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Differentiating among incretin-based therapies in the management of patients with type 2 diabetes mellitus

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Abstract

The glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have become important options for the management of patients with type 2 diabetes mellitus. While the GLP-1R agonists and DPP-4 inhibitors act on the incretin system to regulate glucose homeostasis, there are important clinical differences among the five agents currently available in the U.S. For example, the GLP-1R agonists require subcutaneous administration, produce pharmacological levels of GLP-1 activity, promote weight loss, have a more robust glucose-lowering effect, and have a higher incidence of adverse gastrointestinal effects. In contrast, the DPP-4 inhibitors are taken orally, increase the half-life of endogenous GLP-1, are weight neutral, and are more commonly associated with nasopharyngitis. Differences in efficacy, safety, tolerability, and cost among the incretin-based therapies are important to consider in the primary care management of patients with type 2 diabetes mellitus.

Keywords: type 2 diabetes, exenatide, liraglutide, sitagliptin, saxagliptin, linagliptin, efficacy, safety

Introduction

Treating patients with type 2 diabetes mellitus (T2DM) can be very challenging. Fortunately, new treatment options for T2DM, such as incretin-based agents, provide new opportunities to bring the disease under control, and perhaps slow its progression. More recently, focus has been placed on 'treating to target' glucose approaches rather than waiting for progressive glucose failure. The goal of the treat-to-target approach is to achieve safe glucose targets for each individual with a combination of early lifestyle and pharmacologic therapies. As such, it is important to work with each patient to develop and initiate a lifestyle and pharmacologic treatment plan at the time of diagnosis of T2DM to achieve the glycemic target–generally an A1C < 7.0% [1], within 3 to 6 months. The second and very important part of the treat-to-target approach is to modify treatment as needed to maintain the A1C at the target level [2]. Modifying treatment is, however, often challenging because of hypoglycemia, weight gain, intolerable adverse events, even access to and affordability of newer agents, as well as clinical inertia. These and other glycemic and non-glycemic factors

were considered by the American Diabetes Association/ European Society for the Study of Diabetes (ADA/EASD) [2] and by the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ ACE) [3] when developing their 2009 guideline recommendations. Both groups concluded that, based upon their unique physiologic activity, efficacy, nonglycemic benefits, and safety profiles, agents which act on the incretin system–the glucagon-like peptide-1 (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors– are important options for the management of patients with T2DM. An agent in each class has now been FDA-approved since 2005 and 2006. (Table 1)

The AACE/ACE guidelines, for example, state that the GLP-1R agonists and DPP-4 inhibitors are options as monotherapy for patients with an A1C of 6.5% to 7.5%, as well as in combination with other glucose-lowering agents for patients with an A1C > 7.5% (Figure 1). In this latter situation, the GLP-1R agonists are given a higher priority than the DPP-4 inhibitors because of the greater effect of the GLP-1R agonists in reducing postprandial glucose excursions and their potential for inducing substantial weight loss. The ADA/EASD recommendations take a different approach recommending the GLP-1R

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Table 1 Comparison of GLP-1R agonists and DPP-4 inhibitors.

	GLP-1R Agonists	DPP-4 Inhibitors
Agents currently available in U.S. with dosing information (normal renal function)[31-35]	• Exenatide 5-10 mcg SC BID • Liraglutide 1.2-1.8 mg QD	• Sitagliptin 100 mg PO QD • Saxagliptin 2.5-5 mg PO QD • Linagliptin 5 mg PO QD
Benefits		
Reduction in A1C level*[22-24,26,29,36-45]	0.5%-1.5%	0.5%-0.9%
Reduction in fasting plasma glucose*[29,39-41,49-51]	↓7 to 74 mg/dL	↓11 to 29 mg/dL
Reduction in postprandial glucose*[9,27,51,54,55]	↓41 to 47 mg/dL	↓49 to 68 mg/dL
Weight effect [14,22,24,26,29,37,39-41,44,45,49,50,52,60]	↓1-4 kg	↓0.9 to ↑1.4 kg
Effect on triglycerides [24,29,36,37,39,41,49,60,62]	↓12-40 mg/dL	↑16 mg/dL to ↓35 mg/dL
Reduction in systolic blood pressure [13,14,24,29,36,37,39,41,49,60,62]	↓1-7 mm Hg	0 to ↓3.9 mm Hg
May improve markers of pancreatic β-cell function (such as homeostasis model assessment-β-cell function, fasting insulin, fasting proinsulin to insulin ratio, fasting C-peptide)[8,13,22-24,26,30]	✓	✓
Disadvantages		
Incidence of mild/moderate hypoglycemia**[9,10,24,26,36-39,41,43-45,52,55,64]	0%-12%	0%-4%
Nausea [13,33-35]	26%-28%	0-1%
Hypersensitivity reactions [33-35]	Rare (exenatide)	✓
Antibody formation [31-35,79,80]	30-67% E; 8% L	NR

*As monotherapy or as add-on therapy.

**Generally included asymptomatic hypoglycemia or symptomatic hypoglycemia with blood glucose < 55 mg/dL not requiring third-party assistance.

BID, twice daily; NR, not reported; PO, orally; QD, once daily; SC, subcutaneously

agonists (and thiazolidinediones) as less-validated alternatives to insulin or sulfonylurea as add-on therapy to lifestyle management and metformin (Figure 2). The DPP-4 inhibitors are appropriate for selected but unspecified patients according to the ADA/EASD recommendations, which were published in early 2009.
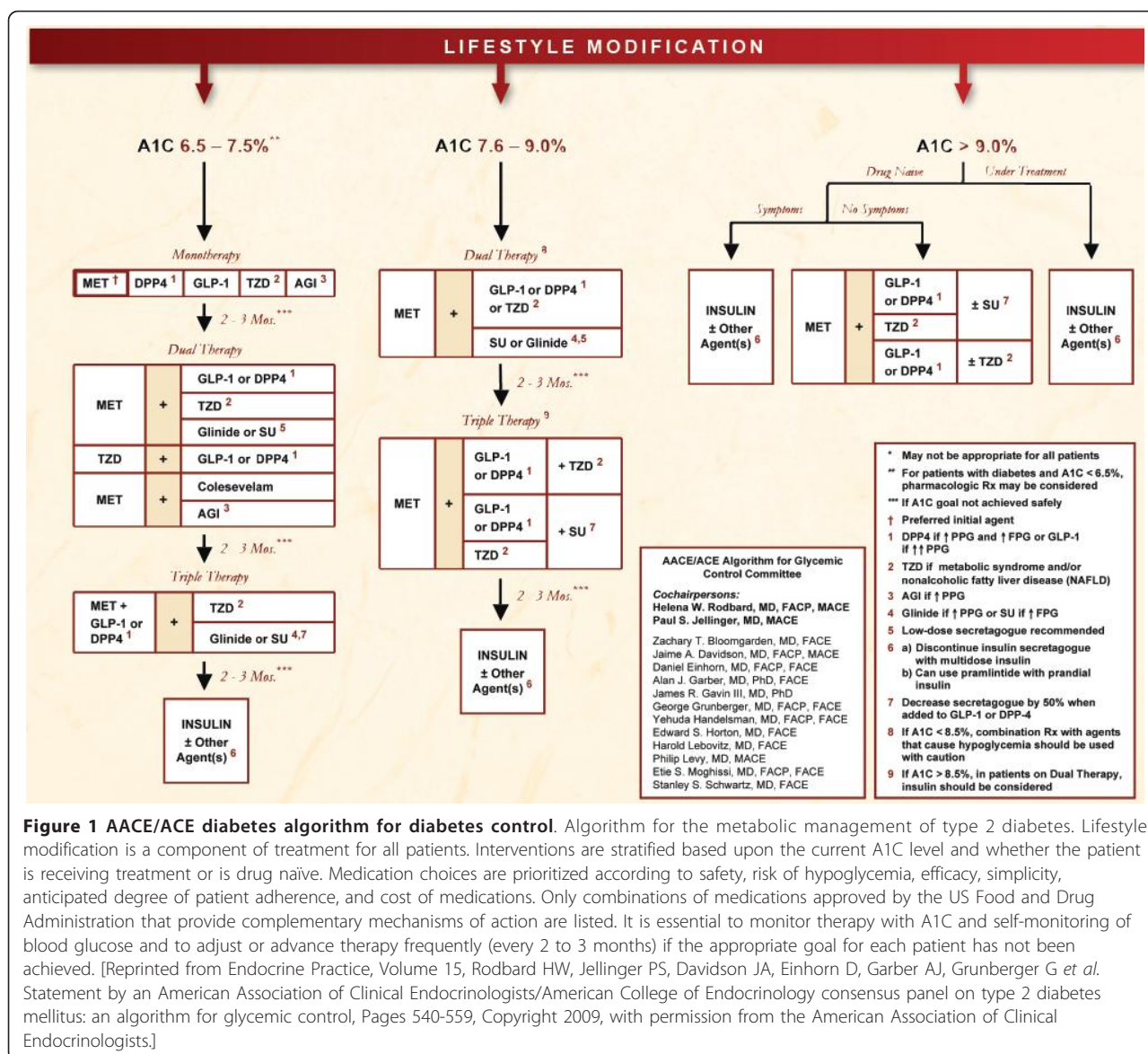
Physiologic Actions
The multifactorial nature of the pathophysiology ofT2DM presents several options for treatment, some of which are not addressed by standard glucose-lowering therapies. Standard glucose-lowering therapies generally improve insulin sensitivity, stimulate insulin secretion, and/or decrease hepatic glucose production. The incretin system exerts somewhat unique actions upon glucose homeostasis. In fact, the incretin system may be responsible for up to 70% of insulin secretion in response to oral glucose or a meal in healthy individuals [4].

Of the two principal incretin hormones, GLP-1 plays a more important role in T2DM since the insulinotropic action of glucose-dependent insulinotropic polypeptide (GIP) is essentially lost in persons with T2DM, while the insulinotropic activity of GLP-1 following administration of pharmacological doses of GLP-1 is preserved [5].

Extensive preclinical investigations with GLP-1 and subsequent clinical investigations with the GLP-1R agonists and DPP-4 inhibitors in humans, including patients with T2DM, have been undertaken to determine the actions of each of these agents in regulating glucose. As expected from studies investigating the actions resulting from administration of GLP-1, stimulation of the GLP-1 receptor directly with a GLP-1R agonist or indirectly with a DPP-4 inhibitor (by inhibiting enzymatic degradation of endogenous GLP-1) serves to increase insulin secretion in a glucose-dependent manner through direct activation of pancreatic islet β-cells [6-10] and to inhibit glucagon secretion in a glucose-dependent manner (ie., only during hyperglycemia) through direct activation of pancreatic islet α-cells [6,8,9,11-14]. Furthermore, administration of GLP-1 or a GLP-1R agonist (but not a DPP-4 inhibitor) has been shown to slow gastric emptying [8,15] and to promote satiety [8,16,17], which leads to weight loss, although neither of these effects is required for the glucose-lowering benefits of the GLP-1R agonists. This difference is thought to be due to the 60 pmol/L pharmacologic level of GLP-1 activity achieved with administration of a GLP-1R agonist [18], which is associated with nausea, compared to the 10 pmol/L physiologic level of endogenous GLP-1 activity achieved from administration of a DPP-4 inhibitor [19].

In addition, exposure to GLP-1 in cell culture [20] or administration of GLP-1 in rodents [21] has been found
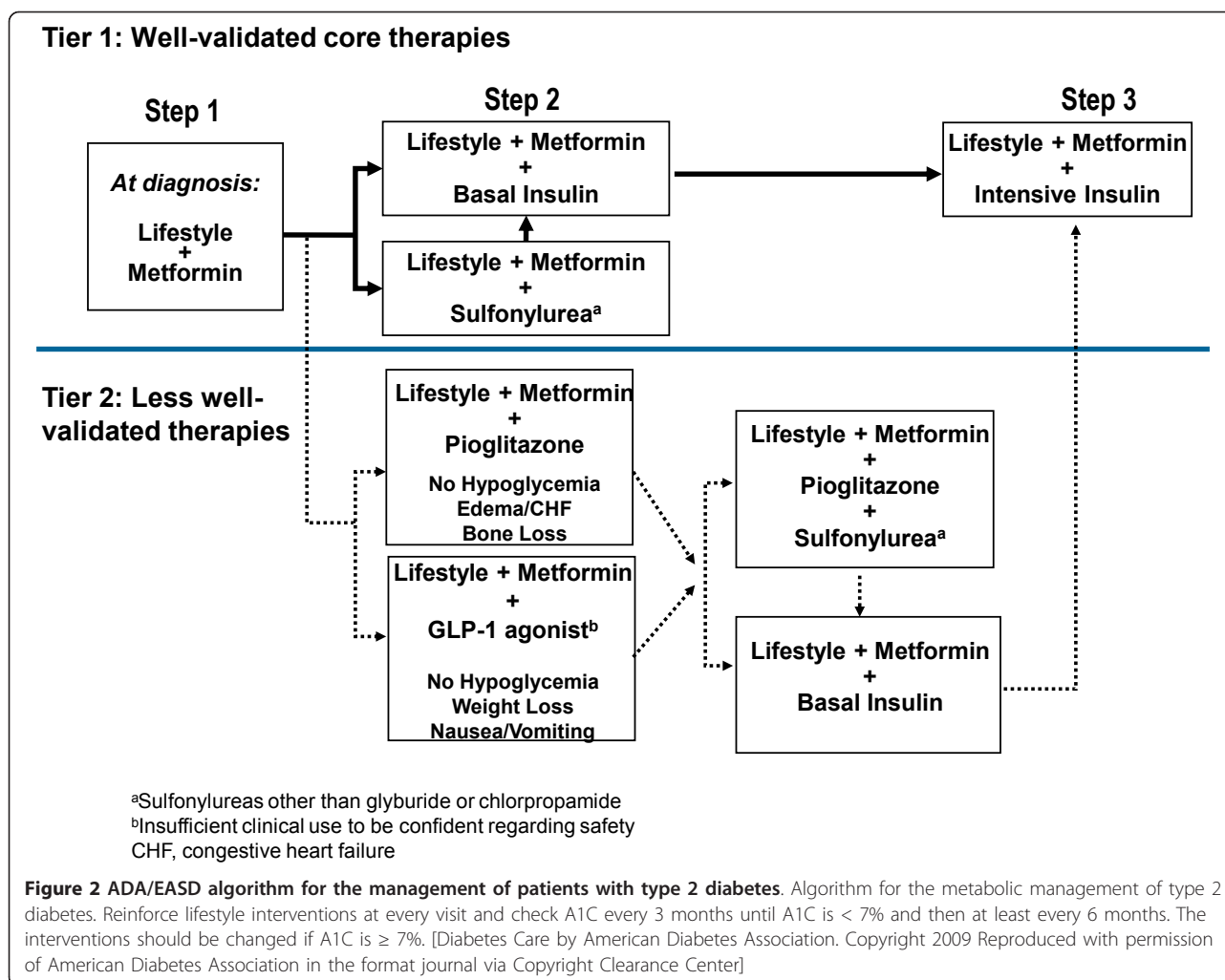
Figure 1 AACE/ACE diabetes algorithm for diabetes control. Algorithm for the metabolic management of type 2 diabetes. Lifestyle modification is a component of treatment for all patients. Interventions are stratified based upon the current A1C level and whether the patient is receiving treatment or is drug naïve. Medication choices are prioritized according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost of medications. Only combinations of medications approved by the US Food and Drug Administration that provide complementary mechanisms of action are listed. It is essential to monitor therapy with A1C and self-monitoring of blood glucose and to adjust or advance therapy frequently (every 2 to 3 months) if the appropriate goal for each patient has not been achieved. [Reprinted from Endocrine Practice, Volume 15, Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control, Pages 540-559, Copyright 2009, with permission from the American Association of Clinical Endocrinologists.]

to promote proliferation, increase differentiation, and prolong survival of pancreatic β-cells. These observations have prompted an assessment of the possible beneficial effects of the GLP-1R agonists and DPP-4 inhibitors on β-cell function in humans. While some trials have demonstrated improvement of surrogate markers of β-cell function, others have not [8,10,13,22-30]. Further investigation is ongoing.

GLP-1 is secreted by the L-cells of the small intestine in response to food ingestion, but undergoes rapid enzymatic degradation by DPP-4. As a consequence, injectable GLP-1R agonists were developed that resist degradation by DPP-4. Exenatide (for twice-daily administration) and liraglutide are the GLP-1R agonists that are currently available in the U.S. In addition, oral

inhibitors of DPP-4 have been developed that prolong the action of endogenous GLP-1. Sitagliptin, saxagliptin, and linagliptin are the three DPP-4 inhibitors currently available in the U.S. The recommended maintenance doses in the current prescribing information are: exenatide 10 μg twice daily [31]; liraglutide 1.2 or 1.8 mg once daily [32]; sitagliptin 100 mg once daily [33]; saxagliptin 2.5 or 5 mg once daily [34]; and linagliptin 5 mg once daily [35].

Findings from Clinical Trials

Incretin-based therapies have been investigated in numerous clinical trials involving patients with T2DM. These trials have typically involved patients with somewhat different characteristics at baseline. Results of trials

Tier 1: Well-validated core therapies

Step 1	Step 2	Step 3
At diagnosis: **Lifestyle + Metformin**	**Lifestyle + Metformin + Basal Insulin**	**Lifestyle + Metformin + Intensive Insulin**
	Lifestyle + Metformin + Sulfonylurea[a]	

Tier 2: Less well-validated therapies

Lifestyle + Metformin + Pioglitazone

No Hypoglycemia
Edema/CHF
Bone Loss

Lifestyle + Metformin + GLP-1 agonist[b]

No Hypoglycemia
Weight Loss
Nausea/Vomiting

Lifestyle + Metformin + Pioglitazone + Sulfonylurea[a]

Lifestyle + Metformin + Basal Insulin

[a]Sulfonylureas other than glyburide or chlorpropamide
[b]Insufficient clinical use to be confident regarding safety
CHF, congestive heart failure

Figure 2 ADA/EASD algorithm for the management of patients with type 2 diabetes. Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is < 7% and then at least every 6 months. The interventions should be changed if A1C is ≥ 7%. [Diabetes Care by American Diabetes Association. Copyright 2009 Reproduced with permission of American Diabetes Association in the format journal via Copyright Clearance Center]

that have compared an incretin-based agent with one or more non-incretin agents are described below to provide a general understanding of the glycemic and non-glycemic effects of the incretin-based agents. To gain a greater understanding of differences among incretin-based therapies, results of head-to-head trials comparing two incretin-based agents are also provided.

Glycemic Effects
A1C
As a consequence of their physiologic actions to regulate glucose homeostasis, the GLP-1R agonists and DPP-4 inhibitors are effective in lowering blood glucose levels, with a more robust effect with the GLP-1R agonists (Table 1). When administered as monotherapy or in combination with metformin or other glucose-lowering therapy, the GLP-1R agonists reduce the A1C level by 0.5% to 1.5% [29,36-41] and the DPP-4 inhibitors by 0.5% to 0.9% [22-24,26,42-45]. Also, patients previously treated with diet and exercise alone have been observed

to achieve a greater A1C reduction with liraglutide than those previously treated with glucose-lowering monotherapy (-1.6% vs -0.7%, respectively) [37]. Patients with a baseline A1C level ≥9.0% appear to experience a greater reduction in A1C with sitagliptin than patients with a baseline A1C level < 8.0% (-1.5% vs -0.6%, respectively) [22]. Similar results have been observed with exenatide [40], liraglutide (baseline A1C ≥10%) [13] and linagliptin [45].

Prospective head-to-head comparative trials have demonstrated differences among the incretin therapies with respect to their efficacy in reducing the A1C level as add-on therapy. In these trials, patients were those who had inadequate glycemic control with metformin-based therapy. In one trial after 26 weeks, exenatide 10 μg twice daily reduced the A1C by 0.8% compared to 1.1% with liraglutide 1.8 mg once daily ($P < 0.0001$) [13]. Another 26-week trial showed that liraglutide 1.2 or 1.8 mg once daily reduced the A1C by 1.2% and 1.5%, respectively, compared to 0.9% for sitagliptin 100 mg once daily ($P < 0.0001$ vs

both liraglutide doses) [30]. After 52 weeks, the A1C reductions from baseline were 1.3% and 1.5% for liraglutide 1.2 and 1.8 mg, respectively, and 0.9% for sitagliptin ($P < 0.0001$ vs both liraglutide doses) [46]. A third trial involved initiation and stabilization of insulin glargine as add-on therapy. After 4 weeks, exenatide (5 μg twice daily for 2 weeks, then 10 μg twice daily for 2 weeks) lowered the A1C 1.8% compared to 1.5% for sitagliptin 100 mg once daily [47]. A fourth trial showed that after 18 weeks, sitagliptin 100 mg once daily lowered the A1C 0.6% compared to 0.5% for saxagliptin 5 mg once daily [48].

Fasting plasma glucose

Fasting plasma glucose (FPG) levels are also reduced when GLP-1R agonists or DPP-4 inhibitors are administered as add-on therapy to other glucose-lowering agents (Table 1). Specifically, reductions in FPG are observed with the addition of a GLP-1R agonist ranging from 7 to 74 mg/dL [29,39-41,49]. The head-to-head comparison of exenatide with liraglutide showed that liraglutide caused a significantly greater reduction of the FPG than exenatide (29 mg/dL vs 11 mg/dL, respectively; $P < 0.0001$), while exenatide caused a significantly greater reduction of the postprandial glucose (PPG) after breakfast ($P < 0.0001$) and dinner ($P = 0.0005$) but not lunch [13].

As add-on therapy, the FPG is reduced 11 to 29 mg/dL with the addition of a DPP-4 inhibitor to existing glucose-lowering therapy [48,50,51], with a greater reduction with sitagliptin compared to saxagliptin (16 mg/dL vs 11 mg/dL, respectively) [48]. The head-to-head comparison of liraglutide with sitagliptin showed that liraglutide reduced the FPG 31 to 37 mg/dL compared to 11 mg/dL for sitagliptin at 1 year ($P \leq 0.0001$) [46].

Postprandial glucose

Reduction in the A1C level observed with the GLP-1R agonists and DPP-4 inhibitors appears to result primarily from the generally greater reduction of the postprandial glucose (PPG) level compared to the FPG level (Table 1) [23,26,37,45,52]. A GLP-1R agonist appears preferred if the PPG level is significantly elevated, while a DPP-4 inhibitor may be preferred if there is modest elevation of both FPG and PPG [53].

Patients on stable doses of metformin and a sulfonylurea who were treated with exenatide 10 μg twice daily experienced significantly greater reduction in PPG excursions following breakfast and dinner than patients treated with insulin glargine once daily (P < 0.001) [54]. When once-daily liraglutide 1.2 mg or 1.8 mg was administered for 26 weeks as add-on therapy with metformin, the PPG level was reduced by 41 mg/dL and by 47 mg/dL, respectively, compared with a reduction of 45 mg/dL for glimepiride 4 mg once daily [55].

Treatment with sitagliptin 100 mg once daily for 18 weeks, when added to metformin, reduced the PPG by

68 mg/dL, compared with a reduction of 14 mg/dL for placebo [27]. Similarly, when saxagliptin is added to metformin therapy at doses of 2.5 mg once daily or 5 mg once daily, versus placebo, the PPG is reduced by 62 mg/dL, 58 mg/dL, and 18 mg/dL, respectively [9]. Linagliptin 5 mg once daily has been shown to reduce the PPG 49 mg/dL over 24 weeks compared to an increase of 18 mg/dL with placebo [51].

Effects on pancreatic β-cell function

Several clinical trials have examined the effects of the GLP-1R agonists and DPP-4 inhibitors on pancreatic β-cell function in persons with T2DM (Table 1). Since direct measurement of pancreatic β-cell function in humans is not possible, studies have measured a variety of surrogate markers. Improvement in some but not all markers has been observed in most studies involving the GLP-1R agonists [13,28,30,36,55,56] or DPP-4 inhibitors [9,50,57,58].

Nonglycemic Effects

The effects of the GLP-1R agonists and DPP-4 inhibitors on nonglycemic parameters also serve to differentiate these agents from other glucose-lowering agents.

Body weight

Among the most important nonglycemic differences is the observation that patients treated with a GLP-1R agonist experienced a mean weight loss of 1 kg to 4 kg in clinical trials (Table 1) [29,37,39-41,49,52]. For example, after 3 years of exenatide treatment, 84% of patients lost weight, with 50% losing at least 5% of baseline body weight [59]. The amount of weight lost increased with higher body mass index [59]. The DPP-4 inhibitors are considered to be weight neutral; however, some patients experience a slight increase in weight, others a slight decrease [14,22,24,26,44,45,50,60]. The difference in weight effect between the GLP-1R agonists and DPP-4 inhibitors probably results from the ability of the GLP-1R agonists to reduce caloric intake by promoting satiety, and possibly by delaying gastric emptying [17,61]. The DPP-4 inhibitors do not appear to promote satiety or delay gastric emptying.

Lipids and blood pressure

While the GLP-1R agonists and DPP-4 inhibitors should not be used as primary therapy for cardiovascular disease, improvements in the lipid profile and reductions in blood pressure may offer additional benefits in an at-risk population with T2DM (Table 1). The mechanism for the lipid-lowering effect of the incretins is unknown, but may be related to their glucose-lowering effects as observed with other glucose-lowering agents or effects on free fatty acid metabolism. The greatest improvement in the lipid profile is observed in the triglyceride level, which is reduced by 12 to 40 mg/dL with the GLP-1R agonists [29,36,37,39,41,49,62], while the change with the DPP-4

inhibitors has ranged from an increase of 16 mg/dL to a decrease of 35 mg/dL [24,60]. Small changes in the LDL-cholesterol and HDL-cholesterol levels have been observed with both the GLP-1R agonists and the DPP-4 inhibitors.

The GLP-1R agonists also have been shown to lower systolic blood pressure 1 to 7 mm Hg; changes in diastolic blood pressure have been similar to placebo [13,29,36,37,39,41,49,62]. The mechanism for blood pressure reduction with the GLP-1R agonists is unclear. While an association with weight loss cannot be ruled out, one investigation involving liraglutide found that the reduction in systolic blood pressure occurred before substantial weight loss [29]. The effects on blood pressure with the DPP-4 inhibitors are limited [24,51,60].

Safety and Tolerability

The good safety and tolerability of the GLP-1R agonists and DPP-4 inhibitors are well documented leading the AACE/ACE guidelines to conclude that the GLP-1R agonists are safer than sulfonylureas or glinides with respect to the risk of hypoglycemia [3]. While the guidelines also note the risk of gastrointestinal side effects (which are usually transitory) with the GLP-1R agonists and excellent tolerability of the DPP-4 inhibitors, some adverse events encountered in clinical practice bear discussion.

Hypoglycemia

A low incidence of hypoglycemia is observed with the GLP-1R agonists and DPP-4 inhibitors, likely because of their glucose-dependent actions on insulin and glucagon secretion (Table 1). For this reason, the ADA/EASD consensus statement recommends a GLP-1R agonist when hypoglycemia is a major concern, such as for those who have hazardous jobs and weight loss is beneficial [2]. Furthermore, the US Federal Aviation Administration includes the GLP-1R agonists and DPP-4 inhibitors in the list of allowable medications for aviators [63]. Severe hypoglycemia (generally defined as symptomatic–such as confusion, blurred vision, sweating–and requiring third-party assistance) has not been observed in trials of exenatide [36,52], liraglutide [37,38], sitagliptin [24,44], saxagliptin [26], or linagliptin [45] as monotherapy. Mild to moderate hypoglycemia (generally defined as asymptomatic or symptomatic with a blood glucose < 55 mg/dL but not requiring third-party assistance) occurs in 4% to 9% of patients receiving monotherapy treatment with exenatide [36,52], 0% to 12% with liraglutide [37,38], 0% to 4% with sitagliptin [22-24], 0-6% with saxagliptin [26], and 0% with linagliptin [45]. A slightly higher incidence of mild to moderate hypoglycemia is observed when incretin-based therapy is combined with 1 or more glucose-lowering agents [9,10,39,41,43,55,64]. However, when combined with a sulfonylurea, mild to moderate

hypoglycemia has been reported by up to 36% of patients treated with the combination of a GLP-1R agonist or a DPP-4 inhibitor [14,65], which necessitates reducing the dose of the sulfonylurea, usually by half.

Nausea and Vomiting

Early experience with the GLP-1R agonists showed that transient nausea was common. This led to a dose titration strategy when initiating therapy, which reduced the incidence of transient nausea to 28% with exenatide and to 26% with liraglutide in a head-to-head comparison; vomiting occurred in 10% and 6%, respectively (Table 1) [13]. Exenatide should be initiated at a dose of 5 μg twice daily and taken within 60 minutes before the morning and evening meals; the dose can be increased to 10 μg twice daily after 1 month based on clinical response [31]. Liraglutide should be initiated independent of meals at a dose of 0.6 mg once daily for 1 week and then increased to 1.2 mg once daily. If the 1.2 mg dose does not result in acceptable glycemic control, the dose of liraglutide can be increased to 1.8 mg once daily to achieve glycemic control [32]. The incidence of nausea with the DPP-4 inhibitors is similar to placebo [22,23,26].

Acute pancreatitis

The possibility of acute pancreatitis, which was first raised by postmarketing reports with exenatide, led to changes in monitoring for its occurrence in subsequent clinical trials with incretin-based agents. These investigations show that acute pancreatitis has been observed rarely in patients treated with exenatide [31], liraglutide [32], and sitagliptin [33], and linagliptin [35]. For example, separate pooled analyses show that the number of cases of pancreatitis per 1000 patient-years was 2.2 for liraglutide (vs 0.6 for comparators) [32], 1.2 for sitagliptin (vs 1.0 for comparators) [33], and 1.7 for linagliptin (vs 0 for placebo) [35]. Similar pooled data for exenatide and saxagliptin are not available. However, establishing exenatide, liraglutide, sitagliptin, or linagliptin as the cause has not been possible because patients with T2DM regardless of treatment have a nearly 3-fold greater risk of pancreatitis compared with those without diabetes [66]. In addition, retrospective analysis of a health insurance database involving nearly 88,000 patients with 1-year follow-up demonstrated a similar risk of pancreatitis with exenatide, sitagliptin, metformin, and glyburide [67]. It is, nonetheless, important to educate patients about risk factors for pancreatitis, eg, gallstones, alcoholism, high triglycerides, and the immediate steps they should take if signs and symptoms suggestive of pancreatitis occur. At present, in patients with a history of pancreatitis, exenatide, liraglutide, and sitagliptin should not be prescribed [31-33], The FDA has required the manufacturers of exenatide, liraglutide, sitagliptin, saxagliptin, and linagliptin to conduct further epidemiologic studies of pancreatitis to clarify this issue [68-72].

Hypersensitivity reactions

Hypersensitivity reactions have been observed with each of the three DPP-4 inhibitors (Table 1). For sitagliptin, the most serious hypersensitivity reaction is Stevens-Johnson syndrome, which requires immediate treatment discontinuation if signs and symptoms of hypersensitivity occur [33]. Urticaria and facial edema occur in 1% to 2% of patients treated with saxagliptin [34], while urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity can occur with linagliptin [35]. Further investigation of hypersensitivity reactions is ongoing with saxagliptin [72] and linagliptin [73], as mandated by the FDA.

Renal failure

Ischemic renal failure has been reported in four patients within two to nine months of starting exenatide [74]. All four patients presented with nausea, vomiting, or decreased fluid intake. In one patient, the renal failure was characterized by ischemic glomeruli with moderate to severe interstitial fibrosis, tubular atrophy, and early diabetic nephropathy. Recovery, which was incomplete in three of the patients upon cessation or dose reduction, was hypothesized to be due to volume contraction. Since exenatide, as well as sitagliptin and saxagliptin, are predominantly eliminated via the kidneys, the dose of these three agents must be reduced when the creatinine clearance is less than 50 mL/minute; exenatide is contraindicated if the creatinine clearance is less than 30 mL/minute [31,33,34]. Liraglutide and linagliptin do not require dosage adjustment in renal dysfunction [32,35].

Long-term Outcomes

The GLP-1R agonists and DPP-4 inhibitors have only become available in recent years, the first being exenatide in April 2005; thus, the long-term efficacy and safety of these 5 agents have not yet been established. Of the numerous ongoing investigations, several have been required by the FDA to clarify the long-term safety of these agents. One investigation relates to exenatide and a possible association between this agent and the development of thyroid cancer, based on postmarketing reports [69]. A second study is a preclinical investigation with liraglutide to determine the lifetime risk of developing thyroid C-cell tumors [70]. During review of the new drug application for liraglutide, the US FDA determined that there is a low risk of thyroid cancer in humans based on changes in rodents at levels of liraglutide many times those anticipated in humans [68]. Other investigation suggests that C-cell hyperplasia in rats and mice may be mediated by a GLP-1 receptor-mediated mechanism [75]. GLP-1 receptor expression in thyroid C-cells in humans and monkeys is low such that exposure to liraglutide at more than 60 times human exposure levels for 20 months did not result in C-cell hyperplasia in monkeys. Further, the level of calcitonin,

a biomarker for medullary thyroid cancer, remained at the lower end of the normal range in humans exposed to liraglutide for 2 years. The FDA has required that an epidemiologic study of thyroid cancer be carried out with exenatide [69], as well as animal studies and monitoring a 15-year cancer registry with liraglutide [70]. In addition, a boxed warning concerning the current findings of medullary thyroid cancer in animals has been included in the prescribing information for liraglutide [32]. An association with sitagliptin [33] or saxagliptin [34] and thyroid cancer has not been identified.

Clinical trials investigating the cardiovascular effects of liraglutide [70], saxagliptin [72], and linagliptin [73] are also required (and are ongoing), since the clinical evaluations of these drugs were completed prior to December 2008 when the FDA adopted new standards regarding cardiovascular safety for all new antidiabetic drugs. These standards were in response to data suggesting a serious risk of cardiovascular events with some medications developed for the treatment of T2DM. Based on available data, the potential for adverse cardiovascular events with liraglutide, saxagliptin, and linagliptin cannot yet be definitively excluded.

These ongoing safety evaluations will better define the long-term safety of the GLP-1R agonists and DPP-4 inhibitors and identify safety issues, if any, earlier than previous and current postmarketing surveillance.

Cost

In addition to efficacy and safety, cost is an important issue in selecting treatment and should be discussed with the patient. The purchase price for therapy with a GLP-1R agonist or DPP-4 inhibitor at a pharmacy is greater than for most other glucose-lowering agents. However, cost can vary substantially depending on formulary status and pharmacy. Also, patient insurance will affect the out-of-pocket cost to the patient since major costs are usually covered by insurance with a copay from the patient that is often dependent on formulary status. While the cost of a medication to the patient is a critical consideration in selecting therapy, the impact of a treatment on other direct and indirect costs also must be considered. Limited data have shown that the annual total cost of medical care ($19,293 vs $23,782, respectively; $P < 0.0001$) and total cost of diabetes-related medical care ($7,833 vs $8,536, respectively; $P < .0001$) with exenatide were significantly lower than with insulin glargine [76], including a lower cost related to the treatment of hypoglycemia [77]. Similarly, preliminary evidence indicates that liraglutide may reduce the total cost of diabetes-related care compared to glimepiride [78]. The analysis included costs due to ocular events and neuropathy leading to amputation. Although these data are preliminary, they are consistent with the clinical

profile of the GLP-1R agonists and DPP-4 inhibitors, as discussed above.

Conclusion

Following diagnosis of T2DM, glycemic control should be achieved within 3 to 6 months and maintained using a treat-to-target approach. Furthermore, treatment failure must not be accepted and must always be addressed quickly. Use of the GLP-1R agonists and DPP-4 inhibitors enables the primary care clinician to approach the management of patients with T2DM in a way that complements other therapies through the actions of these agents on the incretin pathway. This is especially important given that the incretin system is thought to be responsible for up to 70% of insulin secretion in response to oral glucose or a meal. Use of the GLP-1R agonists and DPP-4 inhibitors also enable the clinician to minimize the risk of some of the complications commonly encountered when treating patients with T2DM, such as hypoglycemia and weight gain. For these reasons, the GLP-1R agonists and DPP-4 inhibitors play an important role in the treatment of patients with T2DM, as reflected in recent consensus guidelines. But there are important differences among the incretin-based agents. The GLP-1R agonists require subcutaneous administration, produce pharmacological levels of GLP-1 activity, promote weight loss, have a more robust glucose-lowering effect, and have a higher incidence of adverse gastrointestinal effects. In contrast, DPP-4 inhibitors are taken orally, increase the half-life of endogenous GLP-1, are weight neutral, and are more commonly associated with nasopharyngitis. Although current evidence indicates these agents are safe and generally well-tolerated, the results of ongoing intensive safety evaluations will alert health care practitioners at the earliest possible time to important safety issues, should they occur.

Authors' contributions

MC conceived of the article focus and scope, reviewed and revised the outline, reviewed, revised, and approved the final manuscript, and solely made the decision to submit the manuscript.

Competing interests

• Advisory board: Astra Zeneca, Bristol Myers Squibb, Genentech/Roche
•Speaker bureau: Abbott, Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Forest, Kowa

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