

The Potential Role of GLP-1 Analogues in Cardiovascular Disease Outcomes

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ABSTRACT

Diabetes prevalence is increasing, according to the International Diabetes Federation report in 2013, 382 Millions have diabetes, and the number is expected to rise beyond 592 million by 2035, an increase of approximately 55%. Type2 Diabetes Mellitus (T2DM) is associated with Obesity, Dyslipidemia, and Hypertension. Hypertension plays a major role in the development of Cardiovascular Disease (CVD). The prevalence of hypertension is higher in people with T2DM than the general public. Macro vascular complications are still the primary cause of death in patients with T2DM. Glucagon like peptide-1 receptor agonists (GLP1-RAs) are a new class of Injectable Anti-diabetes Agents (IADA) that provides blood glucose control with weight reduction ability, systolic blood pressure reduction and a noticeable improvement of lipid profile. GLP1-RAs have proven non-inferiority the CVD outcomes. In this review I will discuss the different available members of GLP1-RAs, modes of action and the role of some GUT hormones in the regulation of glucose metabolism. I will also review landmark trials of different types of GLP1-RAs, cost effectiveness and their potential role in the protection from cardiovascular disease, including evidence on weight reduction, HbA1c reduction, systolic blood pressure control and improvement of both lipid and glycemic profiles.

Keywords: GLP-1 receptor agonist; Cardiovascular benefits; HbA1c; Weight loss; CVD Trials

INTRODUCTION

Type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and hypertension are major players in the development of cardiovascular disease (CVD). Macro vascular complications are still the primary cause of death in T2DM. MI and Stroke both contribute to 75% of death in type 2 diabetic patients. Death from myocardial infarction (MI) and stroke is 2-4 times greater than death from coronary artery disease (CAD) in non-diabetic patients.

The GLP1-RAs class has grown in the last decade with several agents available for use in the market. Since the efficacy and tolerability, dosing frequency, administration requirements, and cost may vary between agents within the class, each agent may offer unique advantages and disadvantages. The purpose of this review is to provide an analysis of current head-to-head comparative data of GLP-1 RAs and their cardio protective effects, blood glucose control, weight loss, systolic blood pressure reduction and improvement of lipid profile.

MECHANISM OF ACTION

Exogenous GLP-1 RA have been more recently considered as a

good choice for treating patients with diabetes it works by “incretin effect” [1] intestinal component accounts for 50%- 70% of the total insulin secreted after an oral glucose load [2]. Incretin Effect: The higher insulin response to an oral glucose load compared to the same amount of glucose when administered by the intravenous route (Figure 1). This response depends on gut hormones called Incretins [3]. Incretins are insulinotrophic hormones (increase insulin secretion) after eating- two main types are recognized (Table 1):

- Glucagon like peptide (GLP-1 receptor agonist)
- Glucose Dependant Insulinotrophic Polypeptide (GIP)

GLP-1: Enhances binding to GLP-1 receptor and inhibit it from binding to DDP4 (the enzyme responsible for Incretin degradation). GLP-1 level is normal in normal individuals and type 2 DM, however, GLP-1 is reduced in type 2 DM which result in an equal response of oral glucose to intravenous glucose (Figure 2). A state called: loss of Gastro Intestinal Glucose Disposal (GIGD) [4] (Table 2).

MODE OF ACTION

GLP-1 receptors are available in many part of the human body

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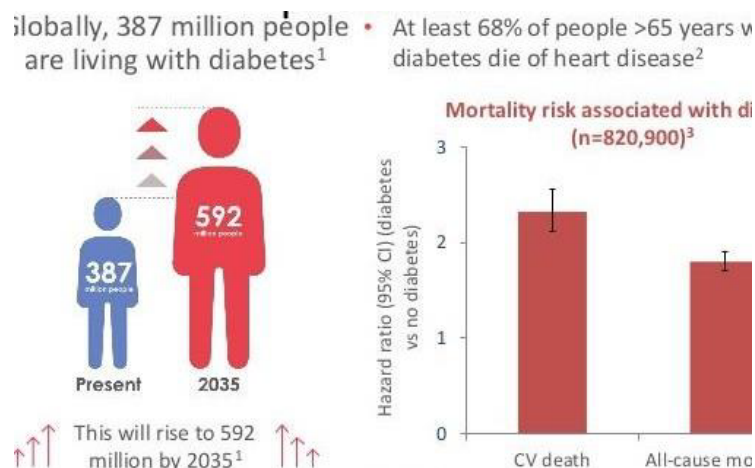


Figure 1: The increase in type 2DM and cardiovascular death.

Table1: Different Types of GLP-1.

| Drug | Brand Name | Dosing Frequency | US FDA Approval Status | EMA approval status | Phase III clinical trial program |
|--------------|---------------------------------|------------------|---------------------------------------|---------------------------|----------------------------------|
| Exenatide | Byetta | Twice daily | Approved 28 April 2005 | Approved 20 November 2006 | AMIGO |
| Liraglutide | Victoza | Daily | Approved 25 January 2010 | Approved 30 June 2009 | LEAD |
| Exenatide | Bydureon | Weekly | Approved 26 January 2012 | Approved 17 June 2011 | DURATION |
| Lixisenatide | Lyxumia® (Europe) | Daily | Submitted Withdrawn 12 September 2013 | Approved 1 February 2013 | GetGoal |
| Albiglutide | Tanzeum® (US) Eperzan® (Europe) | Weekly | Approved 15 April 2014 | Approved 23 January 2014 | HARMONY |
| Dulaglutide | Weekly | Approved 2015 | Approved | AWARD | Weekly |

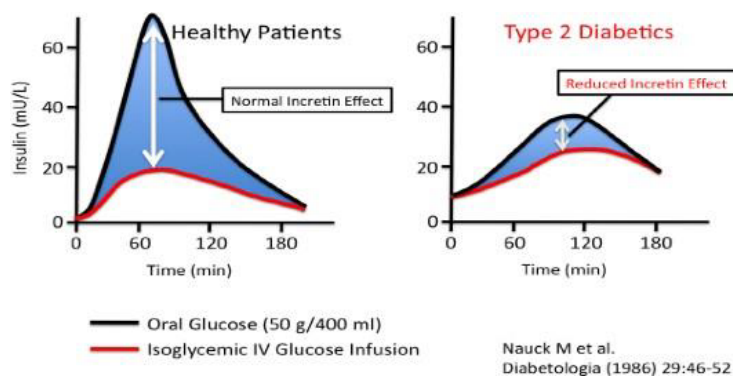


Figure 2: Diabetes and Incretin effect.

which allow the GLP-1 hormone to exert its functions and effects, reducing body weight, systolic blood pressure, HbA1c and lipid profile (Figure 3)

In the Brain: GLP-1 decreases appetite, increase satiety and energy production. Gastro-intestinal Tract (GIT); decrease gastric emptying, motility and increase in gastric acid secretion.

In the Pancreas: GLP-1 stimulates insulin secretion in a blood glucose dependent manner hence decreasing B cell over function, enhancing Beta-cell survival rate, decreasing B- cell apoptosis and preserving B-Cell mass.

In the Liver: GLP-1 decreases hepatic gluconeogenesis and glycogenolysis, decreasing hepatic glucose output.

In the Adipose tissue: GLP-1 increases the triad of lipolysis, free fatty acid synthesis and glucose uptake by adipocytes.

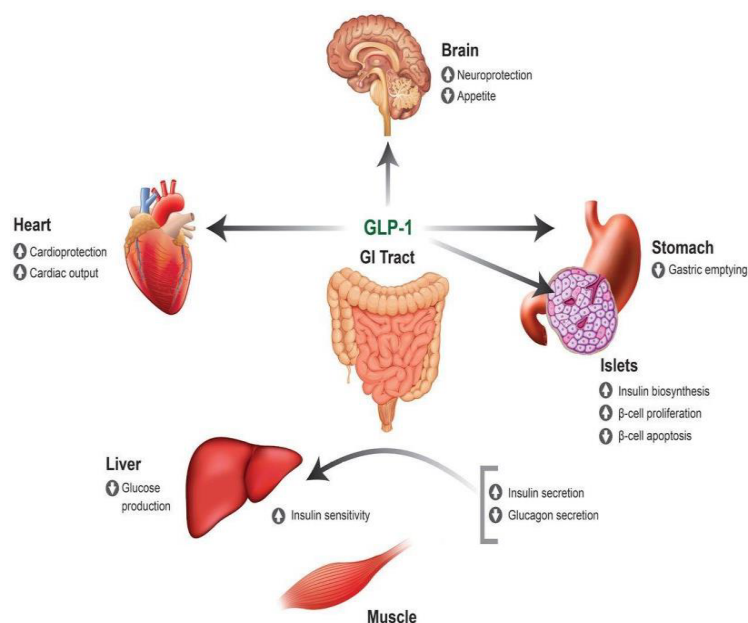
In the Muscle: GLP-1 Increases glycogen production and glucose oxidation. These actions are in favor of weight reduction, decrease in hyperinsulinemia and increase in insulin sensitivity, offering an indirect cardiovascular protection. GLP-1 has a direct CVD protective effect through its action on both the heart and kidney.

In the Kidney: GLP-1 has a Natriuretic effect.

In the Heart: GLP-1 receptors were found in human and animal (mouse) cardiac tissue. In the human coronary artery endothelial cells (HCAEC) and in human umbilical vein endothelial cells (HUVEC). GLP-1R works on cardiac tissue by binding to adenyl cyclase inducing CAMP. The CAMP- GLP-1R complex induces cardiac muscle contractility without increase in intra cellular calcium in cardiac myocytes. Decrease in blood pressure by inducing vasodilatation and natriuresis. The decrease in systolic

Table 2: Glucagon-like peptide 1 receptor agonists (GLP-1 RAs): a comparison of common adverse effects in head-to-head trials.

| Study | Active comparators | Nausea | Vomiting | Diarrhea | Injection-site reactions |
|------------|------------------------|------------------|-----------------|-----------------|--------------------------|
| DURATION-1 | Exenatide 10 µg BID | 50/145 (34.5%) | 27/145 (18.6%) | 19/145 (13.1%) | 17/145 (11.7%) |
| | Exenatide 2 mg QW | 39/148 (26.4%) | 16/148 (10.8%) | 20/148 (13.5%) | 33/148 (22.3%) |
| LEAD-6 | Exenatide 10 µg BID | 65/232 (28.00%) | 23/232 (9.90%) | 28/232 (12.10%) | 21/232 (9.1%) |
| | Liraglutide 1.8 mg QD | 60/235 (25.50%) | 14/235 (6.00%) | 29/235 (12.30%) | 21/235 (8.9%) |
| DURATION-5 | Exenatide 10 µg BID | 43/123 (35.00%) | 11/123 (8.90%) | 5/123 (4.10%) | 16/123 (13%) |
| | Exenatide 2 mg QW | 18/129 (14.00%) | 6/129 (4.70%) | 12/129 (9.30%) | 13/129 (10%) |
| DURATION-6 | Lixisenatide 20 µg QD | 71/276 (25.7%) | 30/276 (10.9%) | 16/276 (5.8%) | 1/276 (0.4%) |
| | Exenatide 10 µg BID | 78/318 (24.50%) | 32/318 (10.10%) | 33/318 (10.40%) | 27/318 (8.5%) |
| GetGoal-X | Lixisenatide 20 µg QD | 111/316 (35.10%) | 42/316 (13.30%) | 42/316 (13.30%) | 5/316 (1.6%) |
| | Exenatide 10 µg BID | 78/318 (24.50%) | 32/318 (10.10%) | 33/318 (10.40%) | 27/318 (8.5%) |
| HARMONY-7 | Albiglutide 50 mg QW | 111/316 (35.10%) | 42/316 (13.30%) | 42/316 (13.30%) | 5/316 (1.6%) |
| | Liraglutide 1.8 mg QD | 40/404 (9.90%) | 20/404 (5.00%) | 60/404 (14.90%) | 52/404 (12.9%) |
| AWARD-1 | Dulaglutide 1.5 mg QW | 119/408 (29.20%) | 38/408 (9.30%) | 55/408 (13.50%) | 22/408 (5.4%) |
| | Dulaglutide 0.75 mg QW | 78/279 (28.00%) | 47/279 (16.80%) | 31/279 (11.10%) | 1/279 (0.4%) |
| | Exenatide 10 µg BID | 45/280 (16.1%) | 17/280 (6.1%) | 22/280 (7.9%) | 0/280 (0%) |
| | Placebo | 71/276 (25.70%) | 30/276 (10.90%) | 16/276 (5.80%) | 1/276 (0.4%) |
| AWARD-6 | Dulaglutide 1.5 mg QW | 61/299 (20.40%) | 21/299 (7.00%) | 36/299 (12.00%) | 1/299 (0.3%) |
| | Liraglutide 1.8 mg QD | 54/300 (18.00%) | 25/300 (8.30%) | 36/300 (12.00%) | 2/300 (0.7%) |

**Figure 3:** GLP-1 effect on different parts of the body.

blood pressure is a separate entity of GLP-1 effect unrelated to weight loss [1].

TYPES OF GLP-1

Six agents are available in the EU market but only 3 have reached the Egyptian market (Exenatide, Liraglutide and Dulaglutide). Semaglutide and once weekly Exenatide will follow soon.

Benefits of GLP_1

Benefits on weight reduction, HbA1c lowering, lipid profile, blood pressure control.

Weight reduction

Weight loss was similar between dulaglutide and exenatide twice

daily but was greater with liraglutide compared to dulaglutide (Figure 4). In the dulaglutide head-to-head comparisons with exenatide twice daily and liraglutide, GI side effects were similar between groups [5,6]. Exenatide bid & weekly, Liraglutide & Dulaglutide have the most weight reduction effect.

HbA1c lowering effect

The results of the clinical trials demonstrated significantly greater reductions in A1C with liraglutide compared to exenatide, and both GLP-1 receptor agonists caused greater reductions than those observed with sitagliptin [7]. Data regarding these four agents from published head-to-head studies suggest that Liraglutide may have the largest A1C lowering capability, followed by dulaglutide, exenatide once weekly and then exenatide twice daily (Figure 5) [8-10]. GLP-1 RA are associated with an A1c reduction of 0.5-1.5%

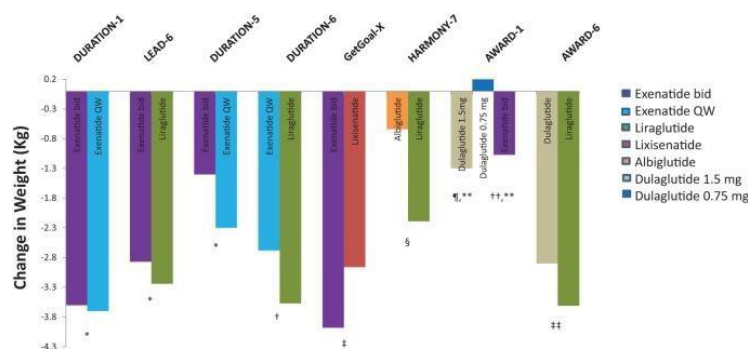


Figure 4: Benefits of GLP-1 on weight Reduction.

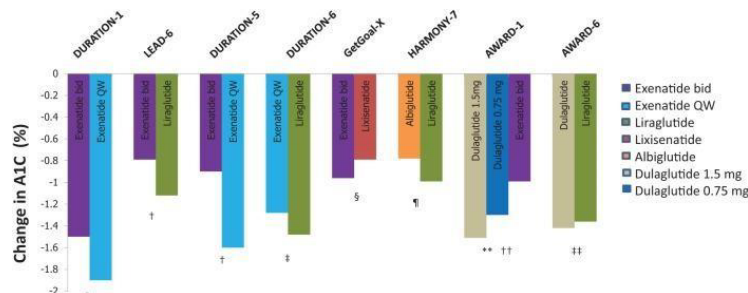


Figure 5: Benefits of GLP-1 on HbA1c.

Table 3: GLP-1RAs summary of head-to-head clinical trials.

| GLP-1 RA: Study name | No. of patients | Median follow-up (years) | % with CV disease* | % of statin use | Baseline age | Baseline HgA1c | Baseline BMI | Primary composite CV outcome HR (95% CI) | P value |
|-----------------------------|-----------------|--------------------------|--------------------|-----------------|--------------|----------------|--------------|--|---------|
| Lixisenatide: ELIXA | 6068 | 2.1 | 100% | 93% | 60.3 | 7.70% | 30.1 | 1.02 (0.89 to 1.17) | 0.81 |
| Liraglutide: LEADER | 9340 | 3.8 | 81% | 72% | 64.3 | 8.70% | 32.5 | 0.87 (0.78 to 0.97) | 0.01 |
| Semaglutide: SUSTAIN-6 | 3297 | 2.1 | 60% | 73% | 64.6 | 8.70% | 32.8 | 0.74 (0.58 to 0.95) | 0.02 |
| Exenatide QW: EXSCEL | 14752 | 3.2 | 73.10% | 74% | 62 | 8.00% | 31.8 | 0.91 (0.83 to 1.00) | 0.06 |
| Albiglutide: Harmony | 9463 | 1.6 | 100% | 84% | 64.1 | 8.70% | 32.3 | 0.78 (0.68 to 0.90) | 0.0006 |
| Dulaglutide: REWIND | 9901 | 5.4 | 31.50% | 66% | 66.2 | 7.20% | 32.3 | 0.88 (0.79 to 0.99) | 0.026 |
| Oral semaglutide: PIONEER 6 | 3183 | 1.3 | 84.70% | 85% | 66 | 8.20% | 32.3 | 0.79 (0.57 to 1.11) | 0.17 |

which is greater than 0.5-1% from DPP4 inhibitors the in head to head Duration clinical trials [11]. Exenatide weekly, Liraglutide & Dulaglutide have the most reduction effect on HbA1c (Table 3).

Lipid profile

Improving lipid profile. liraglutide once daily injection showed significant average reduction in Free Fatty Acids (FFA) by (-0.10) and Triglycerides(-0.18) average difference over 26 weeks trial over non-significant reductions by Exentide twice daily injection. Low Density Lipoprotein (LDL) showed decrease by liraglutide (1.2-1.8) do sage once daily injection between (-0.28-0.23 mmol/L), (-0.25 mmol/l) by Exentide twice daily injection, and (-0.13-0.17 mmol/l) by Exentide once weekly injection. High Density Lipoprotein (HDL) showed no significant increase with liraglutide treatment however, Exentide showed 24% HDL increase by Exentide twice daily injection. In addition Exentide once weekly injections showed improvements of HDL in combination with other drugs as Metformin, DDP4 especially Sitagliptin and Pioglitazone [12].

Blood pressure

Several trials showed the effect of exenatide and liraglutide on cardiovascular markers. The trial showed that Patients under

Exentide treatment showed decrease in both systolic and diastolic blood pressure average decrease in systolic pressure by -3.5 mmHg and by -3.3 in diastolic blood pressures. Liraglutide showed greater reduction systolic blood pressure over diastolic in a 14 week study systolic blood pressure decreased by -5.2 mm Hg to -7.2 mm Hg compared to placebo with no difference in diastolic blood pressure. And reduction rate between (-5.6,-6.7 mm Hg) in a 26 week study of liraglutide in combination with Metformin and Rosiglitazone compared to (-1.1 mm Hg) placebo and also with no difference in diastolic blood pressure [12]. In addition, trials on human and mice showed GLP-1 receptor agonists benefits in heart failure, endothelial lining and myocardial ischemia. First, heart failure clinical trials on human showed at New York Heart Association involved diabetic patients with stage 3-4 heart failure better response with Glp-1 continuous infusion over 12 weeks duration in the form of better left ventricular ejection fraction and 6 minute walk over 48 hours trial of GLP-1 infusion in non-diabetic patients with stage 2-3 heart failure. Second, endothelial lining GLP-1 promoted better endothelial lining of blood vessels through activation of PKA-P13K/AKT-endothelial nitric oxide synthase (eNOS) pathway. Third, GLP-1 role in myocardial ischemia on three trials showed:

- a. Prior coronary Artery bypass graft with 12 hrs. GLP-1 infusion results in decrease insulin demands.
- b. Prior Percutaneous Transluminal Coronary Angioplasty (PTCA) and Drug stent urgent procedure an infusion of GLP-1 specifically Exentide showed 1-3 months smaller infarct size.
- c. Post PTCA for acute myocardial infarction followed by 72 hours of GLP-1 infusion showed improvement in both left ventricular ejection fraction and wall motion [13].

Adverse Effects of GLP-1

Injection site reaction

All of the GLP-1 RA agents are administered as subcutaneous (SC) injections. Although rates of adverse effects differ between specific agents, the most common adverse effects with the GLP-1 RA class are gastrointestinal (GI) related. Exenatide once weekly can cause transient small nodules at the injection site. However, patient satisfaction data indicate that once weekly injections result in higher patient satisfaction compared with twice daily injections [11].

Hypoglycemia

The risk of hypoglycemia is low with GLP-1 RAs and rates were similar across all GLP-1 RA treatment groups in the head-to-head clinical studies; although the risk was increased with concomitant SU therapy [11]. Severe Hypoglycemia was recorded in two of our patients at ADC (AbouSeifien Diabetes Center) treated by Dulaglutide 1.5 weekly with small doses of Meglitides and the hypoglycemic episode lasted for 3 consecutive days. This raises our awareness of never initiating SUs (Sulphonylurea) or Meglitides with once weekly GLP1RAs especially in naive T2DM patients.

The GLP-1 CVD outcome trials

- a) Elixia (Lixisenatide)
- b) Leader (Liraglutide)
- c) Sustain-6 (Semaglutide)
- d) Exscel (Weekly Exenatide)
- e) Harmony (Albiglutide)
- f) Rewind (Dulaglutide)
- g) Pioneer 6 (Oral Semaglutide)

Elixia Study (Evaluation of Lixisenatide)

In ELIXA, the investigational GLP-1 receptor agonist, lixisenatide, neither reduced nor increased cardiovascular events compared with placebo. ELIXA is the first events-driven cardiovascular outcomes study to provide data for a GLP-1 receptor agonist. It was a randomized, double-blind, placebo-controlled trial that enrolled 6,068 subjects with type 2 diabetes and a recent acute coronary syndrome (ACS) event. Subjects were randomized to lixisenatide 10 mcg/d (up- or down-titrated to max 20 mcg/d) or placebo. The primary endpoint was a composite of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina. It occurred in 13.4% of the lixisenatide group vs 13.2% of the placebo group: hazard ratio=1.02; 95% CI: 0.89-1.17). The hazard ratio for the primary outcome plus heart failure hospitalization was 0.97 (95% CI: 0.85-1.10). The hazard ratio for hospitalization for heart

failure was 0.96 (95% CI: 0.75-1.23). The hazard ratio for all-cause mortality was 0.94 (95% CI: 0.78-1.13).

Glycemic control was slightly better with lixisenatide: mean post-baseline difference, -0.27% (95% CI: -0.32 to -0.22). Lixisenatide also showed small but significant benefits for urinary albumin to creatinine ratio (24% vs 24% from baseline to month 24), weight loss (-0.7 kg) and blood pressure (-0.8 mm Hg). There was no increased risk for hypoglycemia in the lixisenatide group; nausea and vomiting were, however, higher for lixisenatide-treated patients. There were no increases in pancreatitis or pancreatic cancer noted [11,14].

CONCLUSION

GLP-1 Receptor agonist was proved by the Action Control Cardiovascular Risk in Diabetes trial (ACCORD) 75% decrease death rate in patients under Exentide treatment. GLP-1 agonist benefits are multiple regarding blood glucose control in the form of reducing Hemoglobin A1c (HbA1c) by 1.1%-1.6%, reducing postprandial excursions, and decreasing weight. Its benefits on CVD in the form of weight reduction 2.4 kg versus placebo and 4.8 kg versus insulin treated patients. In addition to Improve all lipid profile elements and finally reduction in systolic blood pressure. GLP1RAs have a significant role in the therapeutic regimen of T2D with Obesity &/or Metabolic syndrome. The choice among the different members of this class depends on our clinical judgement considering the cardiovascular risk assessment, the GIT tolerance, the finance and the compliance of our patient. METFORMIN - SGLT2 - GLP 1RAs. Is a perfect triad whenever the clinical situation necessitate the use of 3 anti-diabetes agents, But which comes first?

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