UKPDS) 10-year outcomes data in 4,320 newly diagnosed T2DM patients suggest that a sustained decrease in HbA1c of 0.511 percentage points could reduce diabetes complications by 10.7%.<sup>4,5</sup>

Additional analysis of NHANES data showed that in 2003–2004, about 57% of individuals achieved glycemic control, 48% reached BP targets, and 50% achieved target cholesterol goals. Only about 13% of diabetes patients achieved their target goals for all three parameters concurrently.<sup>6</sup>

This article reviews the association between cardiometabolic risk and the current antihyperglycemic treatments for patients with T2DM, with a focus on the role of incretin-related therapies.

## ■ THE IMPORTANCE OF CARDIOMETABOLIC RISK IN T2DM

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among people with diabetes and is the reported cause of mortality in up to 65% of deaths in persons with diabetes in the United States.<sup>7</sup> The risk of CVD is two- to fourfold greater among adults with diabetes than among adults who do not have diabetes.<sup>8</sup> The risk of CVD in patients with T2DM was evident in the UKPDS 17, where macrovascular complications, including CVD, were about twice as common as microvascular complications (20% vs 9%) after 9 years

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of follow-up.<sup>9</sup> A study that involved more than 44,000 patients showed an almost double rate of mortality from all causes among individuals with T2DM compared with those with no diabetes (hazard ratio, 1.93; 95% confidence interval, 1.89 to 1.97).<sup>10</sup> Current guidelines recommend aggressive management of CV risk factors, including BP control, correction of atherogenic dyslipidemia, glycemic control, weight reduction for those who are overweight or obese, and smoking cessation for those who smoke.<sup>3,11</sup> Lifestyle interventions, including weight reduction and appropriately prescribed physical activity, result in reduced CV risk factors, which can help slow the progression of T2DM.<sup>12</sup>

## ■ GOALS OF T2DM THERAPY

Several studies have demonstrated that glycemic control can delay or prevent the development and progression of microvascular complications.<sup>13,14</sup> UKPDS 33 showed that more intensive blood glucose control (median HbA1c 7.0%) in patients with T2DM followed over 10 years significantly ( $P = .029$ ) reduced the risk for any diabetes-related end point by 12% compared with conventional therapy (median HbA1c 7.9%). Most of the risk reduction was accounted for by a 25% risk reduction in microvascular end points ( $P = .0099$ ).<sup>13</sup> Another report (UKPDS 35) demonstrated that HbA1c was strongly related to microvascular effects, with a 1% reduction in HbA1c associated with a 37% reduction in microvascular complications.<sup>14</sup>

### Does intensive glucose control reduce CV risk?

To resolve the ongoing question of whether intensive glucose control can lead to a reduction in CV risk in patients with T2DM, three large, long-term trials were conducted within the last decade.<sup>15–18</sup> Two of these, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trials, each enrolled more than 10,000 previously treated patients with long-standing T2DM. Patients were randomized to standard or intensive glycemic control for 3.5 years in the ACCORD trial and for 5 years in the ADVANCE trial.<sup>15,16</sup>

The ACCORD and ADVANCE trials, along with the smaller Veterans Administration Diabetes Trial (VADT) ( $N = 1,791$ ), failed to show that more intensive glycemic control significantly reduced CVD.<sup>15–17</sup> Additionally, the glycemic control component of ACCORD was halted because of increased mortality in the intensive arm compared with the standard arm.<sup>15</sup> Further analyses of ACCORD data presented at the 69th Scientific Sessions of the American Diabetes Association (ADA) showed that HbA1c values lower than 7.0% did not explain the increased mortality. The 20% higher risk of death for every 1.0% increase in HbA1c greater than

6.0% suggests that glucose concentrations even lower than the general HbA1c goal of less than 7.0% may be appropriate in some patients.<sup>18</sup> The most recent finding from VADT was that CV risk was dependent on disease duration and presence of comorbidities. Intensive therapy seemed to work best in patients with diabetes of less than 15 years' duration, while risk of a CV event was more than doubled with intensive therapy in patients having diabetes for more than 21 years.

### Clarification of treatment goals

A position statement of the ADA and a scientific statement of the American College of Cardiology Foundation and the American Heart Association<sup>19</sup> concluded that the “evidence obtained from ACCORD, ADVANCE, and VADT does not suggest the need for major changes in glycemic control targets but, rather, additional clarification of the language that has consistently stressed individualization.” They state that while the general HbA1c goal of less than 7.0% seems reasonable, even lower HbA1c goals may be appropriate for some patients if they can be achieved without significant hypoglycemia or other adverse effects. Such patients might include those with diabetes of short duration, long life expectancy, or no significant CVD or hypoglycemia. Conversely, higher HbA1c goals may be appropriate for patients with limited life expectancy, a history of severe hypoglycemia, established microvascular or macrovascular complications, significant other comorbid conditions, or longstanding diabetes in whom an HbA1c of less than 7.0% has been difficult to attain despite optimal treatment and diabetes self-management education.<sup>19</sup>

### Long-term risk reduction

A 10-year, postinterventional follow-up study (UKPDS 80) of the UKPDS survivor cohort was reported recently.<sup>20</sup> Results showed that despite an early loss of glycemic differences between patients treated with diet and those treated with intensive regimens (sulfonylurea or insulin; metformin in overweight patients), the pharmacotherapy group demonstrated a prolonged reduction in microvascular risk as well as a significant reduction in the risk for myocardial infarction (15% [ $P = .01$ ] in the sulfonylurea-insulin group and 33% [ $P = .005$ ] in the metformin group) and death from any cause.<sup>20</sup> This suggests that early improvement in glycemic control is associated with long-term benefits in the micro- and macrovascular health of patients with T2DM.

Additionally, the recent long-term follow-up of the Steno-2 study<sup>21</sup> showed that a multifactorial intervention striving for intensive glucose, BP, and lipid control that included the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents not only reduced the risk of nonfatal CVD among patients with T2DM and microalbuminuria, but also had sustained beneficial

effects on vascular complications and on rates of death from any cause and from CV causes. From a health care payer perspective, intensive multifactorial intervention was more likely to be cost-effective than conventional treatment in Denmark, especially if applied in a primary care setting.<sup>22</sup>

## Comprehensive care needed

The lower-than-expected rates of CV outcomes in the ACCORD, ADVANCE, VADT, and Steno-2 studies reinforce the importance of comprehensive diabetes care that treats not only hyperglycemia but also elevated BP and dyslipidemia; these are considered the “ABCs” of diabetes.<sup>11,19</sup> The 2009 ADA standards of medical care guidelines recommend that for most T2DM patients, HbA1c should be maintained at less than 7.0%,<sup>3</sup> while the American Association of Clinical Endocrinologists (AACE) 2007 guidelines state that HbA1c should be 6.5% or less.<sup>11</sup> Both organizations stress the importance of individualized goals, as discussed above, and advocate BP goals of less than 130/80 mm Hg and dyslipidemia goals of low-density lipoprotein cholesterol (LDL-C) less than 100 mg/dL, high-density lipoprotein cholesterol (HDL-C) greater than 40 mg/dL for men and 50 mg/dL for women, and triglycerides less than 150 mg/dL. It is recommended that an optional LDL-C goal of less than 70 mg/dL be considered for individuals with overt CVD.

## CURRENT ANTIHYPERGLYCEMIC TREATMENT STRATEGIES

In response to new insights from clinical research and emerging treatment strategies, disease-specific organizations and medical specialty societies regularly revise and update their treatment guidelines and algorithms. These resources recommend that glycemic progress should be regularly monitored and pharmacologic therapy titrated or new drugs added promptly if glycemic goals are not met after 2 to 3 months.

Several algorithms combine scientific evidence with expert clinical opinion to guide physicians in treating their patients with T2DM. The American College of Endocrinology (ACE)/AACE road maps are designed to help develop individualized treatment regimens to achieve an HbA1c of 6.5% or less.<sup>23</sup> The algorithm from a writing group assembled by the ADA and the European Association for the Study of Diabetes (EASD) similarly promotes pharmacologic treatment together with lifestyle modifications to maintain a glycemic goal of HbA1c less than 7.0%.<sup>24</sup>

## OVERVIEW OF ANTIHYPERGLYCEMIC TREATMENT APPROACHES

Lifestyle measures, medical nutrition therapy, and appropriately prescribed physical activity are recommended for

virtually all patients with T2DM, as well as weight loss for those who are overweight or obese. Unfortunately, many patients cannot achieve glycemic goals with lifestyle measures alone and require the addition of pharmacotherapy.<sup>3</sup> Extensive development of new therapies during the past 15 years has resulted in more than 11 classes of approved antihyperglycemic medications (Table 1) with diverse mechanisms of action and varied effects on HbA1c, body weight, lipids, and other factors.<sup>24–26</sup>

## Initial oral therapy

T2DM is usually treated initially with a single oral agent. Consistent with the progressive nature of the disease, patients often eventually require one or more additional oral agents and in many cases insulin.<sup>13,27</sup> Choice of specific agents is based on individual patient circumstances, including the need for weight loss and control of fasting versus postprandial glucose, the presence of dyslipidemia and hypertension, and the risk for and potential consequences of hypoglycemia.<sup>24</sup> T2DM patients with severely uncontrolled and symptomatic hyperglycemia are best treated, at least initially, with a combination of insulin therapy and lifestyle intervention, often with metformin.

**Metformin.** The recently revised ADA/EASD writing group algorithm recommends that patients not requiring initial insulin begin treatment with metformin at the time of diagnosis unless there are contraindications.<sup>24</sup> Metformin is not associated with hypoglycemia and is considered weight-neutral, although some patients may lose weight.<sup>28</sup>

**Sulfonylureas.** Sulfonylureas stimulate insulin secretion from pancreatic beta cells; their use may be associated with hypoglycemia and weight gain. Mechanisms for weight gain with sulfonylureas include reduction of glucosuria and increased caloric intake to prevent or treat hypoglycemia.<sup>11,28</sup> Nateglinide and repaglinide are nonsulfonylurea oral insulin secretagogues. They result in rapid and relatively short-lived insulin responses and are usually administered three times a day, before each meal. Their use may be associated with weight gain and hypoglycemia.<sup>11</sup>

**Thiazolidinediones.** Thiazolidinediones (TZD) increase insulin sensitivity in muscle, adipose tissue, and the liver. Hypoglycemia is uncommon with TZD monotherapy but weight gain related to increased and redistributed adiposity and fluid retention frequently occurs.

**Alpha-glucosidase inhibitors.** The alpha-glucosidase inhibitors are administered before meals and primarily reduce postprandial hyperglycemia. They are generally weight-neutral.<sup>28</sup>

**Insulin.** Insulin and insulin analogues are the most effective antihyperglycemic agents, but their use can be associated with hypoglycemia and clinically significant weight gain.<sup>28</sup>

**TABLE 1****Currently available antihyperglycemic therapies for T2DM in the United States**

|                                                 | Generic name(s)                                   | Trade name(s)               | Available as generic | Date of FDA approval |
|-------------------------------------------------|---------------------------------------------------|-----------------------------|----------------------|----------------------|
| <b>ORAL TREATMENTS, BY CLASS</b>                |                                                   |                             |                      |                      |
| Sulfonylurea <sup>a</sup>                       | Glipizide                                         | Glucotrol <sup>b</sup>      | Yes                  | May 1984             |
|                                                 | Glyburide                                         | DiaBeta, Glynase, Micronase | Yes                  | May 1984             |
|                                                 | Glimepiride                                       | Amaryl                      | Yes                  | Nov 1995             |
| Biguanide                                       | Metformin hydrochloride                           | Glucophage <sup>c</sup>     | Yes                  | Mar 1995             |
| $\alpha$ -Glucosidase inhibitor                 | Acarbose                                          | Precose                     | No                   | Sep 1995             |
|                                                 | Miglitol                                          | Glyset                      | No                   | Dec 1996             |
| Thiazolidinedione (TZD)                         | Rosiglitazone                                     | Avandia                     | No                   | Jun 1999             |
|                                                 | Pioglitazone                                      | Actos                       | No                   | Jul 1999             |
| Meglitinide (glinide)                           | Repaglinide                                       | Prandin                     | No                   | Dec 1997             |
|                                                 | Nateglinide                                       | Starlix                     | No                   | Dec 2000             |
| DPP-4 inhibitor                                 | Sitagliptin phosphate                             | Januvia                     | No                   | Oct 2006             |
|                                                 | Saxagliptin                                       | Onglyza                     | No                   | Jul 2009             |
| Bile acid sequestrant                           | Colesevelam                                       | Welchol                     | No                   | Jan 2008             |
| Sulfonylurea and biguanide                      | Glyburide and metformin                           | Glucovance                  | Yes                  | Jul 2000             |
| Biguanide and glitazone                         | Rosiglitazone maleate and metformin hydrochloride | Avandamet                   | No                   | Oct 2002             |
| Sulfonylurea and glitazone                      | Rosiglitazone maleate and glimepiride             | Avandaryl                   | No                   | Nov 2005             |
| Biguanide and DPP-4 inhibitor                   | Sitagliptin and metformin hydrochloride           | Janumet                     | No                   | Mar 2007             |
| <b>INJECTABLE TREATMENTS, BY CLASS</b>          |                                                   |                             |                      |                      |
| Regular insulin                                 | Human insulin (regular)                           | Humulin R, Novolin R        | Yes                  | Oct 1982             |
| Intermediate-acting insulin <sup>d</sup>        | Human insulin (NPH insulin)                       | Humulin N, Novolin N        | Yes                  | Oct 1982             |
| Human insulin combinations                      | Insulin regular and NPH insulin                   | Humulin 70/30               | Yes                  | Apr 1989             |
| Rapid-acting insulin analogues                  | Insulin lispro                                    | Humalog                     | No                   | Jun 1996             |
|                                                 | Insulin aspart                                    | Novolog                     | No                   | Jun 2000             |
|                                                 | Insulin glulisine                                 | Apidra                      | No                   | Apr 2004             |
| Long-acting basal insulin analogues             | Insulin glargine                                  | Lantus                      | No                   | Apr 2000             |
|                                                 | Insulin detemir                                   | Levemir                     | No                   | Jun 2005             |
| Combinations (including analogues) <sup>e</sup> | Insulin lispro protamine and insulin lispro       | Humalog Mix 75/25 and 50/50 | No                   | Dec 1999             |
|                                                 | Insulin aspart protamine and insulin aspart       | Novolog Mix 70/30           | No                   | Nov 2001             |
| Amylin analogue                                 | Pramlintide acetate                               | Symlin                      | No                   | Mar 2005             |
| GLP-1 receptor agonist                          | Exenatide                                         | Byetta                      | No                   | Apr 2005             |

<sup>a</sup> Other earlier-generation sulfonylureas (available as generic) include tolbutamide (Orinase), tolazamide (Tolinase), acetohexamide (Dymelor), and chlorpropamide (Diabinese).

<sup>b</sup> Also available in extended-release formulation (Glucotrol XL).

<sup>c</sup> Also available in extended-release formulation (Glucophage XR).

<sup>d</sup> Other intermediate-acting insulins include Lente Humulin, Lente Iletin II, and Lente Novolin.

<sup>e</sup> Premixed insulins include Humulin 70/30 and Novolin 70/30.

DPP-4 = dipeptidyl peptidase-4; FDA = US Food and Drug Administration; GLP-1 = glucagon-like peptide-1; NPH = insulin isophane (Neutral Protamine Hagedorn); T2DM = type 2 diabetes mellitus.

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**Colesevelam.** Colesevelam is a bile acid sequestrant that was recently approved by the US Food and Drug Administration as an antihyperglycemic therapy in people with T2DM. At a dosage of 1.875 g BID or 3.75 g QD in combination with a sulfonylurea, metformin, or insulin therapy, reductions in HbA1c compared with placebo in clinical trials of colesevelam have ranged from  $-0.5\%$  to  $-0.7\%$  ( $P < .02$ ). Frequency of hypoglycemia and weight gain is low with this agent.<sup>26</sup>

**Weight management.** Weight reduction is important for overweight or obese patients with T2DM.<sup>27,28</sup> Even moderate weight loss (5% of body weight) can be associated with improved insulin action and reduced hyperglycemia.<sup>29</sup> Conversely, weight gain has been shown to worsen hyperglycemia and other CV risk factors. Treatment-related weight gain can also lead to decreased regimen adherence, contributing to poor glycemic control.<sup>28</sup>

## THE ROLE OF INCRETIN HORMONES AND INCRETIN-BASED THERAPIES IN T2DM PATIENTS

Over the last few years, the role of incretin hormones and their contribution to diabetes pathophysiology has become more apparent. The incretin effect refers to the observation that orally administered glucose elicits a greater insulin response than does glucose administered intravenously to produce equivalent blood glucose concentrations.<sup>30,31</sup> The incretin effect is diminished in patients with T2DM.

### Hormone mediation of the incretin effect

The two hormones that mediate the incretin effect are GIP (also known as gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide) and glucagon-like peptide-1 (GLP-1).<sup>30,31</sup> GLP-1 has several glucoregulatory actions, including enhancement of endogenous insulin release and suppression of inappropriate glucagon secretion, both in a glucose-dependent manner. Therefore, these effects of GLP-1 occur only when glucose concentrations are elevated, thereby minimizing the risk of hypoglycemia. GLP-1 also regulates gastric emptying; infusions of GLP-1 can slow the accelerated emptying that is often present in T2DM patients. GLP-1 also increases satiety and decreases food intake via a central mechanism.<sup>31</sup>

Because GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), therapeutic use of GLP-1 would require continuous infusion, which is impractical.<sup>30,31</sup> Two strategies have been used to produce incretin-related therapies. One, inhibition of the DPP-4 enzyme, results in a two- to threefold enhancement of endogenous GLP-1. The other, involving agents that resist breakdown by DPP-4 but bind to and activate the GLP-1 receptor, produces glucoregulatory effects similar to those of GLP-1.<sup>30</sup>

Following subcutaneous (SC) injection, GLP-1 receptor agonists enhance insulin secretion and suppress inappropriately elevated glucagon, both in a glucose-dependent manner, as well as slow gastric emptying and enhance satiety.<sup>30</sup> DPP-4 inhibitors provide glucose-dependent enhanced insulin secretion and glucagon suppression, but they do not have the same effects on gastric emptying or satiety.

Clinically, the GLP-1 receptor agonists improve glycemia and are associated with weight loss.<sup>32-35</sup> Adverse gastrointestinal symptoms are relatively common during the first few weeks of treatment. DPP-4 inhibitors improve glycemia but are weight-neutral and are not generally associated with significant gastrointestinal symptoms.<sup>32,36-38</sup>

### Incretin-based therapies

Incretin-based therapies are currently part of the antihyperglycemic armamentarium.<sup>25,32</sup> The AACE guidelines<sup>11</sup> and the ACE/AACE roadmaps<sup>23</sup> include the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor sitagliptin among antihyperglycemic therapies for patients with T2DM. The most recent update of the consensus algorithm statement of a joint ADA/EASD writing group included GLP-1 receptor agonists (but not DPP-4 inhibitors) in tier 2 of preferred agents, especially for patients who have concerns related to weight and hypoglycemia.<sup>24</sup> They noted that DPP-4 inhibitors may be appropriate choices in selected patients.

**DPP-4 inhibitors: sitagliptin, saxagliptin.** Until recently, sitagliptin was the only DPP-4 inhibitor available in the United States. Sitagliptin is approved by the FDA for treatment of T2DM at a recommended oral dosage of 100 mg QD, either as monotherapy or in combination with other oral antihyperglycemic medications. The dosage of sitagliptin should be reduced to 50 mg/day in patients with creatinine clearance (CrCl) levels that are between 30 mL/min and 50 mL/min and to 25 mg/day in those with CrCl less than 30 mL/min.<sup>39</sup>

In a meta-analysis of incretin-based therapies, DPP-4 inhibitors produced a reduction in HbA1c compared with placebo (weighted mean difference of  $-0.74\%$ ; 95% confidence interval,  $-0.85\%$  to  $-0.62\%$ ).<sup>32</sup> DPP-4 inhibitor antihyperglycemic efficacy has been shown to be similar whether used as a monotherapy or add-on therapy.<sup>32,37,38</sup> This same meta-analysis showed DPP-4 inhibitors as having a neutral effect on weight.<sup>32</sup> More recently, a single-pill combination of metformin and sitagliptin was approved.<sup>40</sup>

A study comparing metformin, sitagliptin, and the combination of the two as initial monotherapy in T2DM patients with a baseline HbA1c of 8.8% showed 24-week HbA1c reductions from baseline of  $-0.66\%$  with sitagliptin 100 mg QD,  $-0.82\%$  with metformin 500 mg BID, and  $-1.90\%$  with sitagliptin 50 mg + met-

formin 1,000 mg BID.<sup>41</sup>

On July 31, 2009, the FDA approved another DPP-4 inhibitor, saxagliptin, for the treatment of T2DM either as monotherapy or in combination with metformin, a sulfonylurea, or a TZD.<sup>42</sup>

**GLP-1 receptor agonist: exenatide.** Exenatide, the only FDA-approved GLP-1 receptor agonist, is the synthetic version of exendin-4, which binds to the human GLP-1 receptor and in vitro possesses many of the glucoregulatory effects of endogenous GLP-1.<sup>30,32</sup> Exenatide is indicated as monotherapy or adjunctive therapy for patients with T2DM who have not achieved adequate glycemic control with metformin, a sulfonylurea, a TZD, or metformin in combination with a sulfonylurea or a TZD.<sup>43</sup> Exenatide is administered by SC injection BID at a starting dosage of 5 µg BID for 4 weeks, followed by an increase to 10 µg BID.

Exenatide has been shown not only to enhance glucose-dependent insulin secretion but also to restore impaired first-phase insulin response in subjects with T2DM. Exenatide also helps control postprandial glycemic excursions by suppressing inappropriate glucagon secretion, slowing accelerated gastric emptying, and enhancing satiety. The increased satiety results in decreased food intake and weight loss.<sup>31,44</sup> In a recent head-to-head crossover study, exenatide was shown to be more effective than sitagliptin in lowering postprandial glucose concentrations, increasing insulin secretion, and reducing postprandial glucagon secretion.<sup>45</sup> Exenatide also slowed gastric emptying and reduced caloric intake.

Exenatide, in most studies, resulted in a placebo-subtracted HbA1c reduction of approximately −1.0% and in one study lowered HbA1c from baseline by −1.5%. Completer analyses have shown HbA1c reductions of −1.0% up to 3 years and −0.8% up to 3.5 years. Exenatide has also been associated with a mean weight loss of as much as −3.6 kg at 30 weeks and as much as −5.3 kg at 3.5 years.<sup>33–35,46,47</sup> A 1-year study showed that exenatide improved beta-cell secretory function compared with insulin glargine in metformin-treated patients with T2DM.<sup>48</sup> Long-term data, including findings from completed and intention-to-treat analyses of 82 weeks<sup>49</sup> to at least 3 years<sup>47</sup> have demonstrated that exenatide improved CV risk factors, including those related to BP, lipids, and hepatic injury biomarkers.

### Therapies in development

Incretin-based therapies in development include a novel once-weekly formulation of exenatide; taspoglutide, another once-weekly GLP-1 receptor agonist; and liraglutide, a GLP-1 receptor agonist that is administered once daily.<sup>50</sup> Liraglutide is currently being evaluated in clinical trials as a once-daily SC injection.<sup>51–53</sup> Liraglutide has been reported to reduce HbA1c by −1.1%

at 26 weeks and up to −1.14% at 52 weeks and result in weight loss (up to −2.8 kg at 26 weeks and up to −2.5 kg at 52 weeks) in patients with T2DM who are treatment-naïve or taking other antidiabetes agents, including metformin, sulfonylurea, and TZD.<sup>51–53</sup> Evaluation of the once-weekly formulation of exenatide showed reductions in HbA1c of −1.9% at 30 weeks and −2.0% at 52 weeks with a weight loss of −3.7 kg at 30 weeks and −4.1 kg over 52 weeks of treatment.<sup>46,54</sup>

### CONCLUSION

In the United States, the epidemics of excessive weight and T2DM have contributed to an increased medical risk for many individuals. Comprehensive diabetes treatments targeting not only hyperglycemia but also frequently associated overweight/obesity, hypertension, and dyslipidemia will be required to reduce such risk. Current treatment strategies have evolved based on updated clinical guidelines and trials, as well as practice experience, including those related to newer agents. Incretin-based therapies, such as the GLP-1 receptor agonist, exenatide, and the DPP-4 inhibitors, sitagliptin and saxagliptin, are important additions to the treatment armamentarium, offering a reduction in hyperglycemia and beneficial effects on weight (reduction with exenatide and neutral with sitagliptin), and have been shown to improve several CV risk factors.

### DISCLOSURES

Dr. Blonde reported that he has received research and grant support from Amylin Pharmaceuticals, Inc., Boehringer Ingelheim GmbH, Eli Lilly and Company, F. Hoffmann-LaRoche Ltd., MannKind Corporation, Merck & Co., Inc., Novartis, Novo Nordisk, Pfizer Inc., and Sanofi-Aventis; and honoraria for speaking/consulting from Abbott Laboratories, Amylin Pharmaceuticals, Inc., AstraZeneca, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Daiichi Sankyo Co., Ltd., Eli Lilly and Company, GlaxoSmithKline, Halozyme Therapeutics, LifeScan, Inc., MannKind Corporation, Merck & Co., Inc., Novartis, Novo Nordisk, Pfizer Inc., and Sanofi-Aventis. Dr. Blonde also reported that his spouse is a stock shareholder of Amylin Pharmaceuticals, Inc., and Pfizer Inc. in an account that is not part of their community property. Dr. Blonde reported that he did not receive an honorarium for writing this article.

Dr. Blonde reported that he wrote this article and received no assistance with content development from unnamed contributors. He reported that BlueSpark Healthcare Communications, a medical communications company, assisted with reference verification, proofing for grammar and style, table and figure rendering based on author instructions, copyright permission requests, and identification of topical overlap with other articles in this supplement.

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