# Metabolic and cardiovascular benefits of GLP-1 agonists, besides the hypoglycemic effect (Review)

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Received January 29, 2020; Accepted February 28, 2020

DOI: 10.3892/etm.2020.8714

**Abstract.** Patients with type 2 diabetes exhibit higher cardiovascular risk than normal individuals. Optimal blood glucose levels are rarely achieved in diabetic patients. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a new antidiabetic drug class with multiple metabolic effects. Some trials have evaluated their safety, but it has been recently demonstrated that this new class has cardiovascular benefits, through other mechanisms than glycemic control. The use of GLP-1RAs was associated with a significant reduction of cardiovascular and all-cause mortality, with a safe profile related to pancreatitis or thyroid cancer, as compared with placebo. This review presents the cardiovascular and metabolic benefits of GLP-1 RAs versus placebo, in patients with type 2 diabetes. Semaglutide and liraglutide demonstrated a reduction in cardiovascular events, with similar rates on cardiovascular mortality. Ongoing trials assess the cardiovascular benefits and side effects of dulaglutide treatment. Exenatide and liraglutide demonstrated the decrease of blood pressure values, weight reduction and improvement of dyslipidemia. Liraglutide induced, both *in vivo* and *in vitro*, an improvement of blood circulation, increasing the nitric oxide level and inhibiting the adhesion and procoagulant factors. Also, liraglutide demonstrated beneficial effects on cardiac remodeling after myocardial infarction, but more large trials are required. However, the international guidelines recommend using GLP-1 RAs as first-line therapy in type 2 diabetes patients with high cardiovascular risk or as first-line agents in patients intolerant to metformin.

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*Key words:* type 2 diabetes, glucagon-like peptide-1 receptor agonists, cardiovascular effect, dyslipidemia, atherosclerosis

## 1. Introduction

Diabetes represents one of the most important risk factors for cardiovascular disease; almost half of the diabetic patients die from cardiovascular disease, the leading cause of morbidity and mortality in this group of patients (1,2). The most studied cardiovascular effect of diabetes is obstructive coronary artery disease with rapid progression to ischemic heart failure (3). In terms of cardiovascular risk and prevention, diabetes is considered an equivalent of coronary heart disease. Also, diabetes induces systemic atherosclerosis, cerebrovascular disease and peripheral artery disease.

Good glycemic control in patients with diabetes may prevent cardiovascular complications. However, many of type 2 diabetes patients still have poor optimal glycemic control. Novel therapies target to increase insulin availability by direct insulin injection or indirectly, by medication that stimulates insulin release, increase the response to it, or promote glucose elimination through urinary output.

The type 2 diabetes treatment is based on lifestyle changes and pharmacologic treatment that includes many forms of insulin and oral glucose-lowering agents, such as insulin sensitizers (biguanides, thiazolidinediones), secretagogues (sulfonylureas, meglitinide derivatives), α-glucosidase inhibitors, bile acid sequestrants, and recently peptide analogs (glucagon-like peptide-1 agonists, dipeptidyl peptidase inhibitors, amylinomimetics) and selective sodium-glucose co-transporter-2 (SGLT-2) inhibitors, with glycosuric effect (2).

The increased demand for novel antidiabetic molecules is the result of high cardiovascular mortality and morbidity of diabetic patients. Given the fact that, for example, thiazolidinedione use increased the risk of heart failure, the necessity of creating more cardiovascular-safe glucose-lowering drugs developed a new field of research. Not only that the new categories of drugs demonstrated their non-inferiority in terms of cardiovascular safety compared to older molecules or placebo, but recent trials concluded that some molecules have many cardiovascular benefits, thus including them in international guidelines (2).

Although glucagon-like peptide 1 (GLP-1) mechanism could be affected in type 1 diabetes, GLP-1 RAs are not currently recommended in these patients, due to lack of evidence (4).

In this review, we will present the cardiovascular and metabolic effects of GLP-1 agonists in type 2 diabetes, beyond serum glucose control.

## 2. Mechanism of action of GLP-1 hormone and its pleiotropic effects

Multiple organ dysfunction, with macrovascular and microvascular complications, represent an effect and also a perpetuating factor in diabetes, determining hyperglycemia due to insulin resistance, hence the systemic feature of this disease (5).

Hyperglycemia produces non-enzymatic glycation of proteins, therefore inducing endothelial dysfunction, by creating an imbalance between the oxygen-derived free radicals and endothelial vasodilators. There is also a direct effect on calcium transport and lipid metabolism, leading to diabetic cardiomyopathy. Sympathetic over-expression in heart failure is responsible for increased insulin resistance, reduces insulin secretion and stimulates glucagon release, which induces hepatic gluconeogenesis (6).

The gastrointestinal tract secrets incretin hormones that stimulate insulin release, delay gastric emptying, therefore reducing appetite by inducing satiety. The incretin effect (an acronym for INtestine seCRETion INsulin) represents the higher level of insulin secretion induced by oral administration of glucose than the intravenous way, mainly due to the release of intestinal hormones. These hormones are released only in oral carbohydrates administration, but not intravenously (7). One major hormone is represented by the GLP-1 with short action (maximum two minutes), secreted by the intestinal L-cells, as rapid N-terminal degradation by the dipeptylpeptidase IV enzyme. This mechanism has created the premise of creating GLP-1 analogues resistant to enzyme inhibition (8), therefore with longer action.

On the pancreatic β-cells, GLP-1 induces regeneration, proliferation, and protection against damage by signaling pathways (7). GLP-1 receptors are not limited to the pancreas, the expression of these receptors was observed also in the gastric mucosa, renal tissue, pulmonary tissue, skin and immune cells and even in the hypothalamus, the central inhibitory effect of GLP-1 agonists on appetite (7).

Almost immediately after food ingestion, GLP-1 is secreted into the bloodstream, activates G-protein coupled receptors, increasing the intracellular cyclic adenosine monophosphate and calcium, determining glucose-dependent insulin release (5).

There are numerous circulating forms of GLP-1, but only a few were considered metabolically active, mainly because after the DPP-4 enzyme action, the truncated peptide lacked interaction with the GLP-1 receptor. This situation changed when growing evidence showed that those metabolites have multiple effects, even cardiovascular benefits (5).

GLP-1 agonists stimulate insulin secretion in a glucose-dependent manner, slow the gastric motility, improving early satiety and decreasing the glucagon level after meals, therefore having hypoglycemic effect without hypoglycemia, even after intravenous administration (7). Some GLP-1 agonists are obtained by amino acid modifications of native GLP-1, others are synthetically engineered from lizard saliva isolated peptide, exendin-4, with GLP-1 receptor activating function (5). The final purpose of creating those substances was to induce resistance to DDP-4 action, hence increasing their period of action. GLP-1 agonists are recommended especially if there is a need for weight loss and better glycemic control, aiming at both fasting and postprandial glycemia (5). The most frequent adverse symptoms are gastrointestinal ones, such as nausea, vomiting, and diarrhea.

Liraglutide, albiglutide, dulaglutide, and semaglutide can be used with no restriction related to renal impairment, they have longer half-life and one of the best immunologic tolerability profile. Exenatide and lixisenatide are exendin-4-based agonists that cross the hematoencephalic barrier with direct action on brain GLP-1 receptors and are excreted in urine (5). Table I contains a list of the most important trials with GLP-1 agonists.

## 3. Evidence of cardiovascular effects of GLP-1 agonists

A large meta-analysis demonstrated that, in type 2 diabetes with poor control with metformin and/or sulfonylurea, GLP-1 agonists (exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide) are superior to placebo and other glucose-lowering drugs, such as insulin glargine, DPP-4 inhibitor, thiazolidinedione, and sulfonylurea, in lowering glycemia (16).

Apoptosis activation in cardiac cells contributes to the development of diabetic cardiomyopathy, induced by intracellular lipid accumulation, such as saturated palmitic acids. A major role in this mechanism is represented by the transcriptional

Table I. Trials with GLP-1 agonists.

| Drug | Trials | CVD outcome trial | Year of approbation | Route of administration |
|---|---|---|---|---|
| Exenatide (9) | DURATION | EXSCEL (QW) | 2005 FDA<br>2006 EMA | Short action - subcutaneous injection b.i.d<br>Long action - once/week (QW) |
| Liraglutide (10) | LEAD | LEADER | 2009 EMA<br>2010 FDA | Long action - Subcutaneous injection o.d. |
| Albiglutide (11) | HARMONY | HARMONY OUTCOMES | 2014 FDA and EMA | Long action - Subcutaneous injection once/week |
| Dulaglutide (12) | REWIND | REWIND | 2014 | Long action - Subcutaneous injection once/week |
| Lixisenatide (13) | GETGOAL | ELIXA | 2016 | Short action - Subcutaneous injection o.d. |
| Semaglutide (14,15) | SUSTAIN 1,2<br>NCT01923181<br>NCT02461589 | | 2017 | Long action - Subcutaneous injection once/week |

regulator β-catenin. Regarding this signaling mechanism, GLP-1 agonists have been shown in a study to have a cardioprotective effect on exposure of neonatal rat cardiomyocytes to palmitate, demonstrating that GLP-1 agonists increase the β-catenin signaling, therefore increasing the surviving protein, using the protein kinase B - glycogen synthase kinase 3β pathway and canceling the apoptosis activation (17).

Lixisenatide has demonstrated non-inferiority to placebo, but not superiority on cardiovascular outcome, after hospitalization for acute coronary syndrome or heart failure (hazard ratio, 1.02; 95% confidence interval (CI), 0.89-1.17, P<0.001); the primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina) occurred with no significant difference (13.4 and 13.2% in the lixisenatide and placebo groups, respectively; HR, 1.02; 95% CI, 0.89-1.17) (18).

Semaglutide demonstrated a reduction in cardiovascular events and acute cerebral events in patients with a mean age of 65 years and a mean HbA1c of 8.7%, but with similar rates of cardiovascular mortality (18).

Liraglutide crosses the hematoencephalic barrier where, besides the GLP-1 receptor activation, it has pleiotropic neuroprotective effects, which could represent a viable use for the treatment of neurodegenerative diseases and after intracerebral hemorrhage (19). In a large trial, liraglutide reduced cardiovascular events (nonfatal myocardial infarction, or nonfatal stroke) and cardiovascular mortality compared to placebo in patients with at least one cardiovascular disease (prior myocardial infarction, stroke, or renal failure) or one cardiovascular risk factor. A decreased need was also noted to add a new antidiabetic, lipid-lowering or diuretic medication in the active arm group (20). However, in another trial on patients with established heart failure and systolic dysfunction, liraglutide showed no benefit compared to placebo on the composite outcome (death, rehospitalization) (21).

Cardiovascular benefits of dulaglutide represent the subject of a large ongoing trial (22). Initial results have indicated that dulaglutide does not increase the risk of major cardiovascular events in type 2 diabetic patients. However, the study assesses the side effects of this treatment, and also, hospitalizations for heart failure and angina, cancer and pancreatitis (22).

Exanetide demonstrated its non-inferiority compared to placebo in once-weekly administration (11.4 vs. 12.2% with placebo; HR, 0.91; 95% CI, 0.83-1.0), with lower mean HbA1c in active arm group of 0.5% (23).

Poor control of arterial hypertension in diabetic patients determines an elevated risk of acute cardiovascular events, such as myocardial infarction or stroke (24-26). GLP-1 agonists, such as exenatide and liraglutide, demonstrated in a meta-analysis a beneficial effect on reducing blood pressure in diabetic patients in the early phase of treatment, not related to weight reduction, probably by inhibition of the renin-angiotensin-aldosterone system, improvement of endothelial function and direct activation of specific receptors in the vascular tissue (27).

## 4. Evidence of GLP-1 agonists on metabolism

In diabetic patients, hyperglycemia is not the major risk factor of cardiovascular events, but merely a contributory factor, since intensive glycemic control had no effect on major macrovascular events or cardiovascular mortality, but only in microvascular events in two large trials (28,29). GLP-1 agonists may have beneficial effects on cardiovascular outcomes, by modulating other risk factors, such as endothelial dysfunction, arterial blood pressure, dyslipidemia, and platelet function (30).

Exenatide (in the DURATION trial) and liraglutide (in the LEAD trial) were observed to determine, at the beginning of the trial, a reduction of blood pressure with 1-6.6 mmHg, compared to placebo and other active comparators (5,27). The mechanism is unknown, probably multifactorial, although it was proposed that the blood pressure reduction could be by the activation of GLP-1 receptors in arteries and renal arterioles, producing vasodilatation and inhibition of the renin-angiotensin-aldosterone system (5).

Interestingly, some trials with GLP-1 agonists (liraglutide and exenatide) have noted an improvement of dyslipidemia,

due to an unknown mechanism, but this is not part of the primary outcome of any trial yet. One mechanism could be that optimal glycemic control reduces insulin resistance and improves hepatic lipid metabolism (5).

Another effect of GLP-1 agonists is weight reduction by 0.4-5.1 kg. Treatment with exenatide determined in trials a 4-4.4 kg weight reduction, persistent for 3 years. Liraglutide showed a dose-dependent weight loss, between 1-3.2 kg and, in high doses, 8.4 kg. Lixisenatide and albiglutide did not show a significant weight loss in trials (5).

In diabetes, endothelial function is affected, leading to specific complications due to macrovascular and microvascular disease. On healthy individuals, GLP-1 infusion induced improved circulation due to increased secretion of vascular acetylcholine. In diabetic patients under treatment with metformin, exenatide administration increased the vasodilation of the brachial artery (27).

*In vitro* and *in vivo* studies demonstrated that liraglutide induced inhibition of plasminogen activator inhibitor type-1 and vascular adhesion molecules, and promoted nitric oxide synthase activity, thus raising the possibility of protection mechanisms of GLP-1 RAs effect (27).

Continuous GLP-1 infusion compared to placebo in patients with preserved left ventricular function, scheduled to undergo coronary artery bypass grafting, demonstrated a better glycemic control, decreased use of vasoactive agents and fewer episodes of arrhythmias (31).

In diabetic and non-diabetic patients with myocardial infarction, liraglutide improved the left ventricular ejection fraction. Moreover, in diabetic patients, liraglutide was associated with slowing the progression of left ventricle remodeling after myocardial infarction (27).

There are no trials yet having as a primary outcome the benefit of GLP-1 RAs in diabetic patients with heart failure. The preliminary results of FIGHT trial, that evaluates weight reduction benefit in patients with heart failure, showed that liraglutide was associated with a significant weight reduction and decreased triglyceride levels. However, the cardioprotective effects on patients with reduced left ventricular ejection fraction were not significant (32,33).

However, meta-analyses of GLP-1 RAs studies and three large trials (ELIXA, LEADER, SUSTAIN-6) demonstrated a neutral effect on the risk of hospitalization for heart failure, thus being safe to use in this category of patients (34). Liraglutide, however, showed a reduction of risk of heart failure hospitalization and a significant decrease of cardiovascular and all-cause mortality in diabetic patients with a high risk of cardiovascular disease (34,35), and liraglutide, semaglutide and albiglutide demonstrated a reduction of major adverse cardiovascular events up to 26% (36,37).

## 5. Conclusions

GLP-1 RAs have pleiotropic actions, with intervention on multiple regulation mechanisms. Their safety and efficacy were demonstrated in multiple trials. Due to significant beneficial cardiovascular effects and improved glycemic control, GLP-1 RAs are now recommended in type 2 diabetes patients with increased HbA1c, alongside with first-line therapy and even with insulin treatment. At this moment, a search on ClinicalTrials.gov using as keywords cardiovascular disease and GLP-1 RAs, returns 46 studies, 22 completed and 2 that have preliminary results. This indicates an increased interest in the cardiovascular effects of GLP-1 RAs therapy.

## Acknowledgements

Not applicable.

## Funding

No funding was received.

## Availability of data and materials

Not applicable.

## Authors' contributions

RAI, NB, SB, and CP collected, analyzed and interpreted the patient data regarding the metabolic and cardiovascular benefits of GLP-1 agonists. CCD, AMAS, OGB and MC made substantial contributions to the conception of the work and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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