

REVIEW

Management of Unmet Needs in Type 2 Diabetes Mellitus: The Role of Incretin Agents

Ronald M. Goldenberg MD FRCPC FACE
LMC Endocrinology Centres, Thornhill, Ontario, Canada

ABSTRACT

The leading cause of morbidity and mortality in type 2 diabetes mellitus is cardiovascular disease. There is a need for type 2 diabetes therapies that act in concert with available agents to provide adequate glycemic control without causing hypoglycemia and weight gain, which are associated with increases in cardiovascular risk. Incretin-based agents—dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists—are the newest class of antihyperglycemic therapies. Liraglutide and exenatide, glucagon-like peptide-1 receptor agonists recently approved in Canada, have been shown to effectively lower blood glucose levels while also having beneficial effects on body weight and systolic blood pressure. The objective of this article is to review and discuss incretin-based agents, with a focus on their effects on blood glucose control, body weight and cardiovascular risk factors in patients with type 2 diabetes. Relevant data were obtained by literature search using the EMBASE, MEDLINE and PubMed databases.

KEYWORDS: cardiovascular disease, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, glycaemic control, incretin, type 2 diabetes mellitus

RÉSUMÉ

La principale cause de morbidité et de mortalité chez les patients atteints de diabète de type 2 est la maladie cardiovasculaire. On a besoin de traitements du diabète de type 2 qui agissent de concert avec les médicaments actuels pour produire un bon contrôle de la glycémie sans causer d'hypoglycémie et de prise de poids, facteurs qui sont associés à une augmentation du risque cardiovasculaire. Les analogues des incrétines, soit les inhibiteurs de la dipeptidyl peptidase-4 et les agonistes des récepteurs du peptide 1 apparenté au glucagon (GLP-1), sont les plus récents antihyperglycémisants. On a démontré que le liraglutide et l'exénatide, des agonistes des récepteurs du GLP-1 récemment homologués au Canada, réduisaient efficacement la glycémie et avaient des effets avantageux sur le poids corporel et la tension artérielle systolique. L'article examine les analogues des incrétines et

met l'accent sur leurs effets sur le contrôle de la glycémie, le poids corporel et les facteurs de risque cardiovasculaire chez les patients atteints de diabète de type 2. Les données pertinentes viennent d'une recherche documentaire dans les bases de données EMBASE, MEDLINE et PubMed.

MOTS CLÉS : maladie cardiovasculaire, inhibiteurs de la dipeptidyl peptidase-4, agonistes des récepteurs du peptide 1 apparenté au glucagon, contrôle de la glycémie, incrétines, diabète de type 2

INTRODUCTION

Diabetes affects approximately 285 million persons worldwide, with type 2 diabetes comprising 90% of diagnoses, and the International Diabetes Federation projects that by 2030 approximately 438 million persons worldwide will have diabetes (1). In Canada, the number of individuals with diagnosed diabetes is projected to increase from 1.8 million adults in 2005 to 2.4 million adults in 2016 (2).

Pathophysiological defects that are characteristic of type 2 diabetes include insulin resistance; progressive decline in pancreatic beta-cell function and decreased insulin secretion; hypersecretion of glucagon; increased hepatic glucose production; and abnormalities of the incretin effect after ingestion of a meal (3). The incretin hormones—intestinal peptide hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP)—are normally secreted in response to the oral ingestion of nutrients. GLP-1 potentiates insulin and inhibits glucagon secretion in a glucose-dependent manner; a diminished incretin response may contribute to impaired insulin secretion in patients with type 2 diabetes (4,5).

Common cardiovascular (CV) risk factors such as hypertension, dyslipidemia and obesity complicate the pharmacological management of type 2 diabetes and increase the risk of CV disease (CVD) in these patients (3). Current treatment guidelines recommend the aggressive management of blood glucose and CV risk factors in patients with type 2 diabetes (2), but gaps remain in treating patients to recommended goals for glycemia, blood pressure (BP), lipids and weight (6).

Address for correspondence: Ronald M. Goldenberg, LMC Endocrinology Centres, 531 Atkinson Avenue, Suite 17 Thornhill, Ontario, Canada L4J 8L7. E-mail: ronald.goldenberg@lmc.ca

In this review, treatments that are currently available for the management of type 2 diabetes are discussed, with an emphasis on new and emerging therapies that work in synergy with available treatments to improve the management of hyperglycemia and associated risk factors. EMBASE, MEDLINE and PubMed databases were searched for clinical trials, randomized controlled trials or reviews published between January 2005 and October 2010 using the search terms “type 2 diabetes plus pathogenesis,” “treatment and liraglutide, exenatide, sitagliptin, saxagliptin” or “unmet needs,” and relevant references were selected. Additional articles of relevance were identified from the reference lists of the retrieved publications.

TREATMENT GOALS AND UNMET NEEDS IN TYPE 2 DIABETES

CVD is a leading cause of morbidity and mortality in patients with type 2 diabetes (2). To reduce the risk of CVD, treatment guidelines recommend the aggressive management of CV risk factors (including BP, lipids and obesity), in addition to maintaining optimal glycemic control (2). According to the National Health and Nutrition Examination Survey, the percentage of persons achieving simultaneous glycemic, BP and low-density lipoprotein cholesterol (LDL-C) control increased from 7.0% in 1999–2002 to 12.2% in 2003–2006 ($p > 0.05$) (7). Still, a majority of patients with type 2 diabetes remain above target for one or more treatment goals, despite improvements in therapeutic agents (7). In the Diabetes in Canada Evaluation chart audit conducted from September 2002 to February 2003, approximately 49.0% of the 2473 patients with type 2 diabetes were uncontrolled (glycated hemoglobin [A1C] $\geq 7.0\%$) (8). In addition, many patients with type 2 diabetes had comorbidities associated with elevated blood glucose levels, including hypertension (63.0%), dyslipidemia (59.0%), macrovascular complications (28.0%) and microvascular complications (38.0%).

The latest data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study suggest that intensive therapy with standard antihyperglycemic agents effectively achieves glycemic control, but does not significantly reduce the incidence of CV events in high-risk patients with type 2 diabetes (9). Furthermore, intensive blood glucose lowering in this high-risk population was associated with hypoglycemia and weight gain (9), common side effects of many traditional antihyperglycemic agents, and both associated with increased CV risk. In the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial, severe hypoglycemia was associated with major macrovascular and microvascular events, and death (10). In the ACCORD study, severe hypoglycemia was associated with increased death (11). Although full results

from the Look AHEAD (Action for Health in Diabetes) trial will provide data on the rate of CV events, the 1- and 4-year interim results indicate that weight loss is associated with an improvement in CV risk factors (12,13).

Although all therapies for type 2 diabetes provide some measure of glycemic control, their concurrent impact on hypoglycemia and weight gain is highly relevant when making therapeutic choices. Composite endpoints are commonly used in other complex chronic diseases, and in diabetes, a composite endpoint of A1C reduction, no hypoglycemia and no weight gain may help to identify agents that can provide adequate glycemic control without associated detrimental side effects (14). There is a need for antihyperglycemic therapies with complementary mechanisms of actions that act in concert to address the multiple risk factors associated with elevated blood glucose levels in patients with type 2 diabetes.

CURRENT ANTIHYPERGLYCEMIC AGENTS AND THEIR PLACE IN THERAPY

Pharmacological agents for type 2 diabetes are most effective when individualized to the specific needs of the patient and, when predicated on their effectiveness in lowering blood glucose, any extraglycemic effects that may reduce long-term complications, safety profile, tolerability, ease of use and cost (15).

In the absence of contraindications, metformin is recommended as initial pharmacotherapy for patients with type 2 diabetes (2). Other classes of antihyperglycemic agents are recommended as adjunct agents in patients whose blood glucose levels remain uncontrolled on their initial treatment regimen, or who gradually require additional therapy for managing blood glucose levels as type 2 diabetes progresses. These agents have mechanisms of action that are often complementary, and they may act in synergy to reduce A1C levels in patients with type 2 diabetes (Table 1). Many of these agents are effective at managing glycemic parameters, but do not improve other risk factors associated with elevated blood glucose levels. For example, thiazolidinediones (TZDs) are contraindicated in patients with New York Heart Association Class I to IV heart failure (19,20). Rosiglitazone is not recommended in patients with a history of ischemic heart disease, and is indicated only when all other oral antihyperglycemic agents fail to provide adequate glycemic control or are inappropriate (19,20). Furthermore, weight gain is associated with the use of TZDs, sulfonylureas, meglitinides and insulin, and the latter 3 classes are also associated with hypoglycemia (Table 1). There is a need for agents that do not increase the risk of hypoglycemia or weight gain.

Two new classes of recently approved antihyperglycemic agents—dipeptidyl peptidase-4 (DPP-4) inhibitors and

Table 1. Antihyperglycemic agents approved for the treatment of type 2 diabetes (13,16-18)

Class	A1C reduction, %	Dosing, times/day	Hypoglycemia	Weight effects
Alpha-glucosidase inhibitors	0.5–0.8	3	No	Neutral
Metformin	1.5	1–2	No	Neutral
Sulfonylureas	1.5	1–2	Yes	Gain
Thiazolidinediones	0.5–1.4	1–2	No	Gain
Meglitinides	0.5–1.5	3	Yes	Gain
Insulin	up to >2.0	1–4 (injected)	Yes	Gain
DPP-4 inhibitors	0.5–0.9	1	Rare	Neutral
GLP-1 receptor agonists	0.8–1.5	1–2 (injected)	Rare	Loss

A1C = glycated hemoglobin

DPP-4 = dipeptidyl peptidase-4

GLP-1 = glucagon-like peptide-1

Table 2. DPP-4 inhibitors and GLP-1 receptor agonists: approved indications in Canada (24-28)

	Monotherapy*	Add-on to metformin (dual tx)	Add-on to sulfonylureas (dual tx)	Add-on to metformin and sulfonylureas (triple tx)
DPP-4 inhibitors				
Linagliptin	✓	✓	✓	✓
Saxagliptin	–	✓	✓	–
Sitagliptin	✓	✓	–	✓
GLP-1 receptor agonists				
Exenatide	–	✓	✓	✓
Liraglutide	–	✓	–	✓

*If intolerant to metformin or metformin treatment is contraindicated

DPP-4 = dipeptidyl peptidase-4

GLP-1 = glucagon-like peptide-1

GLP-1 receptor agonists—have been shown to be effective in reducing A1C and blood glucose levels, with low rates of hypoglycemia or weight gain (21). GIP and GLP-1 are secreted following oral ingestion of nutrients and then normally degraded by the enzyme DPP-4 (22). DPP-4 inhibitors such as saxagliptin and sitagliptin prevent the degradation and inactivation of endogenous GLP-1, thereby enhancing insulin secretion and diminishing glucagon secretion in patients with type 2 diabetes in a glucose-dependent manner (22). The magnitude of the effect of DPP-4 inhibitors is limited to endogenous levels of incretin hormones and typically results in a 2-fold increase in endogenous GLP-1. In contrast, GLP-1 receptor agonists such as exenatide and liraglutide are engineered to be resistant to degradation by DPP-4 and to enhance incretin activity by providing pharmacologic levels of GLP-1 receptor stimulation (more than a 5-fold increase) (22,23). A list of DPP-4 inhibitors and GLP-1 receptor agonists approved in Canada for the treatment of type 2 diabetes, and those under development, is provided in Table 2.

DPP-4 inhibitors: saxagliptin, sitagliptin and linagliptin

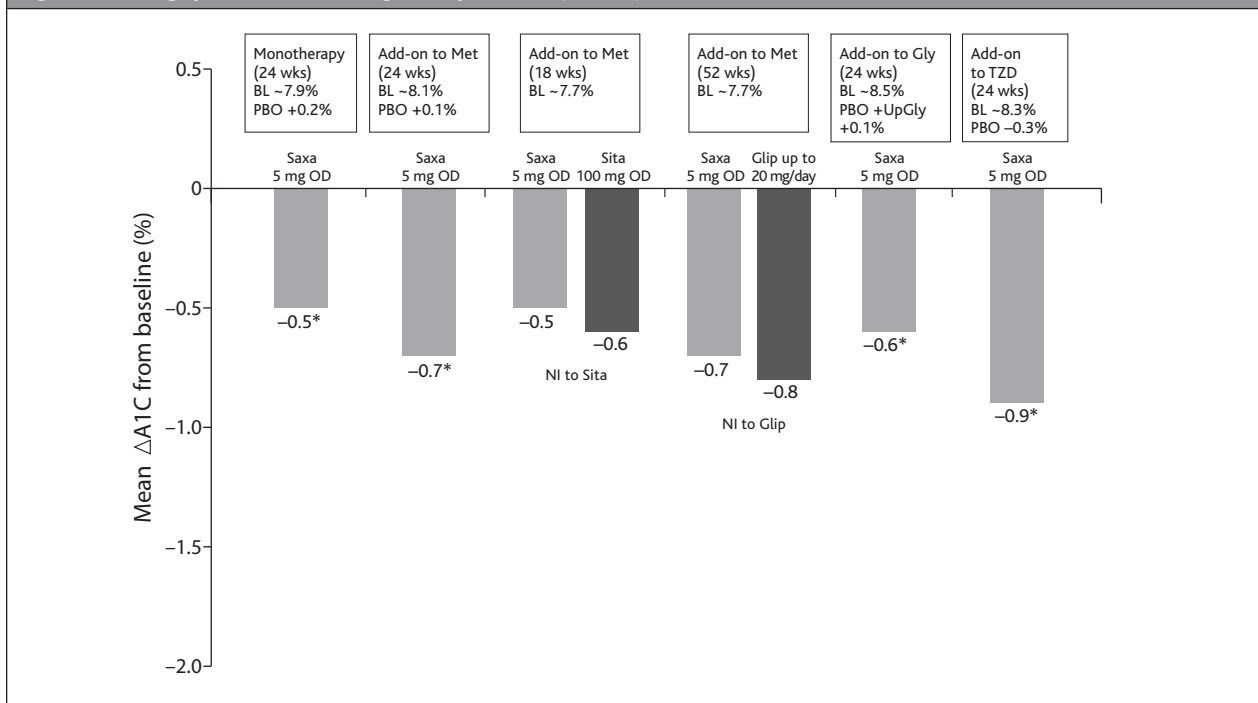
Saxagliptin

In a monotherapy trial, treatment with saxagliptin 5 mg/day resulted in reductions from baseline in A1C and fasting plasma glucose (FPG) of 0.46% ($p < 0.0001$) and 0.50 mmol/L ($p = 0.0074$), respectively (29). In addition, when added to metformin, saxagliptin led to reductions from baseline in A1C and FPG of 0.69% and 1.20 mmol/L, respectively ($p \leq 0.0001$ for both) (30). Similar results were achieved when saxagliptin was added to sulfonylurea or TZD therapy (31,32). Saxagliptin was non-inferior to a sulfonylurea when each was added to metformin, but the sulfonylurea caused more hypoglycemia and weight gain (33). Saxagliptin has also been shown to be non-inferior to sitagliptin when each was added to metformin therapy (34). Figure 1 summarizes the results of the major saxagliptin trials.

Sitagliptin

Treatment with sitagliptin 100 mg/day resulted in reductions from baseline in A1C and FPG of 0.61% and 0.70 mmol/L,

Figure 1. Saxagliptin: A1C lowering in major trials (29-34)

* $p < 0.001$ vs. PBO

A1C = glycated hemoglobin
BL = baseline
Glip = glipizide
Gly = glyburide

Met = metformin
NI = non-inferior
PBO = placebo
Saxa = saxagliptin

Sita = sitagliptin
TZD = thiazolidinedione
UpGly = uptitrated glyburide

respectively ($p \leq 0.001$ for both) when used as monotherapy, and 0.67% and 0.90 mmol/L, respectively ($p < 0.001$ for both) when used in combination with metformin (35,36). Other combination therapy trials that have also demonstrated significant glucose reductions include sitagliptin added to a sulfonylurea, a TZD, metformin plus a sulfonylurea and metformin plus a TZD (37–39). Sitagliptin was shown to produce A1C lowering similar to that of a sulfonylurea or a TZD when each was added to metformin, but the sulfonylurea and TZD caused weight gain, and the sulfonylurea caused more hypoglycemia (40,41). Sitagliptin added to basal or premixed insulin reduced A1C by 0.6% vs. placebo ($p < 0.001$) at the same daily insulin dose in each group (42). Figure 2 summarizes the results of the major sitagliptin trials.

Linagliptin

Linagliptin was approved in Canada in July 2011. Linagliptin 5 mg once daily over 18 to 24 weeks significantly improved glycemic control as monotherapy (43), and in combination with metformin (44) or a sulfonylurea (45,46), with A1C reductions from baseline from 0.4% to 0.7%. These trials also showed no weight changes and low rates of hypoglycemia. A double-blind trial (47) of linagliptin 5 mg/day found A1C decreases similar to that of glimepiride (0.4% vs. 0.5%, respectively) when each was added to metformin over

2 years. This trial also showed significant weight loss (1.4 kg, $p < 0.0001$ vs. 1.3 kg weight gain) and significantly lower rates of hypoglycemia (7.5% vs. 36.1%, $p < 0.0001$) compared to glimepiride. Figure 3 summarizes the results of linagliptin trials.

Adverse effects

DPP-4 inhibitors are generally weight-neutral, have no effect on BP or lipids, and are associated with low rates of hypoglycemia. CV endpoint trials with saxagliptin, sitagliptin and linagliptin are ongoing (48–50).

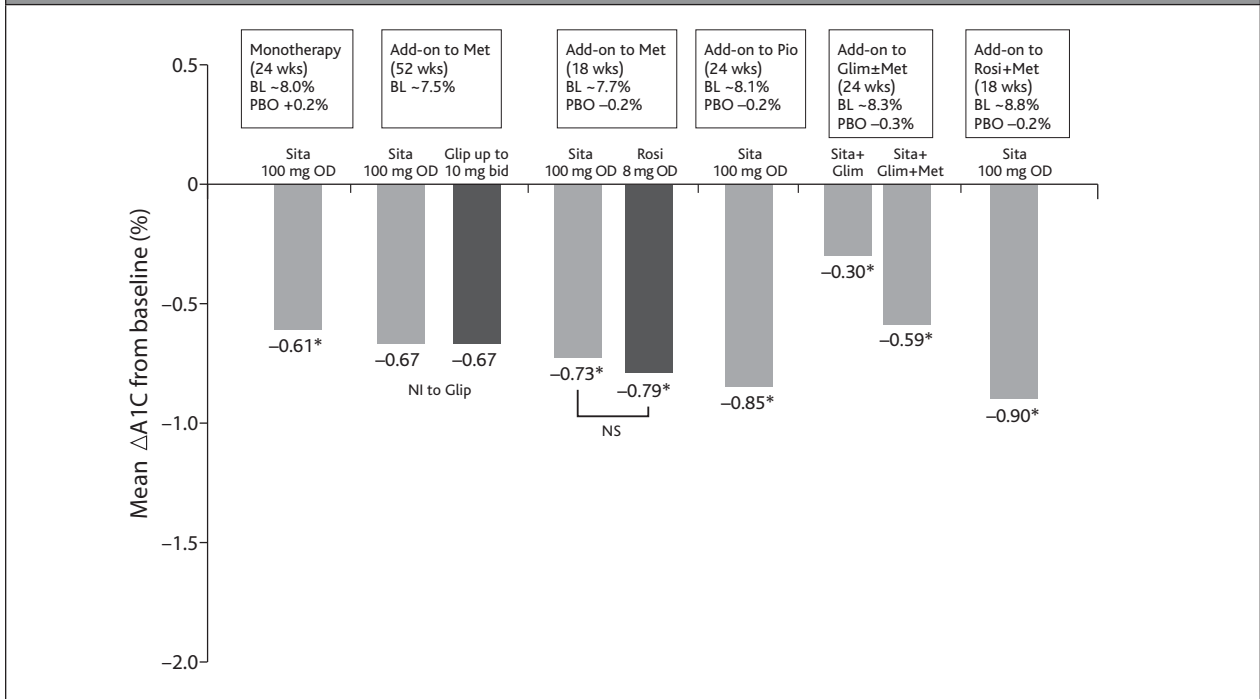
Nasopharyngitis, urinary infection and headache are the most commonly reported adverse effects of DPP-4 inhibitor therapy (30,35,51). There were isolated case reports of pancreatitis with both saxagliptin and sitagliptin in controlled clinical trials, but the incidence was consistent with the expected rate in type 2 diabetes and similar to comparators (52,53).

GLP-1 receptor agonists: exenatide and liraglutide

Exenatide

Exenatide, approved in Canada in January 2011, is the synthetic form of naturally occurring exendin-4, a hormone secreted by the salivary glands of the Gila monster, and is 53% homologous to human GLP-1 (21). Exenatide is initi-

Figure 2. Sitagliptin: A1C lowering in major trials (36–41)



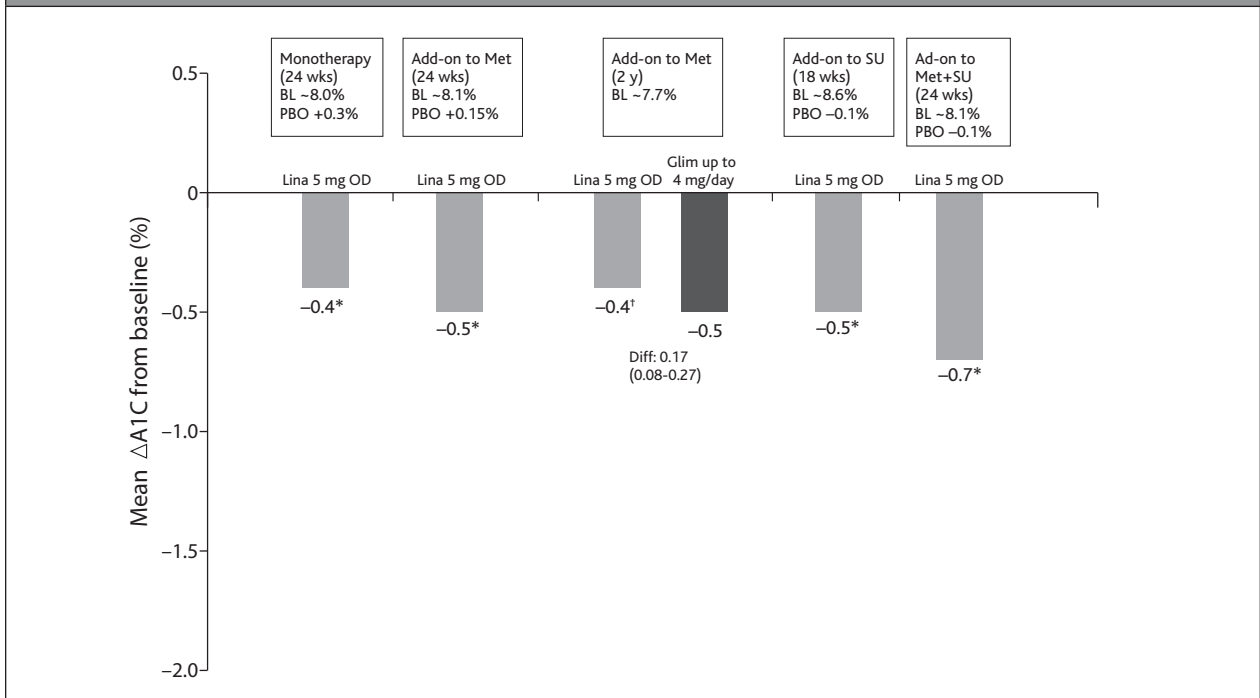
*p<0.001 vs. PBO

A1C = glycated hemoglobin
BL = baseline
Glim = glimepiride
Glip = glipizide

Met = metformin
NI = non-inferior
NS = non-significant
Pio = pioglitazone

PBO = placebo
Rosi = rosiglitazone
Sita = sitagliptin

Figure 3. Linagliptin: A1C lowering in major trials (43–47)



*p<0.0001 vs. PBO or comparator

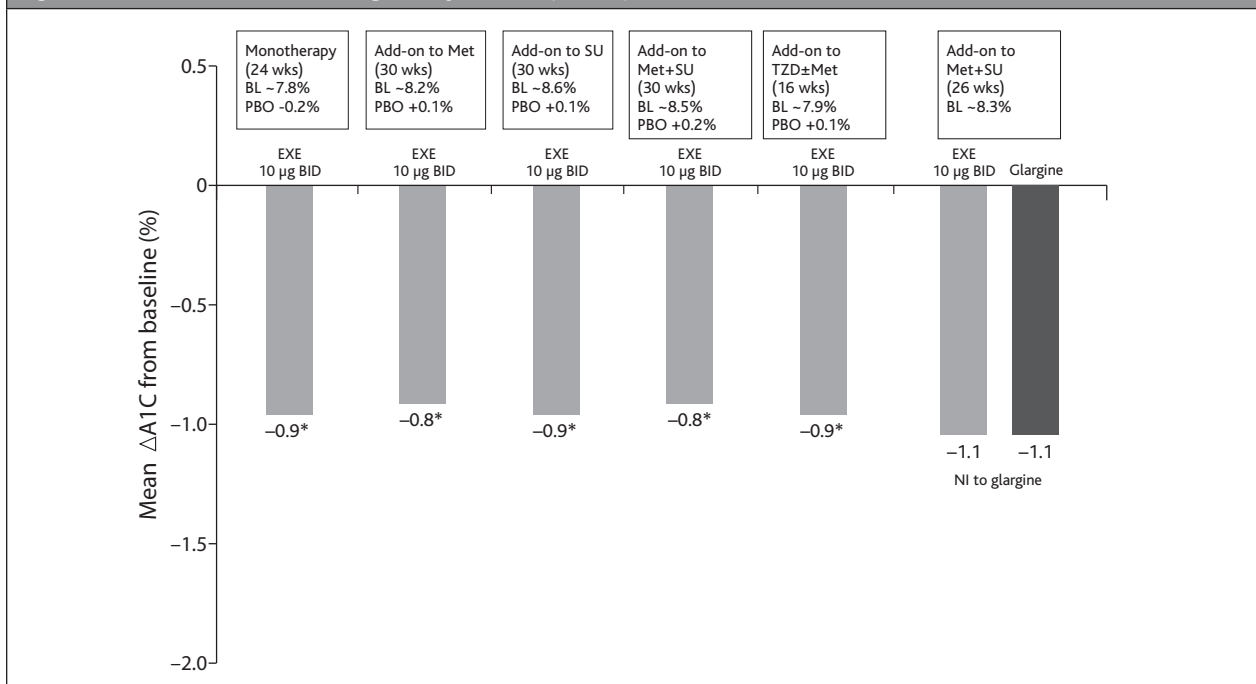
†p=0.0001 for noninferiority

A1C = glycated hemoglobin
BL = baseline
Glim = glimepiride

Lina = linagliptin
Met = metformin
PBO = placebo

SU = sulfonylurea

Figure 4. Exenatide: A1C lowering in major trials (21, 54)



*Significant vs. PBO

A1C = glycated hemoglobin
BL = baseline
EXE = exenatide

Met = metformin
NI = non-inferior
PBO = placebo

SU = sulfonylurea
TZD = thiazolidinedione

ated at 5 µg sc BID for 1 month, then increased to 10 µg sc BID thereafter, administered within 60 minutes before morning and evening meals. Exenatide has been shown to be efficacious as monotherapy or in combination with metformin, sulfonylureas, TZDs or metformin plus a sulfonylurea (21). It was shown to produce A1C lowering similar to insulin glargine (1.1%) when each was added to metformin plus a sulfonylurea, but exenatide was associated with a 2.3 kg weight loss, while glargine patients gained 1.8 kg (54). An integrated analysis of 4 trials that compared exenatide to insulin glargine had similar results (55). Figure 4 summarizes the major exenatide trials.

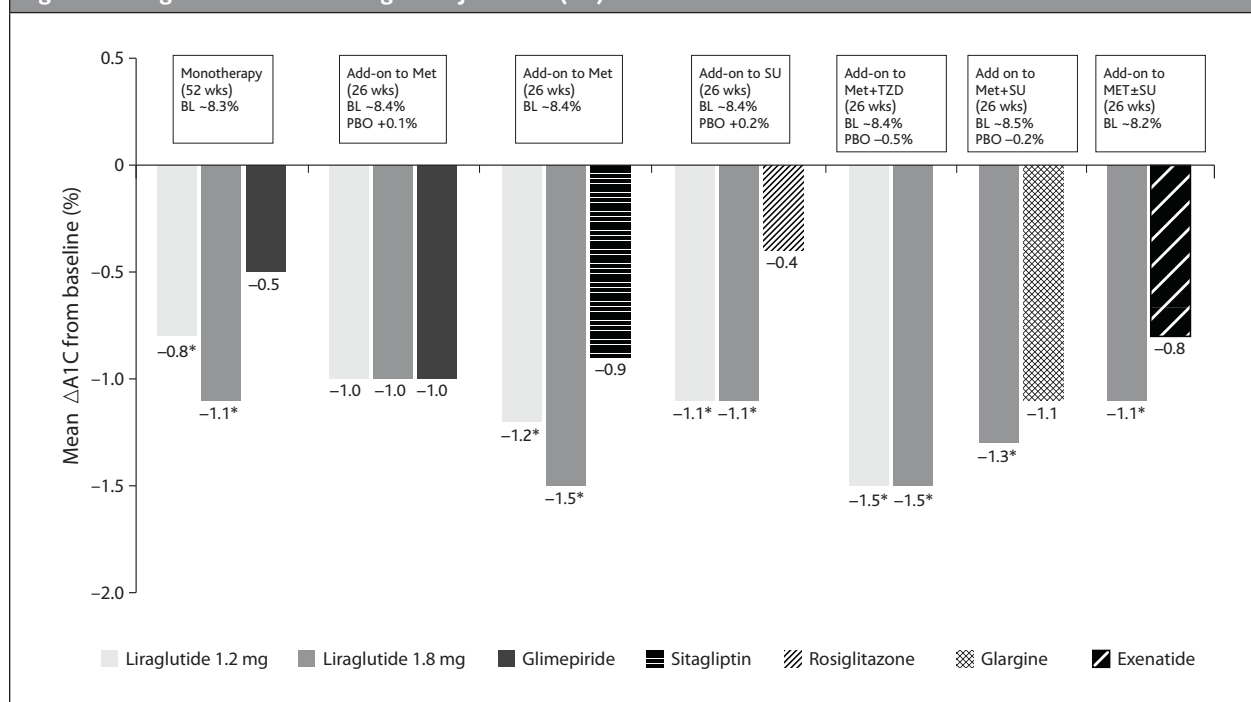
Exenatide has also been compared to premixed insulin aspart 30/70 in 3 studies, with similar A1C lowering in 2 studies, but inferior A1C lowering in the third study (17,56,57). A meta-analysis of 4 placebo-controlled trials showed that exenatide 10 µg sc BID resulted in reductions from baseline in A1C, FPG and body weight of 0.97%, 1.50 mmol/L and 1.25 kg, respectively, ($p < 0.001$ for all) (58). Although it is not indicated for use with insulin, exenatide improved A1C compared to placebo (difference -0.7%, $p < 0.001$) without increased hypoglycemia or weight gain in patients receiving insulin glargine (59). Exenatide treatment was also associated with a significantly greater reduction in systolic BP (SBP) compared with placebo (2.80 mm Hg, $p = 0.0002$), a finding that was not attributable to

weight loss (60). In an open-label extension of 3 exenatide studies, there were also minor but significant improvements in LDL-C, high-density lipoprotein cholesterol and triglycerides (61). As well, exenatide led to greater achievement of the composite endpoint of A1C $\leq 7.4\%$ and weight gain ≤ 1 kg compared with insulin glargine (62).

Liraglutide

Liraglutide is a human GLP-1 analogue with 97% homology to native GLP-1 and was the first GLP-1 receptor agonist approved in Canada (May 2010). Liraglutide is initiated at 0.6 mg sc OD, and should be increased to 1.2 mg OD after at least 1 week if tolerated, with a further increase to 1.8 mg OD if required (24). In the Liraglutide Effect and Action in Diabetes trials (LEAD 1-5), treatment with liraglutide resulted in reductions from baseline in mean A1C levels of up to 1.1% ($p < 0.001$ vs. sulfonylurea) when used as monotherapy, or from 1.0% to 1.5% ($p < 0.001$ vs. placebo, rosiglitazone or glargine) when used in combination with oral agents (metformin, a sulfonylurea, metformin plus a sulfonylurea or metformin plus a TZD) (Figure 5) (18,64-67). Treatment with liraglutide reduced FPG levels by up to 2.4 mmol/L. In LEAD-6, treatment with liraglutide compared with exenatide (combined with either metformin or a sulfonylurea, or both) resulted in reductions from baseline in

Figure 5. Liraglutide: A1C lowering in major trials (63)



*Significant vs. active comparator

A1C = glycated hemoglobin

BL = baseline

Met = metformin

PBO = placebo

SU = sulfonylurea

TZD = thiazolidinedione

A1C and FPG of 1.1% vs. 0.8% ($p < 0.001$) and 1.6 vs. 0.60 mmol/L ($p < 0.001$), respectively. The proportion of participants achieving A1C $< 7\%$ was significantly higher for liraglutide than exenatide (54% vs. 43%, OR 2.02, 95% CI 1.31–3.11) (68). Moreover, patients with type 2 diabetes who switched from exenatide to liraglutide experienced further significant reductions in A1C (0.32%), FPG (0.9 mmol/L), body weight (0.9 kg) and SBP (3.8 mm Hg), with minimal episodes of hypoglycemia or nausea (69).

A meta-analysis of the liraglutide trials found that the proportion of patients achieving the composite endpoint of A1C $< 7.0\%$, no weight gain and no hypoglycemia was significantly higher with liraglutide 1.8 mg than with all active comparators, including sulfonylureas, TZDs, insulin glargine and exenatide. Furthermore, treatment with liraglutide 1.2 mg was associated with significantly more patients reaching this composite outcome compared to sulfonylureas and TZDs (14,63). In a study that compared liraglutide and sitagliptin (as adjuncts to metformin), treatment with liraglutide resulted in a greater reduction from baseline in A1C levels than sitagliptin (1.2% [liraglutide 1.2 mg] and 1.5% [liraglutide 1.8 mg] vs. 0.9% [sitagliptin], $p < 0.0001$) (70) (Figure 5). The composite outcome of A1C $< 7.0\%$, no weight gain and no hypoglycemia was achieved in significantly more patients with liraglutide than sitagliptin (37% [liraglutide 1.2 mg] and 46% [liraglutide 1.8 mg] vs. 14% [sitagliptin],

$p < 0.0001$) (70). In an observational study, liraglutide added to high-dose insulin (mean 192 units) led to a 1.4% reduction in A1C with a 5.1 kg weight loss and a 28% reduction in insulin dose (71).

Liraglutide also resulted in significant reductions in body weight and BP. Weight was reduced by up to 2.5 kg ($p < 0.001$ vs. active comparator) with liraglutide as monotherapy and up to 3.2 kg with liraglutide in combination with oral agents (18,64–67). Treatment with liraglutide compared with exenatide resulted in weight loss of 3.2 vs. 2.9 kg ($p = 0.223$) (68). In addition, liraglutide plus metformin resulted in a greater reduction in body weight compared with sitagliptin plus metformin (3.4 vs. 1.0 kg, $p < 0.0001$) (70). Liraglutide 1.2 and 1.8 mg doses were associated with reductions in SBP ranging from 2.1 to 6.7 mm Hg and 2.3 to 5.6 mm Hg, respectively (18,64–67), a result that cannot be explained by weight loss (72). The liraglutide trials also demonstrated that patients treated with liraglutide 1.8 mg were more likely to achieve the composite endpoint of A1C $< 7.0\%$, SBP < 130 mm Hg and no weight gain than those treated with active comparators, including sulfonylureas, TZDs, insulin glargine, exenatide and sitagliptin (63). In addition to its benefits on glycemia, body weight and SBP, liraglutide has been shown to reduce CV risk markers by significantly lowering LDL-C, triglycerides, free fatty acids, brain natriuretic peptide and high-

sensitivity C-reactive protein levels (73). Ongoing randomized, controlled trials with liraglutide or exenatide will examine the long-term CV effects of both agents (74,75).

Adverse effects

Nausea and vomiting—usually transient and typically occurring in the first few weeks of therapy—are common adverse effects associated with exenatide and liraglutide therapy. Between 45% and 51% of exenatide-treated patients develop nausea, and 10% to 15% experience vomiting (25). In liraglutide trials, 7% to 40% of patients reported nausea and 4% to 17% had vomiting (18,64-68,70). In LEAD-6, nausea was less persistent with liraglutide than exenatide (3% vs. 9% at week 26, $p < 0.0001$) (68). Between 3% and 5% of GLP-1 receptor agonist-treated patients withdrew from studies due to gastrointestinal adverse events (24,25).

Exenatide has been associated with an increase in heart rate of up to 10 bpm in healthy volunteers and +2 bpm in patients with type 2 diabetes, as well as an increase in the PR interval of up to 7 ms and a small but statistically significant QTc interval prolongation (25). An increase in heart rate has been demonstrated in liraglutide-treated healthy volunteers (up to 7–8 bpm) and in clinical trials involving patients with type 2 diabetes (2–4 bpm) (24). PR interval prolongation up to 10 ms and a statistically significant shortening of the QTc interval was demonstrated in liraglutide-treated healthy volunteers (24). The clinical significance of these cardiac electrophysiology findings is uncertain.

Studies in rodents show an increased risk of benign C-cell adenomas and C-cell carcinomas with liraglutide therapy, although the relevance of these findings to humans is unknown (25). There have been isolated cases of pancreatitis in the clinical trials of GLP-1 receptor agonists, but the rate is similar to that expected in a population of patients with type 2 diabetes, and causality has not been proven (76).

Incretin therapies in development

DPP-4 inhibitors in development include vildagliptin and alogliptin, which have shown similar efficacy to currently available DPP-4 inhibitors (77). Additional GLP-1 receptor agonists in development include the once-daily lixisenatide, as well as extended-release formulations administered once-weekly (exenatide QW, albiglutide, dulaglutide, CJC-1134-PC) (78). Exenatide QW has demonstrated greater A1C lowering than exenatide BID, sitagliptin, pioglitazone and insulin glargine (78).

CONCLUSIONS

Patients with type 2 diabetes are frequently unable to meet glycemic as well as lipid and BP treatment goals, thereby

increasing their risk of CVD. Furthermore, traditional anti-hyperglycemic agents are often associated with weight gain and/or hypoglycemia, and have variable effects on CVD risk factors. Incretin agents address unmet needs in type 2 diabetes management by effectively lowering blood glucose levels with little risk of hypoglycemia or weight gain, and are excellent agents for combination therapy with 1 or 2 other oral agents. DPP-4 inhibitors are well-tolerated oral incretin agents that offer efficacious glucose lowering without weight gain or hypoglycemia. GLP-1 receptor agonists are an important new addition to the incretin agents; they offer good efficacy along with the benefits of weight loss and SBP lowering, but transient nausea and vomiting can occur. Among the currently available incretin agents, liraglutide offers better A1C lowering than exenatide and the DPP-4 inhibitors.

ACKNOWLEDGEMENTS

Medical writing services and editorial assistance were provided by Luana Atherly, PhD, of inScience Communications, a Wolters Kluwer business, and Jenna Steere, PhD, of Watermeadow Medical, USA, and were independently supported by Novo Nordisk Canada, Inc.

AUTHOR DISCLOSURES

Assistance for the preparation of this manuscript was provided by inScience Communications, a Wolters Kluwer business (supported by Novo Nordisk Canada, Inc.)

Dr Goldenberg has received research support or honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Company, GlaxoSmithKline, Merck, Novo Nordisk Canada, sanofi-aventis, and Servier.

REFERENCES

1. International Diabetes Federation. Diabetes and impaired glucose tolerance. *Diabetes Atlas*. <http://www.idf.org/diabetesatlas/diabetes-and-impaired-glucose-tolerance>. Accessed November 29, 2011.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2008;32(suppl 1):S1-S201.
3. Rodbard HW, Blonde L, Braithwaite SS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract*. 2007;13(suppl 1):1-68.
4. Nauck M, Stockmann F, Ebert R, et al. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;29:46-52.
5. Vilsboll T, Krarup T, Sonne J, et al. Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2003;88:2706-2713.
6. Ong KL, Cheung BM, Wong LY, et al. Prevalence, treatment, and control of diagnosed diabetes in the U.S. National Health and Nutrition Examination Survey 1999–2004. *Ann Epidemiol*. 2008;18:222-229.
7. Cheung BM, Ong KL, Cherny SS, et al. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. *Am J Med*. 2009;122:443-453.

8. Harris SB, Ekoe JM, Zdanowicz Y, et al. Glycemic control and morbidity in the Canadian primary care setting (results of the Diabetes in Canada Evaluation study). *Diabetes Res Clin Pract.* 2005;70:90-97.
9. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545-2559.
10. Zoungas S, Patel A, Chalmers J, et al; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med.* 2010;363:1410-1418.
11. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ.* 2010;340:b4909.
12. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care.* 2007;30:1374-1383.
13. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med.* 2010;170:1566-1575.
14. Zinman B, Schmidt WE, Moses A, et al. Achieving a clinically relevant composite outcome of an HbA(1c) of <7% without weight gain or hypoglycaemia in type 2 diabetes: a meta-analysis of the liraglutide clinical trial programme. *Diabetes Obes Metab.* 2011.
15. 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.
16. Drucker DJ, Sherman SI, Gorelick FS, et al. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care.* 2010;33:428-433.
17. Bergenstal R, Lewin A, Bailey T, et al. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulphonylurea. *Curr Med Res Opin.* 2009;25:65-75.
18. Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med.* 2009;26:268-278.
19. Avandia (rosiglitazone maleate) [product monograph]. Mississauga, ON: GlaxoSmithKline; 2011.
20. ACTOS (pioglitazone hydrochloride) [product monograph]. Mississauga, ON: Takeda Canada, Inc.; 2011.
21. Gilbert MP, Pratley RE. Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus. *Am J Med.* 2009;122(6 suppl):S11-S24.
22. Nauck MA. Unraveling the science of incretin biology. *Am J Med.* 2009;122(6 suppl):S3-S10.
23. Combettes MM. GLP-1 and type 2 diabetes: physiology and new clinical advances. *Curr Opin Pharmacol.* 2006;6:598-605.
24. Health Canada. Summary basis of decision (SBD) for Victoza. www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2010_victoza_119928-eng.php. Accessed November 29, 2011.
25. Health Canada. Summary basis of decision (SBD) for Byetta. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2011_byetta_128932-eng.php. Accessed November 29, 2011.
26. Health Canada. Summary basis of decision (SBD) for Onglyza. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2010_onglyza_123854-eng.php. Accessed November 29, 2011.
27. Health Canada. Summary basis of decision (SBD) for Januvia. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2008_januvia_103039-eng.php. Accessed November 29, 2011.
28. Trajenta (linagliptin) [product monograph]. Burlington, ON: Boehringer Ingelheim (Canada) Ltd.; 2011.
29. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. *Curr Med Res Opin.* 2009;25:2401-2411.
30. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care.* 2009;32:1649-1655.
31. Chacra AR, Tan GH, Apanovitch A, et al; CV181-040 Investigators. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. *Int J Clin Pract.* 2009;63:1395-1406.
32. Hollander P, Li J, Allen E, et al. Saxagliptin added to a thiazolidinedione improves glycaemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. *J Clin Endocrinol Metab.* 2009;94:4810-4819.
33. Goke B, Gallwitz B, Eriksson J, et al. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int J Clin Pract.* 2010;64:1619-1631.
34. Scheen AJ, Charpentier G, Ostgren CJ, et al. Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev.* 2010;26:540-549.
35. Charbonnel B, Karasik A, Liu J, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care.* 2006;29:2638-2643.
36. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2006;29:2632-2637.
37. Dobs AB, Goldstein A. Triple combination therapy sitagliptin, metformin and rosiglitazone improves glycaemic control in patients with type 2 diabetes. *Diabetes.* 2008;57:Abstract 2152-PO.
38. Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab.* 2007;9:733-745.
39. Rosenstock J, Brazg R, Andryuk PJ, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2006;28:1556-1568.
40. Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulphonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2007;9:194-205.
41. Scott R, Loeys T, Davies, MJ, et al. Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. *Diabetes Obes Metab.* 2008;10:959-969.
42. Vilsboll T, Rosenstock J, Yki-Jarvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab.* 2010;12:167-177.
43. Del Prato S, Barnett AH, Huisman H, et al. Effect of linagliptin monotherapy on glycaemic control and markers of β -cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab.* 2011;13:258-267.
44. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2011;28:1352-1361.
45. Lewin AJ, Arvay L, Liu D, et al. Safety and efficacy of linagliptin as add-on therapy to a sulphonylurea in inadequately controlled type 2 diabetes. *Diabetologia.* 2010;53(suppl 1):S326.
46. Owens DR, Swallow R, Dugi KA, et al. Efficacy and safety of linagliptin

- in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. *Diabet Med*. 2011; epub ahead of print.
47. Gallwitz B, Uhlig-Laske B, Bhattacharaya S, et al. Linagliptin has similar efficacy to glimepiride but improved cardiovascular safety over 2 years in patients with type 2 diabetes inadequately controlled on metformin. *Diabetes*. 2011;60(suppl 1):LB11.
 48. AstraZeneca. Does saxagliptin reduce the risk of cardiovascular events when used alone or added to other diabetes medications (SAVORTIMI 53). <http://www.clinicaltrials.gov/ct2/show/NCT01107886>. Accessed November 29, 2011.
 49. Merck & Co., Inc. Sitagliptin cardiovascular outcome study (0431-082 AM1) (TECOS). <http://www.clinicaltrials.gov/ct2/show/NCT00790205>. Accessed November 29, 2011.
 50. Boehringer Ingelheim Pharmaceuticals. CAROLINA: cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes. <http://www.clinicaltrials.gov/ct2/show/NCT01243424>. Accessed November 29, 2011.
 51. Ahren B, Gomis R, Standl E, et al. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2004;27:2874-2880.
 52. Bristol-Myers Squibb Company. FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM148109.pdf>. Accessed November 29, 2011.
 53. Engel SS, Williams-Herman DE, Golm GT, et al. Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. *Int J Clin Pract*. 2010;64:984-990.
 54. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled diabetes. *Ann Intern Med*. 2005;143:559-569.
 55. Blevins T, Han J, Nicewarner D, et al. Exenatide is non-inferior to insulin in reducing HbA1c: an integrated analysis of 1423 patients with type 2 diabetes. *Postgrad Med*. 2010;122:118-128.
 56. Gallwitz B, Bohmer M, Segiet T, et al. Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. *Diabetes Care*. 2011;34:604-606.
 57. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia*. 2007;50:259-267.
 58. Norris SL, Lee N, Thakurta S, et al. Exenatide efficacy and safety: a systematic review. *Diabet Med*. 2009;26:837-846.
 59. 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.
 60. Okerson T, Yan P, Stonehouse A, et al. Effects of exenatide on systolic blood pressure subjects with type 2 diabetes. *Am J Hypertens*. 2010;23:334-339.
 61. Klonoff DC, Buse JB, Nielsen LL, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic bio-markers in patients with type 2 diabetes treated for at least 3 years. *Curr Med Res Opin*. 2008;24:275-286.
 62. Davies MJ, Donnelly R, Barnett AH, et al. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. *Diabetes Obes Metab*. 2009;11:1153-1162.
 63. Davies MJ, Kela R, Khunti K, et al. Liraglutide—overview of the pre-clinical and clinical data and its role in the treatment of type 2 diabetes. *Diabetes Obes Metab*. 2011;13:207-220.
 64. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet*. 2009;373:473-481.
 65. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. *Diabetes Care*. 2009;32:84-90.
 66. 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.
 67. 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.
 68. 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.
 69. 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.
 70. Pratley RE, Nauck M, Bailey T, et al; 1860-LIRA-DPP-4 Study Group. 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.
 71. Lane W, Weinrib S, Rappaport J, et al. The effect of liraglutide added to U-500 insulin in patients with type 2 diabetes and high insulin requirements. *Diabetes Technol Ther*. 2011;13:592-595.
 72. Henry RR, Fonseca VA, Tabanera Y, et al. Liraglutide, a once-daily human GLP-1 analogue, reduces systolic blood pressure with minimal impact from weight-loss in subjects with type 2 diabetes. *Endocr Rev*. 2010;31 (suppl 1):S2240.
 73. Plutzky J, Garber A, Toft AD, et al. Meta-analysis demonstrates that liraglutide, a once-daily human GLP-1 analogue, significantly reduces lipids and other markers of cardiovascular risk in type 2 diabetes. *Diabetologia*. 2009;52:S299-S300.
 74. Bergenstal R, Daniels G, Mann J, et al. Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial: rationale and study design. *Diabetes*. 2011;60(suppl 1):A612-A613.
 75. Amylin Pharmaceuticals. Exenatide Study of Cardiovascular Event Lowering trial (EXSCEL): a trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus. <http://www.clinicaltrials.gov/ct2/show/NCT01144338>. Accessed November 29, 2011.
 76. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide—the FDA's review of a new antidiabetic therapy. *N Engl J Med*. 2010;362:774-777.
 77. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab*. 2011;13:7-18.
 78. Madsbad S, Kielgast U, Asmar M, et al. An overview of once-weekly GLP-1 receptor agonists—available efficacy and safety data and perspectives for the future. *Diabetes Obes Metab*. 2011;13:394-407.