

## Liraglutide: A Review of its Use in the Treatment of Diabetes Mellitus

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**Abstract:** Among the new therapeutic options for type 2 diabetes care, the incretin-based treatments are considered particularly promising. Two classes of drugs have been developed, GLP-1 receptor agonists and DPP-IV inhibitors, that respectively mimic or prolong the action of the human GLP-1, key-hormone in the glucose homeostasis maintenance.

Liraglutide is a GLP-1 analogue recently approved by the European Medicine Agency (EMA). Efficacy and safety of liraglutide have been tested—in monotherapy and in combination with one or two other antidiabetic treatments—within a comprehensive program of six phase 3 randomized trials (LEAD 1–6), plus three extension phases and several meta-analyses. In the different LEAD studies, the maximum dose of 1.8 mg/day of liraglutide produced after 26 weeks a decrease in HbA1c levels of 1.0%–1.5%, a reduction in fasting blood glucose by about 30 mg/dl, a decrease in body weight of 1–3 Kg, low rates of hypoglycemia, and additional benefits on cardiovascular risk factors. Transient nausea was the most common side effects. Patients treated with liraglutide 1.8 mg had a likelihood from 2 to 11 times greater to achieve one of the two clinically relevant composite endpoints examined (HbA1c < 7%/SBP < 130 mmHg/no weight gain or HbA1c < 7%/no weight gain/no hypoglycemia) as compared with any other placebo/active drugs.

Incretin-based therapy has been currently approved for use as add-on therapy in T2DM patients not adequately controlled on maximum doses of metformin, sulfonylureas, TZDs, or their combination. However, if data on long-term efficacy and safety of these drugs will be confirmed, GLP-1 receptor agonists and especially liraglutide could represent an early strategy to delay disease progression and reduce the burden of diabetes and its complications.

**Keywords:** type 2 diabetes, incretin-mimetics, liraglutide

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*Clinical Medicine Reviews in Vascular Health* 2010:2 11–20

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## Introduction

Maintaining an adequate metabolic control remains a challenge in many patients with type 2 diabetes.<sup>1</sup>

Current American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) treatment guidelines recommend metformin as the first-line anti-hyperglycemic drug for patients with type 2 diabetes.<sup>2-3</sup>

When the first-line treatment with metformin fails within some years from the treatment initiation,<sup>1</sup> the recommended add-on treatment options (sulfonylureas, glitazones and basal insulin) can lead to significant side effects, often causing a delay in therapy intensification.<sup>4</sup> In particular, the fear of hypoglycaemia<sup>5</sup> and weight gain<sup>6</sup> associated with most of the available treatments are among the main causes of clinical inertia.<sup>4</sup>

Prolonged sub-optimal metabolic control is recognized to be responsible for a raising in the risk of serious microvascular and macrovascular complications.<sup>7-9</sup> The importance of an early, intensified approach to metabolic control has been clearly demonstrated by the long-term results of the UKPDS study.<sup>10</sup> This study showed that the benefits of tight blood glucose control extended well beyond the end of the study and persisted after over 10 years (legacy effect), translating into a significant reduction in the risk of microvascular and macrovascular complications, as well as in overall mortality.

On the other hand, several recent trials have shown that lowering of blood glucose to near-normal levels in individuals with a long diabetes duration and elevated cardiovascular risk does not produce the expected benefits on macrovascular complications and mortality.<sup>11,12</sup> In particular, in the ACCORD trial, targeting a HbA1c level < 6.0% was associated with a 22% excess mortality as compared with the standard-therapy group.<sup>11</sup> The excess mortality was principally attributed to the high risk of hypoglycemic episodes related to intensive therapy. An association between hypoglycemia and mortality was also documented in the VADT trial.<sup>12</sup>

As a whole, these data strongly emphasize the need for new early treatments to improve diabetes outcomes.

Among the new therapeutic options, the incretin-based treatments are considered particularly promising.

Two classes of drugs were developed, such as agonists of the incretins-glucagon-like peptide-1 (GLP-1) receptor (exenatide, liraglutide, taspoglutide, AVE0010, albiglutide) and inhibitors of the dipeptidyl peptidase-4 (DPP-IV) (vildagliptin, sitagliptin, alogliptin, saxagliptin).<sup>13-19</sup>

To date, exenatide, sitagliptin, and vildagliptin have been approved by both US and European regulatory agencies for treating T2DM, while saxagliptin has been recently approved by U.S. Food and Drug Administration. The aim of this paper is to review current evidence on the GLP-1 receptor agonist liraglutide, as of November 6th, 2009 it has received marketing authorization in Europe and is available in some European countries. However the drug is so far not approved in other parts of the world.

## Incretin-Based Treatments

GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) play a crucial role in maintaining the normal balance between insulin and glucagon levels. Secretion of these hormones is stimulated by the intestinal absorption of glucose, and leads to an increase in insulin secretion and a decrease in glucagon secretion.<sup>20</sup>

Evidence that incretin activity is impaired in type 2 diabetes<sup>21,22</sup> has prompted investigations on incretin-based therapies. Two classes of drugs were developed, based on a different mechanism of action: GLP-1 mimetics and inhibitors of DPP-IV, that is the enzyme which inactivates native incretins,<sup>14,15</sup> that respectively mimic or prolong the action of the human GLP-1 hormone, playing an important role in the glucose homeostasis maintenance.

Incretin-mimetics,<sup>13-19</sup> like endogenous hormones, stimulate insulin secretion in a glucose-dependent manner and inhibit glucagon release. Besides a reduction in HbA1c and blood glucose levels, a number of additional effects have been described, including a decreased risk of hypoglycaemia<sup>23</sup> in comparison with other classes of diabetes drugs,<sup>5</sup> enhanced satiety, reduced food intake, and weight loss or neutrality. The reasons for the increased satiety are the slowed gastric emptying and a central mechanism.<sup>24,25</sup> Furthermore, a positive effect on pancreatic beta-cell morphology and function, as well as a reduction in



cellular apoptosis have also been described *in vitro*<sup>26–28</sup> and *in vivo*.<sup>29,30</sup>

The direct inhibition of the glucagon release and the paracrine inhibitory effect exerted by the increased insulin secretion, coupled with the preservation of beta-cell function, represent important factors that may contribute to the long-term control of post-prandial hyperglycemia.<sup>15</sup>

In a meta-analysis<sup>31</sup> evaluating the efficacy and safety of GLP-1 mimetics and DPP-IV inhibitors, incretins lowered HbA1c compared with placebo (weighted mean difference,  $-0.97\%$  [95% confidence interval {CI},  $-1.13\%$  to  $-0.81\%$ ] for GLP-1 analogues and  $-0.74\%$  [95% CI,  $-0.85\%$  to  $-0.62\%$ ] for DPP-IV inhibitors) associated with neutral or beneficial effect on body weight and were non-inferior to other hypoglycemic agents. As for the tolerability, treatment with GLP-1 mimetics was associated with gastrointestinal side effects, that tend to attenuate after a few weeks; treatment with DPP-IV inhibitors was associated with a higher frequency of nasopharyngitis, upper respiratory infections, and headache. However, this meta-analysis did not include the most recent data from phase III clinical trials on liraglutide. A more recent meta-analysis on GLP-1 receptor agonists<sup>32</sup> included more complete information on liraglutide. GLP-1 receptor agonists determined a significant improvement of HbA1c in comparison with placebo (weighted mean difference  $-1.0\%$  ( $-1.1$ ,  $-0.8$ ),  $p < 0.001$ ), with a low risk of hypoglycaemia; in placebo controlled trials, liraglutide determined a slightly higher reduction in HbA1c as compared to exenatide. Also this meta-analysis did not include all updated results of randomized clinical trials contributing to the introduction on the market of liraglutide.

Therefore, this review aims to provide a complete overview on liraglutide, as documented in clinical pharmacology studies and in phase III clinical trials assessing its therapeutic efficacy and safety in T2DM patients.

## Liraglutide

Liraglutide (Novo Nordisk, Bagsvaerd, Denmark) is a high-homology analogue of human GLP-1. It was obtained through two modifications in the 30-amino acids chain of native GLP-1, i.e. the replacement of

Lys 34 to Arg and the addition of a C16 fatty acid at position 26 using a  $\alpha$ -glutamic acid spacer. Since only one amino acid is replaced, the resultant molecule shares 97% (36/37 amino acids) sequence identity with native human GLP-1. By contrast, exenatide, that was originally identified as a derivate of Gila monster (*Heloderma suspectum*) venom, shows a much lower homology, sharing only 53% sequence identity with native GLP-1.<sup>33,34</sup>

## Pharmacology

Liraglutide is administered as an isotonic solution by subcutaneous injection. The presence of the fatty acid chain allows liraglutide to self-associate and form heptamers at the injection site depot. The size of the heptamer and the strong self-association have been evoked as the main mechanisms underlying a delayed absorption of liraglutide from the subcutis.<sup>35</sup> Then, when liraglutide has been absorbed in the bloodstream, the fatty acid chain creates reversible binding to serum albumin increasing stability and resistance to metabolism by DPP-IV and reduces renal clearance. All these mechanisms protract the action of liraglutide, so that the half-life of liraglutide is 13 h<sup>34</sup> compared with just 1.5–2.1 min for native GLP-1 and 2.4 h for exenatide.<sup>36</sup> Due to its prolonged duration, liraglutide is suitable for once-daily dosing.

## Clinical Trials

Efficacy and safety of liraglutide as monotherapy and in combination with commonly used antidiabetic drugs were evaluated within a comprehensive phase 3 evaluation consisting of six randomized clinical trials, the “LEAD (Liraglutide Effect and Action Diabetes) program”.<sup>37,38</sup> Overall, the LEAD program involved 6500 people seen in 600 sites in 41 countries worldwide; of the patients recruited, 4445 received liraglutide.

Patients were recruited from across the continuum of disease progression to mimic as closely as possible the spectrum of patients seen in clinical practice:

- LEAD-3<sup>39</sup> was a 52-week randomized trial comparing two doses of liraglutide as monotherapy (1.2 and 1.8 mg/day) to glimepiride (8 mg daily);



- LEAD-1<sup>40</sup> was a 26-week, five-arm trial comparing three doses of liraglutide (0.6, 1.2 and 1.8 mg/day) added to glimepiride 4 mg daily compared with glimepiride 4 mg plus placebo or glimepiride 4 mg plus rosiglitazone 8 mg daily;
- LEAD-2<sup>41</sup> was a 26-week five-arm trial comparing three doses of liraglutide (0.6, 1.2 and 1.8 mg/day) added to metformin 1 g twice daily with metformin monotherapy plus placebo or metformin plus glimepiride 4 mg daily;
- LEAD-4<sup>42</sup> was a 26-week three-arm trial, where patients were titrated to metformin 1 g twice-daily and rosiglitazone 4 mg twice-daily and randomized to add liraglutide (1.2 or 1.8 mg/day) or placebo;
- LEAD-5<sup>43</sup> took into consideration the triple combination of liraglutide with metformin and sulfonylurea; once-daily liraglutide (1.8 mg) in combination with metformin 1 g twice-daily plus glimepiride 2–4 mg once-daily was compared with placebo or treatment with insulin glargine over 26 weeks;
- In LEAD-6<sup>44</sup> patients treated with metformin, sulfonylurea, or their combination were directly randomized to once-daily liraglutide 1.8 mg or twice-daily exenatide 10 microg over 26-week.

The LEAD program was completed in 2007.

Results of an extension phase for LEAD-2,<sup>45</sup> LEAD-3<sup>46</sup> and LEAD-6<sup>47</sup> studies have also been recently presented. In addition, ten meta-analyses<sup>48–57</sup> have also been conducted, pooling the results of individual trials on different parameters, such as metabolic control, blood pressure, body weight, and beta-cell function. The main results of the LEAD trials are shown in Table 1, and can be summarized as follows:

### **Efficacy on Metabolic Control** **Glycated hemoglobin**

Maximum dose of 1.8 mg/day of liraglutide produced a decrease in HbA1c levels of 1.0%–1.5% after 26 weeks in the different LEAD studies, with the maximum reduction being documented when liraglutide was administered in triple combination (Table 1). A meta-analysis<sup>49</sup> confirmed that liraglutide was more effective in reducing HbA1c levels when used as an add-on therapy rather than substituted for a prior oral antidiabetic drug. In a second meta-analysis,<sup>48</sup> treatment with liraglutide 1.8 mg was associated with a likelihood of 66% of reaching HbA1c < 7% against a likelihood of 18%–54% with any other comparator (placebo or active drugs).

**Table 1.** Summary of the results obtained in the LEAD studies.

	<b>Monotherapy</b>			<b>Double combination</b>				
	<b>LEAD 3</b>			<b>LEAD 1</b>				
	<b>Monotherapies with</b>			<b>Glimepiride plus</b>				
	Lira 1.2 mg	Lira 1.8 mg	Gli	Lira 0.6 mg	Lira 1.2 mg	Lira 1.8 mg	Rosi	Plac
Subjects randomized (N)	251	247	248	234	228	233	232	114
Completers (%)	65	70	61	91	86	89	84	73
Change in HbA1c (%)	–0.8	–1.1	–0.5	–0.6	–1.1	–1.1	–0.4	0.2
HbA1c < 7%	43	51	28	23	34	40	21	7
Change in FPG (mg/dl)	–14	–25	–5	–13	–29	–29	–16	18
Change in PPG (mg/dl)	–31	–38	–25	–	–	–	–	–
Weight Change (Kg)	–2.1	–2.5	1.1	0.7	0.3	–0.2	2.1	–0.1
Minor hypoglycemic events/person/yr	0.30	0.25	1.96	0.17	0.51	0.47	0.12	0.17
Nausea (%)	27.5	29.3	8.5	5.2	10.5	6.8	1.7	2.6



The extension phase of LEAD-2, LEAD-3, and LEAD-6 trials<sup>45–47</sup> demonstrated that the efficacy of liraglutide in terms of metabolic control was maintained after 2 years, associated with a lower risk of hypoglycemia and sustained weight loss.

### Blood glucose

The different LEAD trials consistently documented that liraglutide reduced fasting and post-prandial blood glucose (Table 1). A meta-analysis<sup>52</sup> of the different LEAD trials documented that adding liraglutide 1.8 mg to existing therapy reduced fasting blood glucose by 36 mg/dl. Post-prandial blood glucose was reduced on average by 40 mg/dl (Table 1).

### Effect on beta-cell health

GLP-1 preserves beta-cell morphology and function and reduces cellular apoptosis. A meta-analysis<sup>51</sup> evaluated the comparative effect of liraglutide vs. glimepiride on metabolic control in relation to baseline beta-cell function. This meta-analysis showed that liraglutide is effective across the continuum of beta-cell activity, but was even more effective in subjects with baseline comparatively well-preserved beta-cell function, which may imply greater clinical

benefits when liraglutide is initiated early. A final study<sup>57</sup> summarized the impact of liraglutide treatment on beta-cell function in the LEAD 1–5 studies. An increase in HOMA-B between 28% and 34% from baseline vs. comparator was demonstrated with liraglutide 1.8 mg.

### Cardiovascular Protection

In addition to glycometabolic benefits, positive effects of liraglutide on traditional cardiovascular risk factors such as weight loss, blood pressure reduction, and lipid profile improvement were found.

### Effect on satiety and body weight

While DPP-IV inhibitors are neutral on body weight, GLP-1 mimetics are associated with enhanced satiety, reduced food intake, and weight loss. Weight loss is independent from nausea,<sup>58</sup> and is associated with a reduction in waist circumference and visceral adiposity (LEAD 2),<sup>41</sup> well established cardiovascular risk factors. The use of liraglutide is associated with a decrease in body weight of 1–3 Kg after 26 weeks (Table 1). The weight reduction is greater in individuals with higher BMI at baseline, reaching 4.5 Kg in those with BMI > 35 Kg/m<sup>2</sup>.<sup>59</sup> The greatest weight loss

LEAD 2 Metformin plus					Triple combination						Head-to-head	
					LEAD 4 Metformin rosiglitazone plus			LEAD 5 Metformin glimepiride plus			LEAD 6 Metformin and/or sulphonylurea plus	
Lira 0.6 mg	Lira 1.2 mg	Lira 1.8 mg	Gli	PI	Lira 1.2 mg	Lira 1.8 mg	PI	Lira 1.8 mg	PI	Glar	Lira 1.8 mg	Exe
242	241	242	244	122	178	178	177	232	115	234	233	231
86	82	79	86	61	86	75	68	–	–	–	86	81
–0.7	–1.0	–1.0	–1.0	0.1	–1.5	–1.5	–0.5	–1.3	–0.2	–1.1	–1.1	–0.8
28	35	42	36	11	58	54	28	52	15	44	54	43
–20	–29	–31	–23	7	–27	–27	–9	–29	9	–32	–29	–11
–31	–41	–47	–45	–11	–47	–49	–14	–	–	–	–	–
–1.8	–2.6	–2.8	1.0	–1.5	–1.0	–2.0	0.6	–1.8	–0.4	1.6	–3.2	–2.9
–	0.03	0.09	1.23	0.13	0.38	0.64	0.17	1.2	1.0	1.3	1.9	2.6
11	16	19	3	4	29	40	8.6	13.9	3.5	1.3	25	28





was observed when liraglutide was administered in combination with metformin.<sup>41</sup> The about 3 Kg reduction in body weight was maintained after 2-year from treatment initiation.<sup>45</sup> In the head-to-head comparison (LEAD 6),<sup>44</sup> liraglutide produced a greater weight loss (−3.2 Kg) than exenatide (−2.9 Kg). In the extension phase of the LEAD-6 trial (from week 26 to week 40), a switch from exenatide to liraglutide was associated with a further reduction in body weight (−0.9 Kg).<sup>47</sup>

### Blood pressure

A meta-analysis of the LEAD studies specifically explored the effect of liraglutide on systolic blood pressure (SBP).<sup>50</sup> Overall, the average reduction in SBP was of 2.5 mmHg. Reduction in SBP was sustained over 26 weeks, and was greater in patients with high SBP at baseline, reaching 11.4 mmHg in individuals with SBP values between 140 and 190 mmHg at baseline. Liraglutide also reduced diastolic blood pressure by 2–3 mmHg. The reduction in blood pressure was already observed after 2 weeks treatment, even before any significant weight loss, and is probably related to the natriuretic effect and improvement of the endothelial function associated with the use of liraglutide.<sup>58</sup>

### Lipid profile

In a short-term study, liraglutide 1.9 mg/die reduced levels of triglycerides by 22% as compared with placebo.<sup>58</sup> In LEAD 6,<sup>44</sup> reductions of triglycerides and free fatty acids values were significantly greater with liraglutide than with exenatide, while increases in very low-density lipoprotein cholesterol were smaller in the liraglutide group than in the exenatide one. In LEAD 4,<sup>42</sup> a reduction in LDL cholesterol (−10 mg/dl) and triglycerides (−34 mg/dl) levels was found in the liraglutide group, while in the placebo group LDL-cholesterol levels were decreased by 3 mg/dl and triglycerides were decreased by 11 mg/dl. A recent meta-analysis<sup>56</sup> demonstrated that liraglutide significantly improved levels of total cholesterol, LDL-cholesterol, free fatty acids, and triglycerides after 26 weeks, while less consistent results were obtained with all other comparators (rosiglitazone, glimepiride, insulin glargine, exenatide, and placebo). The influence of liraglutide on lipid profile is probably related to weight loss and decreased food intake, rather than to direct mechanisms.

### Safety

Liraglutide was generally well-tolerated. Due to the induction of insulin secretion in a glucose-dependent way, the lower risk of hypoglycemic events associated with incretin-based therapies was also confirmed for liraglutide. The incidence of minor hypoglycemic ranged from 0.09 to 1.9 events/person × year for patients treated with liraglutide 1.8 mg (Table 1), with the highest incidence documented when liraglutide was administered in triple combination with metformin and glimepiride. In the LEAD 6,<sup>44</sup> the incidence rate of minor hypoglycemia was of 2.6 events/person/year in the exenatide group vs. 1.9 events/person/year in the liraglutide group. In the extension of the LEAD-6 trial, switching from exenatide to liraglutide was characterized by a decreased rate of minor hypoglycemia (from 2.6 to 1.3 events/patient/year).<sup>47</sup>

The most common side effect of liraglutide was transient nausea, affecting between 6.8% and 40% of patients treated with 1.8 mg of liraglutide, with substantial variation according to the concomitant oral agents administered (Table 1). The incidence of nausea declined within a few weeks and was attenuated by the 3-week titration scheme.<sup>39</sup> In the head-to-head comparison with exenatide, the incidence of nausea was similar initially, but it was less persistent with liraglutide.<sup>44</sup>

Antibodies to liraglutide were found in less than 15% of patients, as compared to a maximum of 50% of patients treated with exenatide. However, the presence of antibodies did not influence glycemic control nor had a clinical impact.<sup>38</sup>

After exenatide was approved by FDA, a concern emerged that GLP-1 mimetics might increase the risk of pancreatitis. During studies of liraglutide, nine cases of pancreatitis were reported in the liraglutide development program, of whom 8 in the liraglutide group and one in the non-liraglutide group. The rate of pancreatitis was 2.2 in liraglutide-treated subjects and 0.6 in non-liraglutide subjects per 1,000 years of subject exposure.<sup>60</sup>

Long-term safety needs to be further investigated, particularly with reference to thyroid tumors. In fact, thyroid C-cell neoplastic changes have been observed in rodents but not in humans.<sup>60</sup> In the LEAD program, calcitonin concentrations were not affected by the treatment with liraglutide.



## Clinically Relevant Composite Endpoints

In two recent meta-analyses, the achievement of two clinically relevant composite endpoints was evaluated. The simultaneous achievement of HbA1c < 7%, SBP < 130 mmHg, and no weight gain was obtained by 26% of patients treated with liraglutide 1.8 mg, as compared with 3%–16% with placebo/active drugs.<sup>48</sup> The second composite target (HbA1c < 7%, no weight gain, and no hypoglycemia) was achieved by 39% of patients treated with liraglutide 1.8 mg, and 32% of those treated with 1.2 mg as compared with 6%–24% with placebo/active drugs.<sup>54</sup> Patients treated with liraglutide 1.8 mg had a likelihood from 2 to 11 times higher than other comparators to achieve one of the composite endpoints examined (Table 2).

## Japanese Studies

In Japan, 72%–8% of patients are treated with sulphonylureas and a large proportion has BMI levels below 25 kg/m<sup>2</sup>. In addition to LEAD studies, efficacy and safety of liraglutide were tested in the peculiar Japanese population with type 2 diabetes. To this purpose, three trials were performed. In the first study<sup>61</sup> four different doses (0.1, 0.3, 0.6 or 0.9 mg once daily) of liraglutide in monotherapy were compared with placebo in 226 subjects treated for 14 weeks. Liraglutide doses significantly reduced HbA1c by 0.79%, 1.22%, 1.64% and 1.85%, respectively, without weight gain or hypoglycemia. In the second trial,<sup>61,62</sup> 400 subjects were randomly assigned to be treated with liraglutide 0.9 mg once-daily or glibenclamide 1.25–2.5 mg once or twice daily for 24 weeks. The reduction in HbA1c levels was of 1.74 and 1.18%, respectively.

Body weight decreased on average by –0.92 Kg in the liraglutide group, while it increased by +0.99 Kg in the glibenclamide group. In addition, the proinsulin: insulin ratio was significantly improved in favor of liraglutide. The 28-week extension of the trial showed further reduction in HbA1c levels (–1.48% with liraglutide vs. –0.95% with glibenclamide). The third 24-week trial (followed by a 28-week open-label extension) compared liraglutide 0.6 mg or 0.9 mg in combination with sulphonylurea versus sulphonylurea as monotherapy;<sup>63</sup> reduction in HbA1c levels was of 1.09, 1.30 and 0.06%, respectively.

## New Perspectives on Incretin-Mediated Cardiovascular Protection

Recently, a variety of potentially beneficial effects of native GLP-1 and incretin-mimetics on factors affecting cardiovascular risk have been described in animal and human studies.<sup>64–72</sup> Some of these effects were confirmed also with liraglutide. In particular, a significant decrease in some markers of cardiovascular risk, such as PAI-1 and BNP levels, was observed following treatment with liraglutide in a study involving 165 patients with type 2 diabetes, randomized to either placebo or 0.65 mg, 1.25 mg or 1.9 mg liraglutide for 14 weeks.<sup>73</sup> There was a non-significant, but dose-dependent, reduction in hs-CRP levels. There were no treatment effects on levels of adiponectin, leptin, IL-6 and TNF- $\alpha$ .

The reduction in levels of BNP and hsCRP with liraglutide was recently confirmed in a meta-analysis of the LEAD studies.<sup>56</sup>

Experimental studies have shown that GLP-1 has salutary effects on post-ischemic contractile dysfunction

**Table 2.** Comparative odds ratio for composite endpoints.

Comparison	HbA1c < 7.0%, no weight gain, no minor or major hypoglycemia (Odds ratio favoring liraglutide)	HbA1c < 7.0%, SBP < 130 mmHg, no weight gain (Odds ratio favoring liraglutide)
Liraglutide 1.8 mg vs. TZD	10.3***	11.3***
Liraglutide 1.8 mg vs. SU	7.3***	4.3***
Liraglutide 1.8 mg vs. glargine	3.7***	6.1***
Liraglutide 1.8 mg vs. exenatide	2.0**	2.1**

\*\*\*p < 0.001; \*\*p < 0.01.



in animal models of ischemia and reperfusion<sup>74</sup> or in perfused isolated, isovolumic rat heart preparations.<sup>75</sup> GLP-1 infusion also reduced infarct size and myocardial ischemia/reperfusion injury in animal models.<sup>76,77</sup> The protective effects on ischemic and reperfusion injury, mediated by inhibition of apoptosis, have been documented also with exenatide<sup>78</sup> and liraglutide.<sup>79</sup> In particular, in the study by Noyan-Ashraf et al<sup>80</sup> male C57BL/6 mice were treated twice daily for 7 days with liraglutide or saline followed by induction of MI. Survival was significantly higher in liraglutide-treated mice. Liraglutide reduced cardiac rupture and infarct size and improved cardiac output.

## Conclusions

Ideally, any glucose-lowering drug should possess the following properties: long-term efficacy, low risk of hypoglycemia, cardiovascular protection, neutral effect on body weight or weight loss, long-term safety and tolerability. So far, none of the available drug classes fully satisfy all these requirements. Existing evidence suggests that the novel drug class of GLP-1 mimetics, particularly liraglutide, can address most of the unmet needs of diabetes treatment and greatly help in overcoming the barriers leading to clinical inertia and to a delay in the use of insulin.

These drugs have been currently approved for use as add-on therapy in T2DM patients not adequately controlled on maximum doses of metformin, sulfonylureas, TZD, or their combination. GLP-1 receptor agonists could be particularly beneficial in patients whose weight significantly increases cardiovascular risk or those experiencing frequent hypoglycemic episodes. If confirmed in long-term studies, the ability of this drug class to preserve beta-cell function would also broaden their indication to include early phases of the disease, and even diabetes prevention.<sup>80</sup>

In conclusion, if data on long-term efficacy and safety of these drugs will confirm their promising profile, GLP-1 receptor agonists could represent an important therapeutic option, not only as add-on treatments in case of secondary failure, but even more as an early strategy to delay disease progression and reduce the burden of diabetes and its complications.

## Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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