Osteopathic Family Physician (2013) 5, 43–50

ELSEVIER

acofp Osteopathic Family Physician

Evidence from randomized clinical trials demonstrating improved glycemic control with GLP-1 receptor agonists when used with other agents vs other combination therapy strategies

Jeffrey S. Freeman, DO, FACOI

From Philadelphia College of Osteopathic Medicine, Philadelphia, PA.

KEYWORDS:
Type 2 diabetes;
Glycemic control;
GLP-1 receptor agonists;
Incretin;
Hypoglycemia;
T2DM

Incretin-based therapies include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) based therapies. Both classes of agents are predicated on the knowledge that GLP-1, a gut-derived hormone, plays a major role in glucose homeostasis, a fact that has been known for several decades; however, until recently GLP-1 has not been able to be harnessed into a pharmacologically viable target with which to treat type 2 diabetes. GLP-1 receptor agonists (GLP-1 RA) provide supraphysiologic levels of GLP-1, resulting in increased levels of insulin and decreased glucagon secretion, without attendant hypoglycemia risk or risk of weight gain. They are more potent than DPP-4 inhibitors, may result in weight loss, have different adverse effect profiles, and may have other different pharmacological nonglycemic effects than DPP-4 inhibitors. They can be successfully used as part of combination therapy strategies, which is important because type 2 diabetes has multiple pathophysiological defects that need to be addressed to successfully maintain or achieve glucose goals.

Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease state with an intricate pathophysiology, characterized by multiple metabolic defects.[1] The standard therapeutic approach has consisted primarily of insulin, insulin secretagogues (sulfonylureas), insulin sensitizers (metformin and thiazolidinediones [TZDs]), alpha glucosidase inhibitors, and glinides.[2] These agents may improve glycemic control, but with unwanted side effects, particularly hypoglycemia, weight gain, and peripheral edema. Additionally, these agents may not have a positive effect on beta-cell mass or function, both of which are adversely affected over time, making diabetes a progressive disease state.[3]

Incretin hormones, glucose homeostasis, and the development of incretin-based therapies

The major incretin-based therapies include both (dipeptidyl peptidase-4) DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.[4] Incretins are gut-based hormones that have a number of physiologic actions that affect glucose homeostasis. These hormones were first identified many decades ago, when it was noted that the insulin response to intravenously administered glucose differed substantially from orally administered glucose, a phenomenon dubbed the "incretin effect".[5] The incretin effect, thus, is the amplification of insulin secretion exerted by insulinotropic gut hormones. At about the same time, it was observed that individuals with T2DM had a reduced or

Corresponding author: Jeffrey S. Freeman, DO, Philadelphia College of Osteopathic Medicine, 4190 City Avenue, Suite 324, Philadelphia, PA 19131-1626.
E-mail address: JeffreyFreemanDO@aol.com.

1877-573X/$ - see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.osfp.2012.11.001

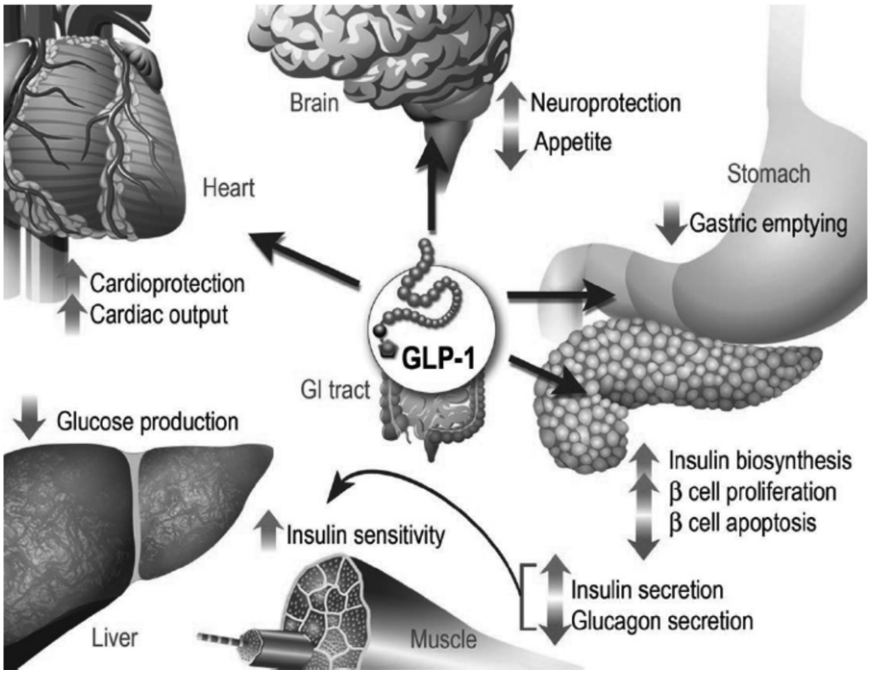


Figure 1

impaired incretin effect.[6] Whether this is a primary or secondary result of diabetes pathophysiology has not been fully elucidated.[7] These gut or incretin hormones that increase insulin levels include both GLP-1 and gastric inhibitory polypeptide, also known as the glucose-dependent insulinotropic peptide. GLP-1, but not gastric inhibitory polypeptide, controls glycemia via additional actions on glucose sensors, inhibition of gastric emptying, food intake, and glucagon secretion.[8] The pleiotropic actions of GLP-1 are summarized in Figure 1.[8] The multiple antidiabetic actions of GLP-1 are summarized in Table 1[9]; note that some of these actions have only been documented in animal systems. The 2 major pancreatic effects of GLP-1 are to increase insulin secretion and reduce glucagon secretion, but only in the presence of high blood glucose levels. Therefore, incretin-based therapies have no intrinsic risk for hypoglycemia.

GLP-1 is rapidly degraded by the enzyme DPP-4. DPP-4 inhibitors were developed that reduce the breakdown of native GLP-1, although the concentration or effect of ambient GLP-1 levels in patients with diabetes may limit the ability of DPP-4 inhibitors to restore the full incretin effect. GLP-1 RAs were also developed that directly raise GLP-1 levels[10,11]; however, GLP-1 RAs need to be given by subcutaneous injection because the hormone is rapidly degraded when administered by the oral route.

Similarities and differences between DPP-4 inhibitors and GLP-1 RAs

These agents, while differing in several ways, share characteristics of glucose-dependent glucose lowering (ie, a low risk of hypoglycemia) without attendant weight gain. Table 2 summarizes some of the differences between DPP-4

Table 1 The multiple antidiabetic actions of GLP-1; some of these actions have only been documented in animal systems

Characteristics of diabetes	Action of GLP-1
Impaired β-cell function	Insulin secretion (glucose-dependent) and biosynthesis Impaired β-cell function (ie, glucose sensitivity, proinsulin:insulin ratio, HOMA-β) Up-regulates genes that are essential for β-cell function (eg, GLUT2 and glucokinase)
Reduced β-cell mass	Increases β-cell proliferation and differentiation* Decreases β-cell apoptosis* Increases β-cell mass*
Glucagon hypersecretion	Decreases glucagon secretion (glucose-dependent)
Overeating, obesity	Decreases gastric emptying, increases satiety, decreases appetite, which leads to decreases in food intake and body weight
Macrovascular complications	Beneficial effects on cardiovascular risk factors
Insulin resistance	Increases insulin sensitivity†

GLUT2 = glucose transporter; HOMA-β = homeostasis model assessment indicating improved beta-cell function.[9]

*Shown in in vitro and preclinical animal models.

†Likely to be secondary to overall improvements in metabolic control.

inhibitors and GLP-1 RAs.[8,12] Their glucose-lowering potency, actual effects on weight, adverse effects, and route of administration are quite different. The reasons for the differences in pharmacologic effects (both positive and negative [ie, gastrointestinal side effects]) hark back to the fact that GLP-1 RAs provide supraphysiologic levels of GLP that are many-fold greater than can be achieved with DPP-4 inhibitors.

A feature they share is targeting several pathophysiological defects in T2DM, making both classes of agents good candidates for use with more traditional agents. Figure 2 provides information on approved and some of the agents in development in the GLP-1 RA and DPP-4 inhibitor class. For a current review on DPP-4 inhibitors, readers are referred to the article by Scheen in *Expert Opinion on Pharmacotherapy*.[13] There is no rationale for the use of DPP-4 inhibitors in combination with GLP-1 RAs, and this is not an approved use for these agents.[14]

The first GLP-1 RA, exenatide, was approved in 2005 and by 2006 was included in the American Diabetes Association and the European Association for the Study of Diabetes treatment algorithm,[2] initially as a second-tier option to agents with which healthcare professionals had more clinical experience. But by 2009, GLP-1 RAs (and DPP-4 inhibitors) were possible therapeutic options included across a background of therapy and in a variety of hemoglobin A1C ranges.[15] Two other GLP-1 RAs are now available, liraglutide (approved in 2010) and a longer-acting version of exenatide, exenatide long-acting release (approved in 2012). They feature prominently in the balancing act of achieving glycemic control with as few adverse side effects as possible.[16,17] Today, both DPP-4 inhibitors and GLP-1 RAs are fully integrated into diabetes treatment algorithms.[7,18]

There are differences among GLP-1 RAs. Exenatide is similar to human GLP-1 with a 53% sequence identity; liraglutide is 97% homologous to human GLP-1. Because of this difference in homology, exenatide is considered an agonist of GLP-1 receptors, while liraglutide is considered a GLP-1 analog that acts on GLP-1 receptors. Because both exenatide and liraglutide act on GLP-1 receptors, we will refer to both agents as GLP-1 RAs.

Table 2 Clinical differences between GLP-1 RAs and DPP-4 inhibitors

Effects/Parameters	GLP-1 RAs	DPP-4 inhibitors
Route of administration	Subcutaneous injection	Oral
Dosing/timing of administration	Twice daily before meals Once daily without regard to meals Once weekly without regard to meals	Once daily
Fasting hyperglycemia*	Reduced	Little effect
Postprandial hyperglycemia*	Reduced	Reduced
Body weight	Reduced	Neutral
Appetite	Suppressed	Neutral
Gastric emptying	Slowed significantly	No effect
Hypoglycemia	Low rates	Low rates
GI adverse effects (AEs)	Nausea, diarrhea	No significant GI AEs
CVD risk factors	Improved	No consistent changes

CVD = cardiovascular disease; FPG = fasting plasma glucose; PPG = postprandial glucose; RAs = receptor agonists.

*DPP-4 inhibitors and short-acting GLP-1 RAs primarily target PPG levels; longer-acting GLP-1 RAs affect both FPG and PPG and thus tend to reduce A1C levels to a greater extent.

Clinical efficacy data for GLP-1 receptor agonists

The clinical trial programs for these agents have been extensive, with studies evaluating use as monotherapy, in combination with other agents including DPP-4 inhibitors, and even direct head-to-head comparisons of GLP-1 RAs. Additionally, the clinical trials include substitute design and switchover design comparing GLP-1 RAs with each other. Overall, a greater proportion of patients with T2DM can achieve the American Diabetes Association recommended A1C goal of $<7\%$ with GLP-1 RAs compared with placebo or other antidiabetic drugs.[19]

Use with metformin

Metformin remains the standard initial therapy for patients with T2DM.[7] A frequent use of incretin-based therapy is as add-on to metformin therapy in subjects with T2DM who have insufficient glycemic control with metformin alone. A recent meta-analysis of >20 studies summarizes the data with either a GLP-1 RA or DPP-4 inhibitor compared with metformin. The reduction in A1C was significantly greater ($P < .001$) in study groups with long-acting GLP-1 RAs (ie, liraglutide once daily, and extended-release exenatide given once weekly) than with exenatide twice a day (bis in die [BID]) and DPP-4 inhibitors, for which there was no statistical difference. Fasting plasma glucose levels also fell significantly more in patients receiving liraglutide or exenatide extended-release than in those given exenatide twice daily or DPP-4 inhibitors given once daily (both $P < .001$). Short-acting exenatide generally has a more profound effect on postprandial glucose levels than on fasting levels. Weight loss was observed in patients receiving any of the GLP-1 RAs, and no substantial

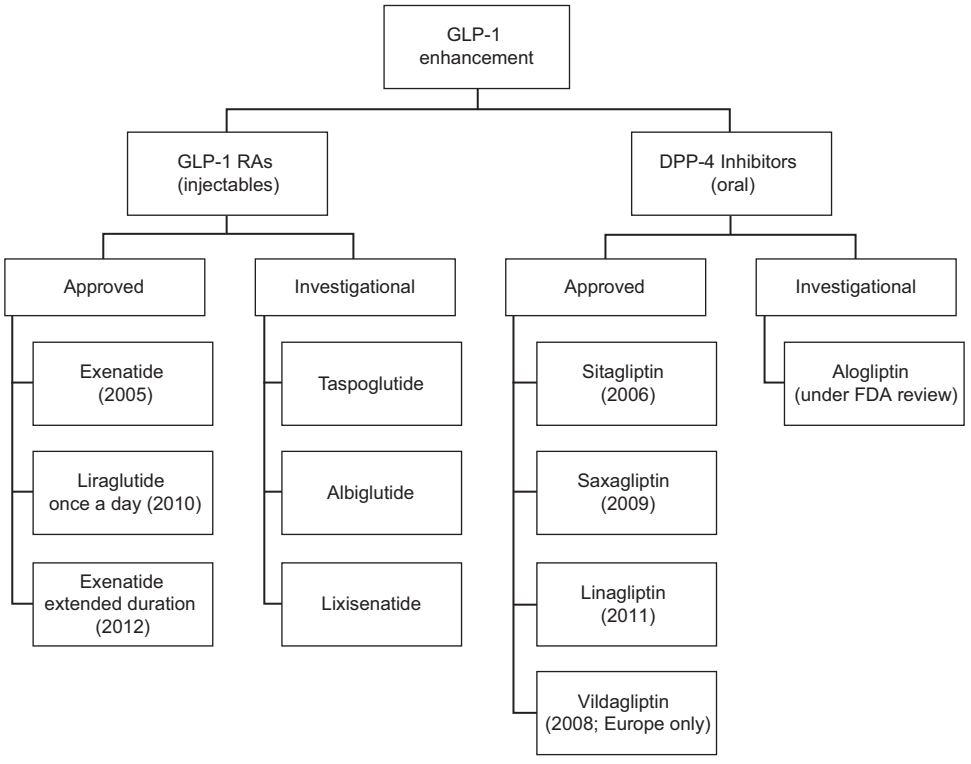


Figure 2 Expanding array of agents to enhance actions of GLP-1 for patients with diabetes.

weight gain was observed in patients receiving DPP-4 inhibitors.[20]

One of the intriguing properties of both exenatide and liraglutide is that many patients lose weight when they are treated with these drugs by reason of their glucose-lowering actions and not necessarily with a side effect of nausea.[21] Given that most patients with T2DM are overweight or obese, and that other drugs used to lower blood glucose may cause weight gain (eg, sulfonylureas, TZDs, and insulin), this is an important clinical feature.

Use with combination oral antidiabetic therapy

GLP-1 RAs have also been evaluated as add-on therapy for patients not achieving glycemic control with 2 oral agents (eg, metformin + sulfonylureas, or metformin + TZDs).[22-24] Early reductions in A1C were observed. Hypoglycemia rates were low, except when used with a sulfonylurea. Therefore, the dose of sulfonylurea may need to be lowered. Sulfonylureas tend to cause weight gain, and the benefit of weight loss typically associated with GLP-1 RAs is attenuated or lost when used in combination with sulfonylureas.

Use compared with insulin

Physicians may choose to add either insulin or GLP-1 receptor agonists to their patients' regimen for those who have poor glycemic control despite therapy with multiple oral agents. While we have traditionally thought of insulin as the most potent agent to lower glucose levels, the doses that are required may result in hypoglycemia. Given that GLP-1 receptor agonists work in a glucose-dependent manner, they are associated with a low risk of hypoglycemia. It is quite interesting to review studies comparing these agents against insulin therapy. The use of exenatide twice daily and liraglutide once daily achieved similar improvements in glycemic lowering compared with once-daily basal insulin in individuals who were suboptimally controlled with oral combination therapy.[24-26] The other significant advantage with use of the GLP-1 receptor agonists was the association of weight reduction rather than weight gain, and less hypoglycemia than with insulin therapy, although there was a higher incidence of gastrointestinal adverse effects reported with GLP-1 RA therapy. These findings support the use of GLP-1 RAs as a treatment alternative in potential insulin-naive subjects with T2DM, who are overweight and suboptimally controlled by combination oral antidiabetic therapy.

Use in combination with insulin

In addition, there are interesting data on the use of exenatide BID with basal insulin analogs. Such studies have found that glucose control can be improved, with a low risk of hypoglycemia, possible weight loss, and with lower or reduced doses of insulin.[27,28] This approach makes sense, given that short-acting exenatide primarily targets postprandial glucose levels and basal insulin as analogs target fasting plasma glucose levels. Recently, the use of the exenatide BID with insulin glargine and liraglutide with basal insulin was approved for combination therapy.

Comparisons with DPP-4 inhibitors

We have alluded to the pharmacological differences between GLP-1 receptor agonists and DPP-4 inhibitors (both considered "incretin-based" therapies). However, in clinical practice, the differences are often confused, and patients may believe that the agents are quite similar. They may consider DPP-4 inhibitors as an oral GLP-1 receptor agonist vs a once-daily injectable (liraglutide), twice-daily injectable (exenatide), or once-weekly injectable (exenatide extended-release) product. It is therefore helpful for clinicians to clarify these unique properties between classes of products.

The goal for many clinicians who manage diabetes is to achieve optimum glucose control with weight loss and a minimum number of hypoglycemic episodes. The addition of GLP-1 receptor agonist therapy to metformin achieved this goal more often than did addition of maximum daily doses of a DPP-4 inhibitor.[29-32] What patients should understand is that GLP-1 receptor agonists are able to lower blood glucose levels more effectively with the added benefit of weight loss than DPP-4 inhibitors, and that one class is not simply the oral or injectable version of the other. In fact, treatment satisfaction studies have shown that an injectable GLP-1 receptor agonist may lead to greater treatment satisfaction than oral DPP-4 inhibitor therapy, potentially by facilitating greater improvement in glycemic control, weight loss, and perception of greater treatment efficacy.[33,34]

Comparisons among available GLP-1 RAs

As noted above, there are currently 3 approved GLP-1 receptor agonists: 2 forms of exenatide and 1 of liraglutide.

Exenatide can be injected twice daily before meals (exenatide BID) or once weekly (exenatide extended duration); the latter encompasses dissolvable poly-(D,L-lactide-co-glycolide) microspheres.[35] The primary difference between these 2 formulations is the plasma concentration over time. With the long-acting formulation there is a continuous delivery. Two clinical trials have examined the similarities and differences in the safety and efficacy of these formulations. The use of exenatide extended-release formulation vs twice daily resulted in greater reductions in A1C, fasting plasma glucose levels and postprandial glucose levels, and body weight in the DURATION-1 and DURATION-5 studies (Table 3). There were fewer gastrointestinal adverse effects with the longer-acting formulation.[36,37] Therapeutic concentrations of exenatide extended duration are achieved in approximately 2 weeks, with steady state concentrations occurring by 6-7 weeks.[38] If switching patients to a once-weekly formulation, the time to achieve steady state should be taken into account.

Liragluide is administered once daily without regard to meals. It has been compared with exenatide twice daily in a head-to-head trial,[39] with an extension phase where patients on exenatide were switched to liraglutide.[40] In the original trial, patients with inadequately controlled T2DM on maximally tolerated doses of metformin, a sulfonylurea, or both were randomized to liraglutide once daily or exenatide twice daily. Liraglutide reduced fasting plasma glucose and A1C more than exenatide. Postprandial glucose lowering was greater with exenatide. Weight loss was similar between both products, and liraglutide was associated with less persistent nausea and less hypoglycemia than exenatide.[39] Patients receiving exenatide were switched to liraglutide, and those on liraglutide continued with liraglutide in the extension study. Switching resulted in further improvements in glycemic control, further reductions in body weight, and improvements in systolic blood pressure (Figure 2).[40]

A very recent study has been published comparing the safety and efficacy of once-weekly exenatide and once-daily liraglutide in >900 patients with T2DM in an open-label randomized trial. Both once-daily liraglutide and once-weekly exenatide led to improvements in glycemic control, with greater reductions noted with liraglutide (A1C reductions: −1.48% vs −1.28%). These findings, plus differences in injection frequency and tolerability (nausea, diarrhea, and vomiting were more frequent with exenatide once weekly [21% vs 9%; 13% vs 6%; 11% vs 4% respectively]), could inform therapeutic decisions for treatment of patients with T2DM (Figure 3).[41]

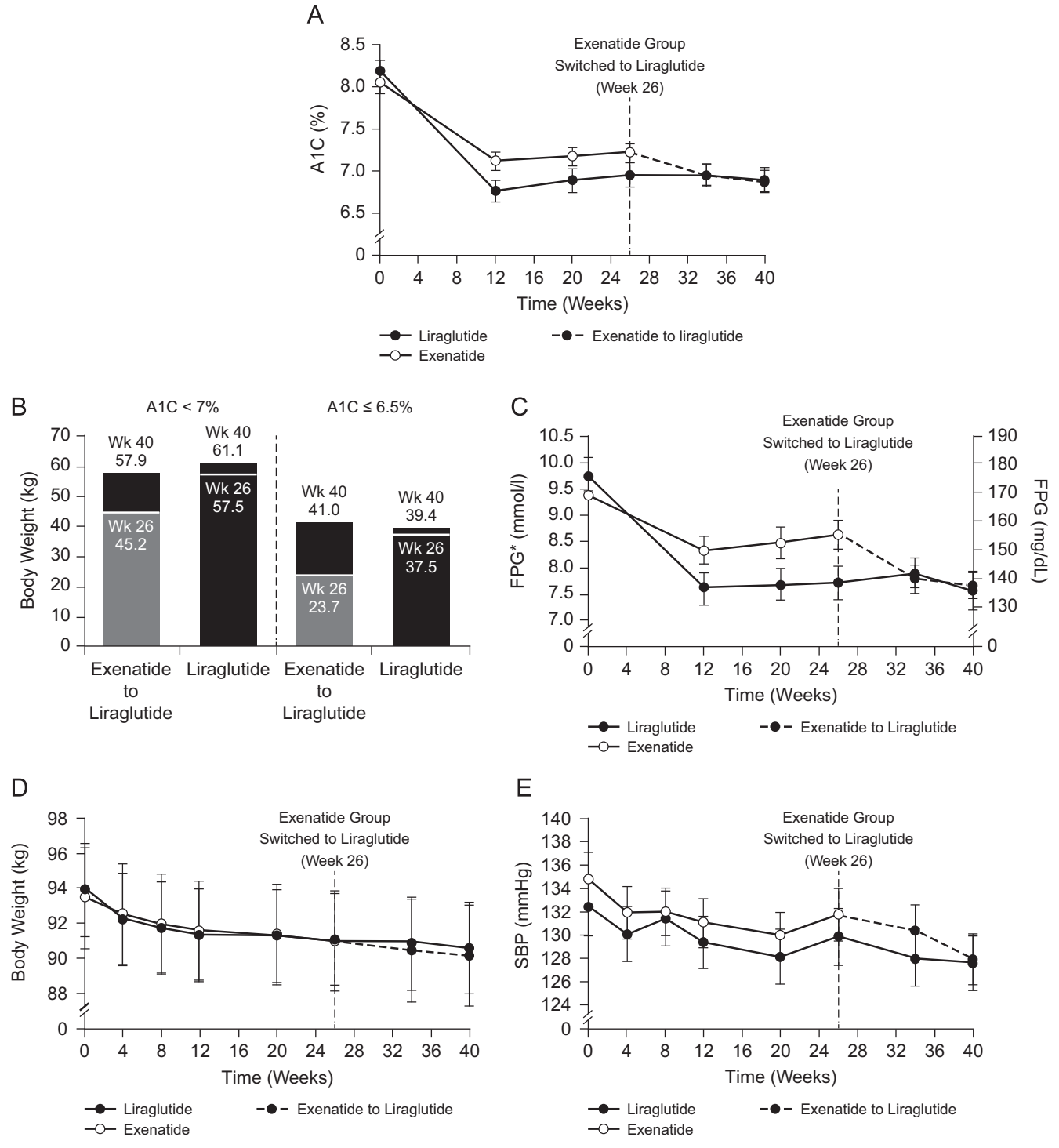
Cardiovascular (CV) effects

GLP-1 receptors are expressed in the heart and vasculature, prompting evaluation of their physiological role and pharmacological stimulation, both in healthy and disease states. GLP-1 receptor agonists may have direct and indirect effects on the CV system.[42] The weight loss associated with these agents may contribute to some of the improvements

Table 3 Clinical differences between exenatide as a twice-daily and once-weekly therapy for T2DM

	DURATION-1		DURATION-5	
	Exenatide, BID	Exenatide extended-release, once weekly	Exenatide, BID	Exenatide extended-release, once weekly
A1C, %	−1.5	−1.9	−0.9	−1.6
FPG, mg/dL	−25	−41	−12	−35
Weight, kg	−3.6	−3.7	−1.4	−2.3

FPG = fasting plasma glucose.[37,36]



FPG, fasting plasma glucose; SBP, systolic blood pressure

Figure 3

that are noted in CV risk factors among patients treated with GLP-1 receptor agonists (eg, improvements in systolic blood pressure, lipid profiles, and markers of inflammation),[43,44] although there are data suggesting that these effects may be independent of weight loss.[45] Results from ongoing prospective studies assessing CV outcomes are keenly awaited.[46]

Summary

Incretin-based therapy provides an option for improving glycemic control. As reviewed, adding GLP-1 RA therapy to oral antidiabetic drugs may be a good treatment option for patients with T2DM. Studies continue to accumulate, which illustrate the advantages of incretin-based therapies over

previous combination therapy strategies in the quest to achieve good glycemic control with as few adverse effects as possible. The benefits of possible weight loss may motivate patients to accept injectable therapies. Studies continue that compare the use of incretins vs insulin and use with insulin. Studies and clinical experience continue to accumulate comparing the use of available GLP-1 receptor agonists with DPP-4 inhibitors in efforts to further establish the differences between incretin-based therapies. More is being learned about the CV safety and the possible CV benefits of these agents. Incretin-based therapies appear to be overcoming some of the limitations of previous therapies in that they target multiple aspects of T2DM pathophysiology with a low risk of hypoglycemia and weight gain and with the potential for other pleiotropic effects.

Role of the funding source

This supplement is supported by an educational grant from Novo Nordisk Inc.

Disclosure statement

Jeffrey S. Freeman, DO, FACOI (Chair), states that he is a member of the speakers' bureau for Novo Nordisk Inc, Merck & Co Inc, Boehringer Ingelheim, Eli Lilly and Company, Amylin Pharmaceuticals, Inc, and Astra Zeneca.

Acknowledgments

Kate Mann, PharmD, assisted with editorial development under the auspices of E&S MedEd Group, Inc.

References

1. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773–795
2. Nathan DM, Buse JB, Davidson MB, et al: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29:1963–1972
3. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. *Diabetes Care*. 2009;32(suppl 2):S151–S156
4. Drucker DJ. Enhancing incretin action for the treatment of type 2 diabetes. *Diabetes Care*. 2003;26:2929–2940
5. Nauck MA, Homberger E, Siegel EG, et al: Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986;63:492–498
6. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;29:46–52
7. Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012
8. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3:153–165
9. Holst JJ, Deacon CF, Vilsboll T, Krarup T, Madsbad S. Glucagon-like peptide-1, glucose homeostasis and diabetes. *Trends Mol Med*. 2008;14:161–168
10. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705
11. Drucker DJ. Enhancing the action of incretin hormones: a new whey forward? *Endocrinology*. 2006;147:3171–3172
12. Davidson JA. Incorporating incretin-based therapies into clinical practice: differences between glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors. *Mayo Clin Proc*. 2010;85:S27–S37
13. Scheen AJ. A review of gliptins in 2011. *Expert Opin Pharmacother*. 2012;13:81–99
14. Freeman JS, Gavin 3rd JR, Spellman CW. Common patient concerns about the use of glucagon-like peptide-1 receptor agonists in diabetes mellitus management. *J Am Osteopath Assoc*. 2012;112:S22–S24
15. Rodbard HW, Jellinger PS, Davidson JA, 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. *Endocr Pract*. 2009;15:540–559
16. Nathan DM, Buse JB, Davidson MB, et al: Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32:193–203
17. Rodbard HW, Jellinger PS, Davidson JA, 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. *Endocr Pract*. 2009;15:540–559
18. Handelsman Y, Mechanick JI, Blonde L, et al: American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011;17(suppl 2):1–53
19. Esposito K, Mosca C, Brancario C, Chiodini P, Ceriello A, Giugliano D. GLP-1 receptor agonists and HBA1c target of $<7\%$ in type 2 diabetes: meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2011;27:1519–1528
20. Deacon CF, Mannucci E, Ahren B. Glycaemic efficacy of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors as add-on therapy to metformin in subjects with type 2 diabetes-a review and meta analysis. *Diabetes Obes Metab*. 2012
21. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *Br Med J*. 2012;344:d7771
22. Zinman B, Gerich J, Buse JB, et al: Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 met + TZD). *Diabetes Care*. 2009;32:1224–1230
23. Riddle MC, Henry RR, Poon TH, et al: Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metab Res Rev*. 2006;22:483–491
24. Russell-Jones D, Vaag A, Schmitz O, et al: Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met + SU): a randomised controlled trial. *Diabetologia*. 2009;52:2046–2055
25. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143:559–569
26. Diamant M, Van Gaal L, Stranks S, et al: Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. *Diabetes Care*. 2012;35:683–689
27. Arnolds S, Dellweg S, Clair J, et al: Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: a proof-of-concept study. *Diabetes Care*. 2010;33:1509–1515

28. Buse JB, Bergenstal RM, Glass LC, et al: Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med.* 2011;154:103–112
29. Bergenstal RM, Wysham C, Macconell L, et al: Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet*. 2010;376:431–439
30. Wysham C, Bergenstal R, Malloy J, et al: DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Med.* 2011;28:705–714
31. Pratley R, Nauck M, Bailey T, et al: One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. *Int J Clin Pract*. 2011;65:397–407
32. Pratley RE, Nauck M, Bailey T, et al: Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet*. 2010;375:1447–1456
33. Davies M, Pratley R, Hammer M, Thomsen AB, Cuddihy R. Liraglutide improves treatment satisfaction in people with type 2 diabetes compared with sitagliptin, each as an add on to metformin. *Diabet Med.* 2011;28:333–337
34. Best JH, Rubin RR, Peyrot M, et al: Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. *Diabetes Care*. 2011;34:314–319
35. DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P. Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther*. 2011;13:1145–1154
36. Drucker DJ, Buse JB, Taylor K, et al: Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240–1250
37. Blevins T, Pullman J, Malloy J, et al: DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:1301–1310
38. Aroda VR, DeYoung MB. Clinical implications of exenatide as a twice-daily or once-weekly therapy for type 2 diabetes. *Postgrad Med.* 2011;123:228–238
39. Buse JB, Rosenstock J, Sesti G, et al: Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374:39–47
40. Buse JB, Sesti G, Schmidt WE, et al: Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care*. 2010;33:1300–1303
41. Buse JB, Nauck M, Forst T, et al: Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2012
42. Verges B, Bonnard C, Renard E. Beyond glucose lowering: glucagon-like peptide-1 receptor agonists, body weight and the cardiovascular system. *Diabetes Metab*. 2011;37:477–488
43. Courreges JP, Vilsboll T, Zdravkovic M, et al: Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with type 2 diabetes. *Diabet Med.* 2008;25:1129–1131
44. Klonoff DC, Buse JB, Nielsen LL, et al: Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24:275–286
45. Bunck MC, Diamant M, Eliasson B, et al: Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition. *Diabetes Care*. 2010;33:1734–1737
46. Fonseca VA. Ongoing clinical trials evaluating the cardiovascular safety and efficacy of therapeutic approaches to diabetes mellitus. *Am J Cardiol.* 2011;108:52B–58BB