REVIEW

Incretin-Based Therapies: Focus on Effects Beyond Glycemic Control Alone

Jaime A. Davidson

ABSTRACT

Type 2 diabetes is associated with a high prevalence of comorbidities resulting from hypertension, dyslipidemia, and hyperglycemia. Inadequate management of these risk factors will eventually result in detrimental health consequences. Thus, the effect of a drug on factors such as weight, cardiovascular (CV) risk factors, and adherence is important to consider. A review was undertaken of the recent medical literature describing the extraglycemic characteristics of the two classes of incretin-based therapies—glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors. PubMed searches were performed to identify published data on incretin therapies that describe their effects on CV risk factors, CV events, and factors related to medication adherence. The maintenance or loss of weight associated with the use of GLP-1RAs and DPP-4 inhibitors is well described in the medical literature. These agents also appear to be associated with a modest decrease in blood pressure and a reduced risk of CV events. In addition, several characteristics of incretin therapies may improve rates of medication adherence, such as generally favorable tolerability profiles (particularly with DPP-4 inhibitors), the availability of formulations that simplify treatment regimens, and a low risk for hypoglycemia. The literature on incretin therapies describes a number of clinical characteristics that are relevant to the management of extraglycemic risk factors. As part of a holistic treatment strategy, these properties constitute important considerations for tailoring therapy to individual patients with type 2 diabetes.

Keywords: Dipeptidyl peptidase-4; Glucagon-like peptide-1; Incretin therapies; Type 2 diabetes

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INTRODUCTION

The high prevalence of comorbidities associated with type 2 diabetes exerts a significant socioeconomic burden on the US healthcare system. For example, diabetes is the leading cause of end-stage renal disease [1]. One retrospective study of >91,000 patient records reported an incidence of chronic kidney disease of ~15% in individuals with both type 2 diabetes and hypertension, compared with only 1.1% and 1.5% in patients with diabetes or hypertension alone, respectively [2]. Diabetes is also a leading cause of blindness in US adults. A recent pooled analysis of data from more than 23,000 patients reported that the prevalence of diabetic retinopathy may be as high as 35% [3]. Approximately 7 million patients with diabetes had retinal disease in 2005, and it has been predicted that this number will increase to 19 million by the year 2050 [4].

Against this background, physicians must take into consideration a complex set of variables when discussing treatment options with patients who have type 2 diabetes. In the current era of medical research, the clinical and pharmacologic characteristics of antidiabetic agents are being evaluated in greater depth than just a few decades ago and, as a result, our understanding of these medicines now extends far beyond their role in glycemic control.

While the effects of a drug on factors such as weight, cardiovascular (CV) risk, and medication adherence were once considered secondary to the efficacy of the drug for reducing blood glucose, now many patients and physicians consider such factors when choosing medications to meet agreed upon therapy goals. In this regard, incretin-based therapies have demonstrated a favorable set of clinical characteristics that are well suited to this type of holistic approach to the management of type 2 diabetes. The aim of this article is to review the recent medical literature describing such characteristics for the two classes of incretin-based therapies—glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors.

MATERIALS AND METHODS

PubMed searches were conducted for literature describing the extraglycemic effects of incretin-based therapies. The following terms were used to search among English language publication titles in the PubMed database: (incretin[ti] OR glp-1[ti] OR exenatide[ti] OR liraglutide[ti] OR (glucagon[ti] AND peptide[ti])); (dipeptidyl[ti] OR dpp-4[ti] OR sitagliptin[ti] OR saxagliptin[ti] OR vildagliptin[ti] OR linagliptin[ti]); (tolerab* OR [effect* AND side OR adverse]) AND (discontin* [ti] OR adher* [ti] OR non-adher* [ti] OR nonadher* [ti] OR complian* [ti]); (weight [ti] OR bmi [ti] OR body mass [ti]); (cardiovasc*[ti] OR lipid*[ti] OR pressure[ti] OR cholesterol[ti]). When needed for more targeted searches, results were restricted to clinical trials or were expanded to title/abstract using the appropriate PubMed limiters. Initial literature searches were conducted from 30 August to 18 December 2012, with additional searches on specific topics as required to update the review. No date restrictions were specified. PubMed abstracts were qualitatively reviewed and individually selected based on their relevance to the review topic. Articles that were considered relevant based on an assessment of an abstract were obtained and further evaluated, with attention to references cited for further resources.

CARDIOVASCULAR RISK

Weight

In obese individuals, the risk of developing type 2 diabetes is elevated ∼sevenfold relative to those with normal body weight [5]. The presence of diabetes and obesity elevates the risk (individually and in combination) of numerous complications and comorbidities, including CV disease, hypertension, and stroke. Cardiovascular disease alone is responsible for ∼65% of deaths in patients with type 2 diabetes [6]. Therefore, given that most individuals with type 2 diabetes are obese, weight reduction is a key strategy to reduce morbidity and mortality.

The Action for Health in Diabetes (Look AHEAD) study was designed to provide a quantitative assessment of the association between modest weight reduction in overweight/obese patients with type 2 diabetes and the incidence of severe CV events (heart disease, stroke, and CV-related deaths). The study began in 2001 and was scheduled to complete in 2014. In the first year of Look AHEAD, patients participating in intensive lifestyle intervention ($N = 2,503$) lost ∼7–9% of body weight [7]. This was associated with a 25–33 mg/dL decrease in serum triglycerides (TG) and a 5–8 mmHg reduction in systolic blood pressure (SBP). As a reference for the clinical relevance of this magnitude of blood pressure (BP) reduction, in the United Kingdom Prospective Diabetes Study (UKPDS), each 10 mmHg reduction in SBP was associated with an 11% reduced risk of myocardial infarction, a 12% reduction in the risk of any diabetes complications, and a 13% reduction in the risk for microvascular disease [8]. In addition, the 7–9% reduction in body weight in Look AHEAD was also associated with a

2–5 mg/dL increase in high-density lipoprotein cholesterol (HDL-C), and a 4–7 mg/dL decrease in low-density lipoprotein cholesterol (LDL-C) [7]. For reference, note that a 23-mg/dL decrease in total cholesterol (TC) can reduce the risk of coronary heart disease by up to 30% [9–12]. Thus, significant improvements in CV risk factors may be achieved through modest reductions in body weight.

The Look AHEAD study was terminated early based on the results of an interim analysis [13]. It was determined that the rate of severe CV events in the treatment group (intensive lifestyle intervention) was not significantly different from that in the control group (diabetes support and education) and that given the 11-year study duration, this was not likely to change. Although the intensive lifestyle intervention has been discontinued, patients will continue with follow-up as a means of assessing any potential long-term effects of the intervention, for example, through metabolic memory (the 'legacy effect'). The results of the long-term follow-up of patients participating in Look AHEAD will help to more specifically inform treatment decisions related to lifestyle intervention.

Clinically significant weight loss is potentially within the pharmacologic effect of GLP-1RAs (Fig. 1). In clinical trials, weight loss with exenatide [14–17] and liraglutide have generally ranged from 2% to 4% of initial body mass (Table 1) [14–54]. The Liraglutide Effect and Action in Diabetes (LEAD) trials showed that up to one-quarter of patients lost >5% of body weight over 26 weeks [55]. Patients participating in clinical trials of linagliptin, saxagliptin, and sitagliptin have typically shown a −1% to +1% change in body weight (Table 1; Fig. 1), and thus these agents are considered weight-neutral. Considering the important benefits of weight

loss, and conversely the increased health risks associated with further weight gain, these features of incretin therapies represent an important consideration for patients with (or at risk for developing) CV disease. This is in contrast to several other classes of therapy; for example, the use of insulin, sulfonylureas (SUs), and thiazolidinediones is associated with weight gain. Although it has not been demonstrated that the magnitude of weight gain associated with any antihyperglycemic therapy leads to a significant increase in the risk of CV disease/events, it nevertheless remains an essential goal of therapy for patients with type 2 diabetes to achieve some degree of weight loss—or at the very least to prevent further weight gain [56]. In settings in which agents that induce weight gain must be

used (for example, as the result of driving factors such as tolerance or medication history), the concomitant use of incretin-based therapies should be considered as a means to minimize additional weight gain.

In this regard, several studies have demonstrated the weight-mitigating effects of incretin therapies when used in conjunction with insulin. As a recent example, Lind et al. [57] examined the effects of adding exenatide ($n = 21$) or liraglutide ($n = 40$) to the antihyperglycemic regimen of patients taking insulin and permissibly other oral antidiabetic drugs (OADs). Most patients (69%) were taking metformin and multiple daily insulin injections (53%); fewer were taking a basal insulin only (34%) or an SU (2%). After a mean of 7 months, weight decreased by 7 kg (15 lbs; 6% of initial
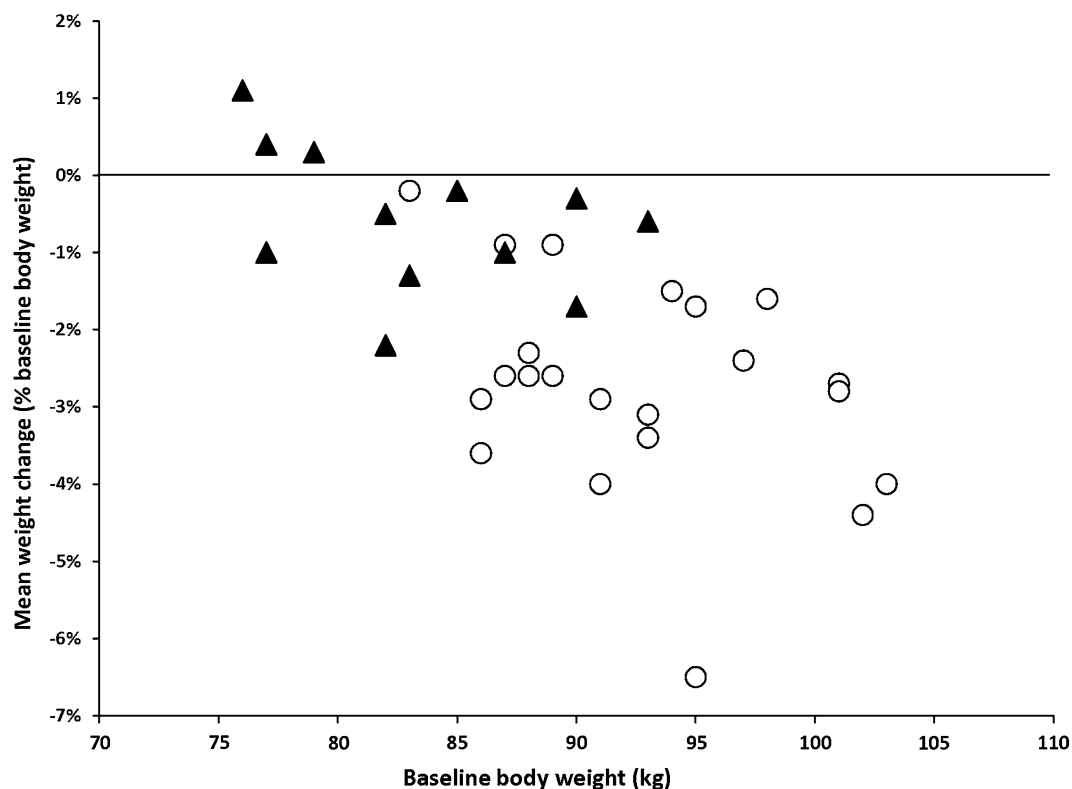
Fig. 1 Weight change with incretin therapies as a function of baseline body weight. Data correspond to the studies described in Table 1. Data shown for DPP-4 inhibitors (solid triangles) and GLP-1RAs (open circles). GLP-1RA glucagon-like peptide-1 receptor agonists, DPP-4 dipeptidyl peptidase-4

Table 1 Weight changes with incretin therapies

	Study	Treatment	Baseline weight (kg)	Mean weight change in kg (% body weight)
GLP-1RA				
Liraglutide	LEAD-1:	Lira 1.8 mg + SU	83	−0.2 (−0.2)
	Marre et al. [18]	Rosi + SU	81	+2.1 (+2.6)
	LEAD-2:	Lira 1.8 mg + Met	NR	−2.8
	Nauck et al. [19]	Placebo comparator		−1.5
		SU comparator		+1.0
	LEAD-3:	1.8-mg Lira monotherapy	93	With nausea >7 days: −3.4 (−3.6)
	Garber et al. [20]			With nausea ≤7 day: −2.3 (−2.4)
		SU comparator	93	With nausea >7 days: −1.4 (−1.5)
				With nausea ≤7 day: +1.2 (+1.3)
	LEAD-4:	Lira 1.8 mg + Met + TZD	NR	−2.0
	Zinman et al. [21]	Placebo comparator		+0.6
	LEAD-5:	Lira 1.8 mg + Met + SU	86	−1.8 (−2.1)
	Russell-Jones et al. [22]	Placebo comparator	86	−0.42 (−0.49)
		Insulin glargine comparator	85	+1.6 (+1.9)
	LEAD-6:	Lira 1.8 mg	93	−3.2 (−3.4)
	Buse et al. [23]	Exe comparator	93	−2.9 (−3.1)
Exenatide	DURATION-1:	Exe once weekly	103	−4.1 (−4.0)
	Buse et al. [24]	Exe twice daily switch to once weekly	102	−4.5 (−4.4)
	DURATION-2:	Exe once weekly	89	−2.3 (−2.6)
	Bergenstal et al. [25]	Sita 100 mg	87	−0.8 (−0.9)
		Pio	88	+2.8 (+3.0)
	DURATION-3:	Exe once weekly	91	−2.6 (−2.9)
	Diamant et al. [26]	Insulin glargine	91	+1.4 (+1.5)
	DURATION-4:	Exe once weekly	88	−2.0 (−2.3)
	Russell-Jones et al. [27]	Met	86	−2.0 (−2.3)
		Pio	86	+1.5 (+1.7)
		Sita	89	−0.8 (−0.9)
	DURATION-5:	Exe once weekly	97	−2.3 (−2.4)
	Blevins et al. [28]	Exe twice daily	94	−1.4 (−0.5)
	Apovian et al. [29]	Exe 10 μg + Met + SU + LM	95	−6.2 (−6.5)
		Placebo + Met + SU + LM	95	−4.0 (−4.2)
	Bunck et al. [30]	Exe 10–20 μg	91	−3.6 (−4.0)
		Insulin glargine comparator	92	+1.0 (+1.1)
	Buse et al. [15]	Exe 10 μg + SU	95	−1.6 (−1.7)
		Placebo comparator		
	Davies et al. [31]	Exe 10 μg	101	−2.7 (−2.7)
		Insulin glargine	98	+3.0 (+3.1)
	DeFronzo et al. [16]	Exe 10 μg + Met	101	−2.8 (−2.8)
		Placebo comparator		
	Gallwitz et al. [32]	Exe 10 μg + Met	NR	−4.1
		Insulin aspart 70/30 + Met		+1.0
	Glass et al.[a] [33]	Exe twice daily + Met + SU	87	−2.3 (−2.6)
		Insulin (glargine or aspart) + Met + SU	86	+1.8 (2.1)
	Heine et al. [14]	Exe 10 μg	88	−2.3 (−2.6)
		Insulin glargine comparator	88	+1.8 (+2.0)
	Kendall et al. [17]	Exe 10 μg + Met + SU	98	−1.6 (−1.6)
		Placebo comparator		

Table 1 continued

	Study	Treatment	Baseline weight (kg)	Mean weight change in kg (% body weight)
	Klonoff et al. [34]	Exe + multiple[b]: 3 years	NR	BMI <30: −3.9
				BMI ≥30: −5.8
	Moretto et al. [35]	Exe 10 μg	86	−3.1 (−3.6)
		Placebo comparator	86	−1.4 (−1.6)
	Nauck et al. [36]	Exe 10 μg + Met + SU	86	−2.5 (−2.9)
		Insulin aspart + Met + SU as comparator	83	+2.9 (+3.5)
DPP-4 inhibitors				
Sitagliptin	Raz et al. [37]	Sita 100 mg	93	−0.6 (−0.6)
		Placebo	90	−0.7 (−0.8)
	Aschner et al. [38]	Sita 100 mg	85	−0.2 (−0.2)
		Placebo	85	−1.1 (−1.3)
	Nauck et al. [39]	Sita 100 mg + Met	90	−1.5 (−1.7)
		Glipizide + Met	90	+1.1 (+1.2)
	Wainstein et al. [40]	Sita 50 mg + Met 500 mg FDC twice daily	83	−1.4 (1.7)
		Pio	81	+3.0 (3.7)
	Srivastava et al. [41]	Sita	NR	−0.1
		SU	NR	+0.5
	Pérez-Monteverde et al. [42]	Sita + Met	83	−1.1 (−1.3)
		Pio	82	+3.4 (+4.1)
	Reasner et al. [43]	Sita 50 mg + Met 1,000 mg FDC twice daily	NR	−1.6
		Met	NR	−1.6
Saxagliptin	Rosenstock et al. [44]	Saxa 5 mg	90	−0.23 (−0.3)
		Placebo	93	−1.03 (−1.1)
	Chacra et al. [45]	Saxa 5 mg + SU	76	+0.8 (+1.1)
		Placebo + SU	76	+0.3 (+0.4)
	Jadzinsky et al. [46]	Saxa 5 mg + Met	82	−1.8 (−2.2)
		Met monotherapy	83	−1.6 (−1.9)
	DeFronzo et al. [47]	Saxa 5 mg + Met	87	−0.87 (−1.0)
		Placebo + Met	87	−0.92 (−1.1)
Linagliptin	Del Prato et al. [48]	Lina 5 mg	79	NR; NS
		Placebo	79	NR; NS
	Taskinen et al. [49]	Lina 5 mg + Met	82	−0.4 (−0.5)
		Placebo + Met	83	−0.5 (−0.6)
	Owens et al. [50]	Lina 5 mg + SU	77	+0.3 (+0.4)
		Placebo + SU	77	−0.1 (−0.1)
	Haak et al. [51]	Lina 5 mg	79	+0.2 (+0.3)
		Met 1,000 mg twice daily	80	−0.5 (−0.6)
		Lina 2.5 mg + Met 1,000 mg twice daily	77	−0.8 (−1.0)
		Placebo	77	−0.7 (−0.9)
	Gomis et al. [52]	Pio	83	+1.3 (1.6)
		Lina 5 mg + Pio	78	+2.7 (3.5)
	Gomis et al. [53][c]	Lina 5 mg + multiple: 2 years	79	−0.03 (0.04)
	Gallwitz et al. [54]	Lina 5 mg + Met	86	−1.4 (1.6)
		SU + Met	87	+1.3 (1.5)

BMI body mass index, *Exe* exenatide, *FDC* fixed-dose combination, *GLP-RA* glucagon-like peptide-1 receptor agonist, *Lina* linagliptin, *Lira* liraglutide, *LM* lifestyle management, *Met* metformin, *NR* not reported, *NS* non-significant, *Pio* pioglitazone, *Rosi* rosiglitazone, *Sita* sitagliptin, *Saxa* saxagliptin, *SU* sulfonylurea, *TZD* thiazolidinedione

[a] Glass et al.: pooled data from Nauck et al. [36] and Heine et al. [14]

[b] Klonoff et al.: patients from Buse et al. [15], DeFronzo et al. [16], and Kendall et al. [17], continued in an extension study

[c] Gomis et al.: patients from Del Prato et al. [48], Taskinen et al. [49], Owens et al. [50], and Gomis et al. [52] continued in an extension study

body weight), and daily insulin doses decreased by 39 units. The mean glycosylated hemoglobin (HbA1c) decreased from 8.9% to 7.9%. Taken together, the results of this study demonstrated that the combined use of incretin therapy and insulin is more advantageous than insulin alone. This strategy was equally effective for glycemic control, lower doses of insulin were needed and, rather than gaining weight as would be expected with initiation of insulin therapy, patients actually lost weight.

Blood Pressure

The effects of incretin therapies on other CV risk factors and on immediate cardiac outcomes are subjects of ongoing research, but evidence to date has demonstrated a favorable effect on several variables. For example, in an analysis of six trials, including more than 2,000 patients treated with exenatide, the mean placebo-adjusted SBP reduction was −2.8 mmHg [58]. Patients with baseline SBP ≥130 mmHg showed mean SBP reductions of −3.8 mmHg. A more recent meta-analysis by Vilsbøll et al. [59] reviewed the literature on twice-daily exenatide and liraglutide, demonstrating that SBP reductions in published studies range from 1 to 6 mmHg. This included analysis of the pivotal trials of exenatide [24–28] and liraglutide [18–23], in which the mean SBP was typically recorded as a secondary outcome. Comparable or better results may be expected with once-weekly exenatide; in a trial that compared once-weekly exenatide with the original twice-daily formulation, the mean SBP reductions from baseline were −2.9 and −1.2 mmHg, respectively [28]. Multiple meta-analyses have recently been conducted in review of the CV effects of DPP-4 inhibitors [60–64]. In these reports, the mean change in

SBP was generally in the range of 1–4 mmHg for linagliptin [61] and saxagliptin [60].

The mechanism by which these agents reduce BP is not yet clear. One retrospective analysis combined data from three exenatide trials ($N = 686$ patients) to assess the relationship among SBP reduction, weight loss, and glycemic control [65]. This study utilized a method of internal referencing, whereby patients were categorized into groups according to those achieving HbA1c reduction and weight loss greater or less than the weighted mean. Patients above the weighted mean for HbA1c reduction, weight loss, or both had, respectively, 30%, 61%, and 88% higher chances of lowering SBP <130 mmHg (compared with those below the mean). This suggests that blood glucose-lowering and weight loss may contribute independently to BP-lowering, with synergism when both factors are combined; however, at this time, such interpretation is still preliminary and requires further study as other unknown factors may also contribute. One recent study in 61 patients receiving exenatide for a mean of 1.4 years evaluated the correlation between weight loss and SBP reduction and concluded that the BP reduction was not significantly associated with weight loss [66].

Lipids

One study reported a significant improvement in fasting TC and HDL-C with exenatide therapy [67], which is consistent with an earlier report that demonstrated significant improvements in fasting TG and TC, HDL-C, and LDL-C with this agent [34]. Postprandial measurements have also shown lipid improvement with exenatide; Meier et al. [68] reported a non-significant increase in postprandial TG (−0.023 mmol/L) versus

baseline, compared with a significant +0.33 mmol/L increase in the placebo group. Other exenatide studies have shown no significant change in lipid parameters [15, 16, 29, 35]. Liraglutide therapy has been shown to improve TC and LDL-C and to significantly decrease fasting TG by up to 36 mg/dL [69, 70]. One of the pivotal liraglutide phase 3 studies (LEAD-6) directly compared exenatide and liraglutide, including analysis of lipid parameters [23]. Relative to exenatide, liraglutide led to a similar reduction in TC (−0.2 versus −0.1 mmol/L), LDL-C (−0.5 versus −0.4 mmol/L), and TG (−0.4 versus −0.2 mmol/L).

A recent meta-analysis of the literature on DPP-4 inhibitors specifically evaluated the effects of these agents on lipid parameters [64]. This analysis concluded that treatment with DPP-4 inhibitors was associated with significant improvements in TG (−0.1 mmol/L), but not HDL-C. Although an overall significant reduction in TC (−0.2 mmol/L) was determined, evaluation of DPP-4 inhibitors on an individual basis suggested that the US-approved agents had no significant effect on TC. This report did not include data on linagliptin, although another meta-analysis by Johansen et al. [61] included an assessment of lipid data reported in published linagliptin studies. Linagliptin reduced TG by 0.1 mmol/L from baseline (P value not reported) and did not appear to influence TC.

CARDIOVASCULAR EVENTS

The effect of DPP-4 inhibitors on the occurrence of CV events has been retrospectively evaluated by meta-analysis [60–63]. Monami et al. [62] reviewed 33 placebo-controlled studies of DPP-4 inhibitors and, as part of their analysis, included an assessment of CV events. These

authors reported an odds ratio (OR) for CV events of 1.04 (0.70–1.55) versus placebo for patients taking a DPP-4 inhibitor. Meta-analyses of individual DPP-4 inhibitors have demonstrated ORs for CV events of 0.43 [95% confidence interval (CI) 0.23, 0.80] for saxagliptin [60], and 0.34 (95% CI 0.16, 0.70) for linagliptin [61]. While not drawn from prospective studies powered to specifically evaluate such outcomes, these ORs represent a significant reduction in the risk of CV events and merit further investigation.

To this end, several prospective clinical trials are currently in progress. The CAROLINA study (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes; NCT01243424) has a targeted enrollment of ~6,000 patients with type 2 diabetes. With a planned duration of up to 8 years, this study will investigate the long-term impact of treatment with linagliptin on CV morbidity and mortality in patients with type 2 diabetes who are at an elevated CV risk and compare the outcome against treatment with the SU glimepiride. Comparable trials are also in progress for other DPP-4 inhibitors. The TECOS study (Trial Evaluating Cardiovascular Outcomes With Sitagliptin; NCT00790205) will compare the impact of usual care with and without add-on sitagliptin on CV outcomes in an estimated 14,000 patients followed for up to 5 years. SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction; NCT01107886) enrolled 16,496 diabetic patients with either established CV disease or at high risk for CV events, and compared a primary composite CV endpoint in patients taking saxagliptin for up to 5 years versus placebo [71]. Data show that the primary non-inferiority safety endpoint has been met; saxagliptin does not increase CV events

compared with placebo when added to the patient's standard-of-care regimen (with or without other antidiabetic medications). Since results did not show a decrease in the risk of overall CV events with saxagliptin versus comparators, the trial did not meet the primary efficacy objective of superiority [72].

When fully available, these studies will provide long-term data on the CV effects of DPP-4 inhibitors in patients with type 2 diabetes. These data will address an important need in the medical literature, particularly considering that some data have suggested an exacerbation of CV risk with the more commonly prescribed SUs, especially when used in combination with metformin. For example, in the UKPDS study, the early addition of metformin to an SU was associated with a 96% increase in diabetes-related deaths compared with continued SU use [73]. Later studies provided additional data that described this association. One study reported an adjusted 43% increase in total mortality and an adjusted 70% increase in CV mortality in patients taking an SU versus metformin [74]. A retrospective review of the UK General Practice Research Database showed that the combination of metformin and SU increased mortality by 24–61% ($P = 0.001$) and heart failure by 18–30% relative to metformin monotherapy [75]. Meta-analyses on this subject have also described adverse outcomes associated with SU-metformin combination therapy [76, 77].

Considering the high prevalence of CV mortality in patients with diabetes, the importance of medications with favorable CV safety profiles cannot be understated. At the very least, medications for the treatment of diabetes should be neutral if not actively preventive with regard to CV risk factors and outcomes. The current literature on incretin-based therapies is promising in this respect and,

in the coming years, we can expect the CV literature to provide a more detailed view of these and other antidiabetic therapies.

SUSTAINABILITY OF THE PRESCRIBED REGIMEN

Discontinuation of adherence to prescribed therapies remains an important obstacle to achieving treatment goals in patients with type 2 diabetes. Intolerability is the most common factor leading to medication discontinuation [e.g., hypoglycemia, gastrointestinal (GI) disturbances], although other factors such as natural history, complex daily regimens, out-of-pocket costs, and declining efficacy may also play a role. For example, a survey-based study of 2074 patients with type 2 diabetes found that over a 2-week period, 57% of participants reported symptoms of hypoglycemia, 28% reported constipation or diarrhea, and 21–26% experienced headaches, water retention, or weight gain. The important finding from this study in relation to adherence was that each additional tolerability issue was associated with a 28% increase in medication non-adherence [78].

Hypoglycemia

Hypoglycemia is one of the more common tolerability/side effect issues leading to medication discontinuation. Incretin-based therapies induce the secretion of insulin from pancreatic tissue only in the presence of elevated blood glucose (e.g., 'glucose-dependent insulin secretion'); these agents therefore pose a low risk for hypoglycemia. A recent claims database analysis specifically examined hypoglycemic events in more than 212,000 patients taking OADs from January 1999 through September 2008 [79]. The rates

of hypoglycemia were significantly increased in patients taking SU compared with those not receiving SU [hazard ratio, 1.58 (1.51, 1.65)], were significantly decreased in patients taking a DPP-4 inhibitor versus those not taking a DPP-4 inhibitor [OR 0.79 (0.65, 0.95)], and were not significantly different between patients taking metformin versus those not taking metformin. Importantly, the incidence of at least one hypoglycemic event was associated with medication discontinuation. In this study, medication discontinuation was determined as a gap of $\geq$30 days within a 6-month interval following the hypoglycemic event. Compared with patients with no hypoglycemic events, in those who had one or more episodes, the OR for medication discontinuation was 1.26 (1.22, 1.31). Given the low rates of hypoglycemia associated with incretin-based therapies, these agents may serve to improve medication adherence in patients with intolerability issues related to hypoglycemia.

Medication Adherence Rates

Although the specific metric of medication adherence may vary across studies, the consensus perspective evident in the literature is that a large proportion of patients do not continue to take the antihyperglycemic medications prescribed by their physicians for the long term. Two of the largest studies exploring medication adherence utilized the Veterans Administration (VA) database. In a study of records from more than 56,000 veterans with type 2 diabetes taking OADs (years 2000–2002), 23% of patients were categorized as non-adherent, as defined by a medication possession ratio (MPR) <80% after 1 year [80]. A later re-evaluation of the VA database (years 2005–2007) demonstrated a somewhat higher rate of non-adherence (30%)

using the 1-year MPR ($N = 444,418$) [81]. One study that reviewed the medical literature for data on adherence (years 2000–2005) reported similar results, showing that 42% of patients had a 1-year MPR <80% (35 studies) [82]. Based on only these results, one might conclude that approximately one-third of patients with type 2 diabetes can be expected to take less than 80% of their prescribed medication. A more recent study of patients taking exenatide ($n = 3,262$) compared adherence rates with patients taking insulin glargine ($n = 3,038$) [83]. Using the 1-year MPR, 32% of patients taking exenatide and 42% taking glargine were categorized as non-adherent.

Although there are no studies that specifically evaluate adherence rates in patients taking DPP-4 inhibitors, several publications have reviewed the discontinuation and adverse event (AE) rates of these agents in clinical trials. For example, Karagiannis et al. [84] reported that AE-related discontinuation rates in trials of DPP-4 inhibitors (nine sitagliptin studies, six vildagliptin studies, three saxagliptin studies, and one linagliptin study) were lower than in patients taking metformin monotherapy (relative risk 0.69, 0.51–0.94). Recently, Singh-Franco et al. [85] reported another meta-analysis that included an assessment of discontinuation rates in five published and four unpublished trials of linagliptin. The overall rate of AEs in this analysis was not significantly different from placebo, nor were withdrawals due to AEs significantly different between linagliptin (2.4%) and placebo (3.1%), which is consistent with the results of another meta-analysis of linagliptin trials [85, 86]. A pooled analysis of data from sitagliptin trials ($N = 10,246$ patients with type 2 diabetes) showed that the rates of discontinuation due to AEs were similar in patients receiving

sitagliptin versus comparators (4.4% versus 4.5%, respectively) [87]. These results are consistent with data from meta-analyses and systematic reviews showing an acceptable safety and tolerability profile for DPP-4 inhibitors [63, 84].

Within the incretin-mimetics class, the most commonly occurring tolerability issue stems from GI side effects (e.g., nausea, abdominal discomfort, and vomiting) [88]. These may occur in up to 30% of patients, although the incidence of GI symptoms usually declines within the first month of therapy [89–91]. No studies have yet been published that describe adherence rates in patients taking the recently approved once-weekly formulation of exenatide. However, provided that the efficacy, AE profile, and rate of discontinuation of the once-weekly formulation is not significantly different from the older twice-daily formulation [92], it may be expected that patient adherence to the once-weekly formulation may be improved as a result of its simpler dosing schedule.

Lastly, it has been shown that simplification of the dosing schedule can lead to significant improvements in medication adherence using fixed-dose combination (FDC) therapies. For example, a retrospective database review recently showed that patients with diabetes who were categorized by their physicians as adherent to their prescribed antihyperglycemic medication regimen were five times more likely to be taking an FDC than those who were described by physicians as non-adherent [93]. Initiation of treatment with an FDC is associated with greater adherence when compared with patients receiving the same medications as 'loose-pill combination.' Authors of an analysis of seven studies that compared these strategies concluded that adherence was 13% greater in patients who started on FDCs [94]. Cheong et al. [95] demonstrated that when patients already taking loose-pill combinations ($N = 14,762$) were switched to a comparable FDC ($N = 7,570$), adherence increased by 12%.

Each of the four Food and Drug Administration-approved DPP-4 inhibitors has been developed with an FDC formulation (combination with metformin). Thus, when considered along with their excellent tolerability profiles, the availability of FDCs with these agents proffers a means of increasing medication adherence in patients with type 2 diabetes.

CONCLUSION

Diabetes is a multifactorial disease with a high prevalence of comorbidities resulting from hypertension, dyslipidemia, and hyperglycemia. Inadequate management of these three physiologic risk factors in patients with type 2 diabetes will eventually lead to a debilitating loss of function in multiple organ systems. Therefore, each of these risk factors must be brought under control as early as possible following diagnosis, and their control must be maintained throughout the course of the disease. Emphasis in the medical literature has tended to focus on glycemic control, in part due to the rapid expansion of the number of antidiabetic agents that require evaluation of efficacy. However, in recent years, it has become evident that key pharmacologic characteristics of antihyperglycemic medications reach beyond an effect on blood glucose. The assessment of new medications for the treatment of type 2 diabetes is now more comprehensive than in the earlier decades of OAD research. The GLP-1RA and the DPP-4 inhibitors are the first classes of new antidiabetes treatments that needed

demonstration of CV safety as a regulatory approval requirement. Moreover, long-term safety trials are in progress, with results from the first studies showing no increase in overall CV risk [72, 96]. Thus, we have at our disposal a wealth of information describing the range of actions of glucose-lowering medications in patients with type 2 diabetes.

Guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists (AACE) stress an individualized approach to care, which includes consideration of patient preferences, medication cost, potential class-related side effects, and the effects of treatments on body weight and hypoglycemia risk [56, 97]. In the AACE algorithm, GLP-1RA and DPP-4 inhibitors are recommended after metformin based on their therapeutic profiles indicating few AEs or possible benefits [97]. For GLP-1RA, added benefits include weight loss, improvement in BP, and a decrease in inflammatory markers. The side effect profile for GLP-1RAs, however, can be difficult for some patients because of the potential for nausea, and even vomiting. Patients also may be resistant to an injectable therapy. For DPP-4s, benefits include oral administration with good patient acceptance and an excellent tolerability profile, resulting in few patient requests to switch therapy. When discussing therapy options, a patient-centered communication style focused on the patient's foremost problems and how they are feeling physically is important [98]. Clinicians can use practical terms about how incretin therapy options address patient concerns, such as fear of weight gain with add-on therapy. The underlying mechanisms of incretin-based therapies may represent a novel approach to the management of type 2 diabetes, given that these agents may act through multiple signaling pathways to effect changes not only in glucose

homeostasis, but possibly in other physiologic processes as well. For example, there is some evidence that GLP-1 receptors may have a direct influence in BP regulation and other cardiac functions [99]. In addition, whether GLP-1RAs and DPP-4 inhibitors have a direct effect on blood lipids seems an unanswered question, with some studies reporting null and others significant results. However, in the near future, we may expect a clearer understanding of these extraglycemic effects of incretin therapies and, for the time being, our task is to tailor best practices to fit the current evidence.

The synthesis resulting from this review of the literature yields two main conclusions about the extraglycemic effects of incretin therapies. In addition to their well-known influence on the maintenance or loss of weight, the use of GLP-1RAs and DPP-4 inhibitors appears to be associated with a modest decrease in BP and a reduced risk for CV events. Secondly, several characteristics of incretin therapies may improve rates of medication adherence such as the availability of formulations that simplify treatment regimens (e.g., once-weekly exenatide, DPP-4/metformin FDCs), a low risk for hypoglycemia, and generally favorable tolerability profiles, particularly with DPP-4 inhibitors.

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