GLP-1 receptor agonists role in diabetes management and all-cause mortality reduction

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Received: December 2023. Accepted: January 2024; Published: February 1, 2024.
Citation: Ishfark Ahmed et al. GLP-1 receptor agonists role in diabetes management and all-cause mortality reduction. World Family Medicine. February 2024; 22(2): 37-44. DOI: 10.5742/MEWFM.2024.95257012

Abstract

An appealing therapeutic approach for the management of type 2 diabetes mellitus (T2DM) is glucagon-like peptide receptor agonists (GLP-1 RA), which have a number of implications, including glycemia control through insulin activation and glucagon release inhibition as well as decreasing adiposity by improving satiety. From August, 2023, ScienceDirect and PubMed databases were searched for terms “GLP-1”, “GLP-1 receptor agonist”, “diabetes mellitus”, “all-cause mortality rate”, “cardioprotection” and “Renal protection”. The published literature was taken from August 22, 2023 to September 05, 2023. Inclusion criteria were clinical studies, diabetic patients, and FDA-approved GLP-1 receptor agonist. Exclusion criteria were preclinical studies and non-diabetic patients. There is now a handful of GLP-1 RA in use, and others are being researched. GLP-1 RA is frequently taken in conjunction with other medications that decrease blood sugar. In the upcoming decade, hybrid compounds with dual or triple activities as well as more powerful and long-lasting medications are predicted to be developed. Major adverse cardiovascular events (MACE) are reduced by this GLP-1 RA in T2DM patients and offer renal protection. The aforementioned class of drugs is also known to reduce all-cause mortality in people with T2DM. In individuals for whom insulin was considered an option following failure of oral hypoglycemic medications, the emergence of GLP-1 analogues is an important improvement to the treatment toolbox. The published research on using GLP-1 RA for treating T2DM is compiled in the present review. It also provides a summary of the clinical trials that suggest GLP-1 RA play a role in reducing all-cause mortality rates.

Keywords: Glucagon-like peptide receptor agonists; Diabetes mellitus; Cardioprotection; Renal protection; All-cause mortality rates.

Introduction

Diabetes is becoming prevalent worldwide. Beta-cell function gradually deteriorates, needing a gradual increase in treatment intensity in order to achieve or maintain glycemic control. According to the most recent diabetes treatment recommendations, each patient should receive individualized care (1). When choosing pharmacological therapy, the clinician should take the patient's preferences, cardiovascular comorbidities, likelihood of hypoglycemia, effect on body weight, associated cost of therapy, and risk of side effects into account (2). The glucagon-like peptide 1 receptor agonists (GLP-1 RA) are becoming attractive type 2 diabetes mellitus (T2DM) treatment choices since clinical studies demonstrate that they successfully reduce A1C and weight with little hypoglycaemia risk. The proglucagon gene is used to release GLP-1 in the small intestine's L cells. The hypothalamus, kidney, lung, heart, skin, and pancreatic ducts are just a few of the organs that it binds to (3). GLP-1's main mechanism of action involves promotion of insulin release from the glucose-dependent pancreatic islets.

When GLP-1 binds to its receptors, adenylate cyclase is activated, which raises cAMP levels. Protein Kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factor 2, referred to as Epac2, also rise in response (4). Furthermore, PKA induces membrane depolarization, action potential formation, and calcium influx in addition to activating L-type voltage-dependent calcium channels (VDCC) (5). The action potential's duration is lengthened as a consequence of postponed rectifying K+ channels being closed in a PKA-dependent manner. Ryanodine receptors (RYR) and inositol 1,4,5-trisphosphate (IP3)-mediated Ca+2 release is likewise brought about by PKA. When IP3 and DAG are produced by Epac2 and Rap1, respectively, Ryanodine Receptor (RyR) and Inositol-3-Phosphate Receptor (IP3R) are activated, resulting in CICR (Calcium-Induced Calcium Release). In the end, all of these mechanisms raise cytoplasmic Ca+2, which triggers mitochondrial ATP production and the exocytotic ejection of insulin from insulin granules.

GLP-1 also slows down stomach emptying, which is crucial for controlling postprandial glycaemic excursions because it prevents glucose from entering the bloodstream quickly. These drugs are successful in treating T2DM and obesity due to the curative potential of these effects. In addition to these well-known effects, GLP-1 additionally reduces blood pressure, postprandial triglyceride, and free fatty acid concentrations (6). Furthermore, it has been shown to limit stomach emptying, limit unnecessary post-meal glucagon release, and reduce food consumption (7). There is evidence for beneficial cardiovascular effects from several GLP-1 RAs. In the past ten years, the number of GLP-1 RAs available for usage in the US and Europe has increased.

The literature on the use of GLP-1 RA in the treatment ofT2DM has been compiled in the present article. It also overviews a list of clinical studies implying the role of GLP-1 RA role in all-cause mortality reduction. We present this article in accordance with the narrative review reporting checklist.

Methods

From August, 2023, ScienceDirect and PubMed databases were searched for terms "GLP-1", "GLP-1 receptor agonist", "diabetes mellitus", "all-cause mortality rate", "cardioprotection" and "Renal protection". The published literature was taken from August 22, 2023 to September 05, 2023. Inclusion criteria were clinical studies, diabetic patients, and FDA approved GLP-1 receptor agonist. Exclusion criteria were pre-clinical studies and non-diabetic patients. All the authors carried out the literature search for collating the data prevalent for drafting the manuscript (Table 1).

Role of GLP-1 receptor agonists in management of diabetes

List of FDA-approved GLP-1 receptor agonists in management of diabetes

Since the authorization of exenatide, the first medication in the class, a variety of GLP-1 RA have become authorized in the US. These include the intermediate-acting drug liraglutide, the short-acting drug exenatide (BID), and the long-acting drugs such as exenatide (QW), albiglutide, and dulaglutide. Additionally, recently approved in the US is lixisenatide (used once daily) (8).

Adverse impacts and safety issues of GLP-1 agonist

Themostfrequentsideeffectis GIintolerance,whichincludes nausea, vomiting, and diarrhea. Yet, with a progressive dose-escalation technique, they can be somewhat mitigated as they are often moderate, temporary, and dose-dependent (9). Exenatide and exenatide LAR treatments result in the development of anti-exenatide antibodies, which are typically not accompanied by a decline in the effectiveness of therapy (9). Patients with high antibody titres still experienced less of a decline in levels of HbA1c (10). Due to a dearth of a convincing molecular hypothesis along with information from randomized controlled trials, worries regarding pancreatitis and pancreatic cancer have not been established (11). In a comparable manner, large-scale human investigations that monitored serum calcitonin concentrations did not confirm the increased prevalence of C-cell hyperplasia and medullary thyroid cancer that was observed in rat studies (12). Additionally, GLP-1 RAs have been linked to a spike in heart rate of 2-3 beats per minute and a decline in systolic blood pressure of 2–3 mmHg (13). The negative effects are dependent on the pharmacokinetic characteristics of GLP-1 RA, with short acting drugs having a greater likelihood of GI problems and long-acting drugs having more chronotropic consequences.

Table 1: The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	22.08.2023 - 05.09.2023
Databases and other sources searched	ScienceDirect, PubMed
Search terms used (including MeSH and free text search terms and filters)	GLP-1, GLP-1 receptor agonist, diabetes mellitus, all cause mortality rate, Cardioprotection; Renal protection
Timeframe	22.08.2023 - 05.09.2023
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion criteria: Clinical studies, diabetic patients, FDA approved GLP-1 receptor agonist; Exclusion criteria: Pre-clinical studies, non-diabetic patients
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All the authors carried out the literature search for collating the data prevalent for drafting the manuscript.

List of studies implying the clinical beneýts of GLP-1 receptor agonists in management of diabetes

Initial investigations suggested the first evidence suggesting GLP-1 might be a potential target in T2DM treatment in a trial that indicated GLP-1 intravenous (IV) infusion to participants with diabetes lowered the insulin demand to meal consumption. Subsequently, a number of clinical and exploratory studies supported the anti-diabetic effect of GLP-1. One particularly significant study showed improved glycemic control and weight loss in T2DM participants after receiving persistent subcutaneous infusions of GLP-1 for a time period of six weeks (14). The active variant of GLP-1 becomes inactivated quickly by peptide truncation via eliminating the N-terminal dipeptide end by the enzyme dipeptidyl peptidase-4 (DPP-4), which presented a hurdle in the establishment of GLP-1-based therapy. To solve this problem, two different approaches have been investigated. The application of GLP-1 RA, which are mainly resistant to DPP-4's effects, is one option. The other is to suppress DPP-4, which prevents GLP-1 from being inactivated and consequently extends and intensifies the effects of the endogenous incretin hormone. After several decades of development, both of these strategies are now widely used in the therapeutic care of type 2 diabetes around the world (15).

In patients with uncontrolled T2DM taking metformin, the GetGoal-X clinical study assessed the safety and efficacy of lixisenatide to exenatide administered twice daily (16). In the lixisenatide group, the mean variation in A1C was 0.79%, versus 0.96% in the exenatide twice daily group. Both groups experienced a significant loss in body weight, while exenatide caused the loss to be larger. In comparison to exenatide twice daily, lixisenatide showed marginally reduced rates of recorded side effects of GI, with statistically lower rates of nausea ($p < 0.05$). Both groups' symptoms seemed to get better over time, however, the twice-daily exenatide group took a little longer (5 weeks) than the lixisenatide group (3 weeks) to achieve the said effect. The frequency of hypoglycemia was different in this experiment than the others, which was noteworthy because lixisenatide had statistically lower episodes of symptomatic hypoglycemia than exenatide twice daily ($p < 0.05$).

Administration of albiglutide for once a week and liraglutide once daily have been compared in the HARMONY-7 research (17). Liraglutide was preferred due to a larger A1C reduction of 0.21%. Liraglutide significantly decreased fasting blood sugar levels more ($p = 0.0048$). In addition, liraglutide greatly improved weight loss. Liraglutide and albiglutide groups' average weight changes were 2.16 and 0.64 kg, respectively, with an average difference of 1.55 kg. Due to its once-weekly formulation, albiglutide had statistically larger injection site responses ($p = 0.0002$) than the control group.

In patients with uncontrolled T2D who had been put on either diet, or oral treatments, the DURATION-1 study evaluated exenatide once a week compared with exenatide two times a day(18). When contrasted to the twice-daily formulation, exenatide once weekly substantially decreased A1C after a time span of 30 weeks ($p = 0.0023$). Exenatide once weekly had a higher success rate than exenatide twice daily in terms of patients meeting their target A1C of less than 7% ($p = 0.0039$). Over the course of the 30-week research period, both groups experienced similar reductions in

body weight, with the exenatide weekly and twice-daily groups experiencing reductions of 3.7 and 3.6 kg from baseline, respectively. Buse and co-workers performed a DURATION-1 extension study that spanned a time period of 52 weeks(19). As part of the extension research, patients who were initially randomized to take exenatide twice daily were switched to exenatide once weekly for an additional 22 weeks, whereas those on exenatide once weekly continued to take it for the remainder of the study. Exenatide was initially taken once weekly, and after 52 weeks, patients who remained taking it once a week maintained their A1C improvements (2.0%), while those who switched from receiving it two times a day to once weekly further dropped their levels of A1C to reach the same decline as those who had been taking it once weekly initially.

In the clinical study named LEAD-6 trial (9), patients on maximally tolerated dosages of anti-diabetic drugs such as metformin, sulfonylurea, or both were randomized to receive liraglutide or exenatide twice daily. Liraglutide significantly lowered A1C more than exenatide twice daily, while also increasing the patient percentage obtaining an A1C of 7% ($p = 0.0015$). Both the overall weight reduction ($p = 0.22$) and the percentage of participants who lost weight were comparable between the treatment groups. Exenatide twice daily and exenatide once weekly showed comparable rates of diarrhea in the DURATION-1 study but a greater frequency of nausea and vomiting was noted, according to Drucker DJ, Buse JB, Taylor K, et al (18). There were more injection-site reactions with the once-weekly formulation, as symptoms, particularly itching, were more prevalent with injectable sustained-release drugs, which degrade over time (20).

Lixisenatide at a dose of 20 mcg once daily and liraglutide at a dose of 1.8 mg once daily were investigated in a 26-week randomized control trial by a group of researchers as a complementary treatment to metformin (21). In comparison to lixisenatide, treatment with liraglutide significantly reduced A1C (1.8% against 1.2%, $p<0.0001$). Additionally, liraglutide demonstrated superior decrease in plasma glucose levels as compared with lixisenatide ($p<0.0001$). Corresponding to this, a considerably higher proportion of patients using liraglutide achieved their A1C target of less than 7%. Comparable body weight decreases were seen with both medications (4.3 kg for liraglutide vs. 3.7 kg for lixisenatide, $p = 0.23$).

In the clinical research known as PIONEER-4, semaglutide, the first oral GLP-RA, was evaluated against liraglutide delivered subcutaneously and placebo in a randomized controlled experiment for a time period of 52 weeks. At the outset, the enrolled patients were either on metformin or an SGLT-2 inhibitor (22). Assessing changes in A1C from baseline to week 26 was the main objective. It was observed that oral semaglutide was non-inferior to liraglutide in reducing A1C at 26 weeks ($p<0.0001$). Comparing oral semaglutide and liraglutide, there were no appreciable changes in the proportion of patients who met their A1C target of below 7% ($p = 0.1530$). Oral semaglutide caused a considerable weight loss in the enrolled patients at 26 weeks ($p =0.0003$) compared to liraglutide. Oral semaglutide significantly decreased A1C higher than liraglutide did following 52 weeks of treatment schedule ($p< 0.0001$).

In another clinical research PIONEER-9, oral semaglutide monotherapy versus liraglutide was evaluated (23). For a time span of 52 weeks, patients were randomized to receive one of three oral semaglutide doses, the doses being 3 mg, 7 mg, and 14 mg, liraglutide at a dose of 0.9 mg, or a placebo. Japanese individuals receiving oral antihyperglycemic treatment participated in this study. Using the maximum dose permitted in Japan as a benchmark, researchers utilized a dose of liraglutide of 0.9 mg. At 26 weeks, semaglutide at a dose of 14 mg significantly reduced A1C when compared with liraglutide ($p = 0.0272$). Compared to individuals on liraglutide, a significantly greater percentage of those receiving semaglutide 14 mg ($p = 0.0152$) of patients met a target A1C of less than 7% at 26 weeks. But following 52 weeks, no significant difference was observed in the A1C decrease between the patient pool taking oral semaglutide 14 mg and liraglutide ($p = 0.0632$). In the treatment arm, oral semaglutide 14 mg demonstrated a more substantial body weight loss from baseline relative with liraglutide at weeks 26 ($p< 0.0001$) and 52 ($p <0.0001$).

In the PIONEER-10 study, Japanese patients with T2DM who were on oral antihyperglycemic medication received either oral semaglutide at doses of 3, 7, or 14 mg for 57 weeks, or SC dulaglutide at a dose of 0.75 mg (24). The maximum dose of dulaglutide that has been licensed for use in Japan led to the dosage of 0.75 mg being chosen. The number of treatment-related adverse events (AEs) throughout a 57-week period was the primary objective. Changes in A1C and weight from baseline level at 52 weeks were secondary objectives. When compared to dulaglutide, oral semaglutide when administered at a dose of 14 mg, significantly reduced A1C at 52 weeks ($p = 0.0170$). A1C drop with dulaglutide was larger than with semaglutide at an administered dose of 3 mg ($p = 0.0005$) and comparable to semaglutide at a dose of 7 mg. When compared to dulaglutide, substantially more number of patients on semaglutide 14 mg ($p = 0.0016$) attained an A1C objective. In comparison to dulaglutide, the doses of semaglutide of 3 mg, 7 mg, and 14 mg all significantly reduced the body weight of the enrolled patients.

List of studies implying the role of GLP-1 receptor agonists role in all-cause mortality reduction

T2DM patients, especially those with concurrent CV disease (CVD), have greater rates of cardiovascular (CV) morbidity and death than other groups (25,26). Extensive glucose reduction in T2DM patients lowers microvascular disease, but its impact on cardiovascular events or death is modest and debatable (27). In this situation, the US FDA mandated in 2008 that all novel T2DM therapy drugs to undergo a CV safety assessment (11). Since then, numerous clinical trials have been developed to evaluate the effects of GLP-1 RA treatment on CV outcomes.

The following section (Table 2) lists a number of clinical studies implying the GLP-1 RA role in all-cause mortality reduction.

Table 2: Clinical studies implying the role of GLP-1 receptor agonists role in all-cause mortality reduction

Participants	Objective	Result	Interpretation	Reference
21135	To determine how GLP-1 RA therapy, in comparison to placebo, affects clinically significant outcomes in T2DM patients, such as all-cause mortality, nonfatal myocardial infarction (MI), cardiovascular mortality, nonfatal stroke, and hospitalizations for heart failure (HF).	Patients taking a GLP-1 RA experienced an 11% reduction in the risk of all-cause death. Regarding HF-related hospitalization rates, non-fatal MI, non-fatal stroke, and cardiovascular death (CVD), there were considerably no statistically significant differences between the groups.	In type 2 diabetics with elevated CV risk, the GLP-1 RA medication lowered all-cause mortality compared to placebo. No effect was observed on the hospitalization rate for HF, nonfatal MI, nonfatal stroke, or CVD.	28
60080	A meta-analysis of the most recent data from outcome trials in T2DM patients about the cardiovascular advantages and hazards associated with the use of GLP-1 RA was studied.	There was no discernible heterogeneity between structural homology of GLP-1 RA or the eight other groupings tested, and GLP-1 RA lowered MACE by 14% (p <0 0001). With no rise in severe hypoglycemia risk, retinopathy, or pancreatic side effects, GLP-1 RA decreased all-cause mortality by approximately 12% (p=00001), hospital admission for heart failure by 11% (p=0013), as well as the composite renal outcome by 21% (p<00001).	Irrespective of structural homology, GLP-1 RA decreased the probability of every aspect of MACE, all-cause mortality, hospitalization for HF, and deteriorating kidney function in T2DM patients.	29
56251	To assess the effectiveness and security of GLP-1 RA in T2DM patients for the avoidance of stroke	Nonfatal strokes (p = 0.002) and all strokes (p = 0.001) were both decreased by 16% by GLP-1R agonists. GLP-1R agonists decreased all-cause mortality by 12% (p = 0.0007), cardiovascular mortality by 12% (p = 0.002), and MACE by 13% (p = 0.0003) overall. Subsequent analyses showed that patients who had previously experienced myocardial infarction or nonfatal strokes had a lower incidence of incident MACE (p< 0.0001).	GLP-1R agonists are helpful for preventing primary stroke, MACE, and cardiovascular death in type 2 DM patients. Additional RCTs are required to assess their contribution to secondary prevention of stroke.	30

56 004	To synthesize the information by performing a comprehensive review and meta-analysis of cardiovascular outcome trials with GLP-1R agonists.	Treatment with a GLP-1 RA decreased MACE by 12% (p< 001). No statistically significant heterogeneity was observed among the treated groups. The HRs for fatal or non-fatal MI, fatal or non-fatal stroke, and CVD were noted to be 0.88 (p=0003), 0.84 (p<0·001), and 0.91 (p=0043), respectively. A broad combined kidney outcome such as the appearance of new-onset macroalbuminuria decreased eGFR or a rise in creatinine, advancement to ESKD, or death linked to kidney causes was noted to be reduced by GLP-1 receptor agonist treatment by 17% (p=0001), primarily due to a decline in urinary albumin excretion. No risk of severe hypoglycemia, pancreatitis, or pancreatic cancer was seen to be increased.	T2DM patients who receive treatment with GLP-1 RA experienced favorable outcomes in terms of their cardiovascular, mortality, and kidney health.	[31]
14752	To investigate the cardiovascular consequences of supplementing standard care with once-weekly exenatide administration in type 2 diabetic patients	3-point MACE was noted to be 11.4% in the exenatide group whereas it was 12.2% in the placebo group	Frequency of MACE among patients with type 2 diabetes, whether or not they had a history of cardiovascular illness, did not vary noticeably between those who were administered exenatide and those who received a placebo.	[32]
3297	To determine if semaglutinide administration led to first instance of CVD, non-fatal MI, or non-fatal stroke among the enrolled group of patients with diabetes mellitus.	↓ 3-point MACE: 6.6% of semaglutide group of patients compared to 8.9% of placebo users. Non-fatal stroke: 1.6% in semaglutide group vs 2.7% in placebo group was observed	The prevalence of CVD, non-fatal MI, or non-fatal stroke was considerably lower among patients taking semaglutide than among those taking a placebo in T2DM patients who were at elevated risk for CVD, a finding that supported semaglutide's noninferiority.	[33]

Conclusions

Treatment of T2DM benefits significantly from the GLP-1 RA family. All of the class's medications have shown considerable A1C reductions, and overall, their effects on weight are positive with little risk of hypoglycemia. The negative side effects (primarily GI and injection site reactions), requirement for SC injection, and expense of GLP-1 RAs could constrain their widespread use. Despite there being issues about the connection between the usage of GLP-1 agonists and incidence of certain side effects, preclinical and clinical investigations have found no conclusive evidence of that connection in T2DM patients. GLP-1 agonist benefits in cardio-, neuro-, and nephroprotective actions but not in diabetes, which have been demonstrated in preclinical trials. The most popular diabetes medications in the future may be GLP-1 agonists, surpassing those that are already on the market. GLP-1 agonists have prospective for diabetes treatment without the need for insulin as they are less harmful, more specific, and presently accessible drug therapies have significant limitations. When choosing any particular drug within the class for patients who would gain from treatment with GLP1-RA, medical professionals should take into account the existing research addressing comparable effects on A1C and weight, adverse effect incidences, administration needs, and associated therapy cost.

Funding
None
Acknowledgments
None
Conþicts of Interest: The authors have no conflicts of interest to declare.

References

1.Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2020 executive summary. Endocr Pract 2020; 26: 107-39. https://doi.org/10.4158/cs-2019-0472.
2.American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2021. Diabetes care 2021; 44: S111-24. https://doi.org/10.2337/dc21-s009.
3.Lee YS, Jun HS. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. Metabolism 2014; 63: 9-19.https://doi.org/10.1016/j.metabol.2013.09.010.
4.Leech CA, Chepurny OG, Holz GG. Epac2-dependent rap1 activation and the control of islet insulin secretion by glucagon-like peptide-1. Vitam Horm 2010; 84: 279-302. https://doi.org/10.1016/b978-0-12-381517-0.00010-2.
5.Doyle ME, Egan JM. Mechanisms of action of glucagon-like peptide 1 in the pancreas. Pharmacol Ther 2007; 113: 546-93. https://doi.org/10.1016/j.pharmthera.2006.11.007
6.Meier JJ, Gethmann A, Götze O, et al. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. Diabetologia 2006; 49: 452-8. https://doi.org/10.1007/s00125-005-0126-y.
7.Koliaki C, Doupis J. Incretin-based therapy: a powerful and promising weapon in the treatment of type 2 diabetes mellitus. Diabetes Ther 2011; 2: 101-121. https://doi.org/10.1007/s13300-011-0002-3.
8.Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. Diabetes Spectr 2017; 30: 202-210. https://doi.org/10.2337/ds16-0026.
9.Buse JB, Rosenstock J, Sesti G, et al. LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374: 39-47. https://doi.org/10.1016/s0140-6736(09)60659-0.
10.Buse JB, Garber A, Rosenstock J, et al. Liraglutide treatment is associated with a low frequency and magnitude of antibody formation with no apparent impact on glycemic response or increased frequency of adverse events: results from the Liraglutide Effect and Action in Diabetes (LEAD) trials. J Clin Endocrinol Metab 2011; 96: 1695-1702. https://doi.org/10.1210/jc.2010-2822.
11.Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs - FDA and EMA assessment. N Engl J Med 2014; 370: 794-7. https://doi.org/10.1056/nejmp1314078.
12.Hegedüs L, Moses AC, Zdravkovic M, et al. GLP-1 and calcitonin concentration in humans: lack of evidence of calcitonin release from sequential screening in over 5000 subjects with type 2 diabetes or nondiabetic obese subjects treated with the human GLP-1 analog, liraglutide. J Clin Endocrinol Metab 2011; 96: 853-60. https://doi.org/10.1210/jc.2010-2318.
13.Chilton R, Wyatt J, Nandish S, Oliveros R, Lujan M. Cardiovascular comorbidities of type 2 diabetes mellitus: defining the potential of glucagonlike peptide–1-based therapies. Am J Med 2011; 124: S35-53. https://doi.org/10.1016/j.amjmed.2010.11.004.
14.Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: a parallel-group study. Lancet 2002; 359: 824-30. https://doi.org/10.1016/s0140-6736(02)07952-7.
15.Piya MK, Tahrani AA, Barnett AH. Emerging treatment options for type 2 diabetes. Br J Clin Pharmacol 2010; 70: 631-44.https://doi.org/10.1111/j.1365-2125.2010.03711.x.
16.Rosenstock J, Raccah D, Korányi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care 2013; 36: 2945-51. https://doi.org/10.2337/dc12-2709.
17.Pratley RE, Nauck MA, Barnett AH, et al. HARMONY 7 study group. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014; 2: 289-97. https://doi.org/10.1016/s2213-8587(13)70214-6.
18.Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study.

Lancet 2008; 372: 1240-50. https://doi.org/10.1016/s0140-6736(08)61206-4.
19.Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1 Study Group. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care 2010; 33: 1255-61. https://doi.org/10.2337/dc09-1914.
20.Garbutt JC, Kranzler HR, O'Malley SS, et al. Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. Jama 2005; 293: 1617-25. https://doi.org/10.1001/jama.293.13.1617.
21.Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. Diabetes Care 2016; 39: 1501-9. https://doi.org/10.2337/dc15-2479.
22.Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019; 394: 39-50.https://doi.org/10.1016/s0140-6736(19)31271-1.
23.Yamada Y, Katagiri H, Hamamoto Y, et al. PIONEER 9 investigators. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. Lancet Diabetes Endocrinol 2020; 8: 377-91. https://doi.org/10.1016/s2213-8587(20)30075-9.
24.Yabe D, Nakamura J, Kaneto H, et al. PIONEER 10 Investigators. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. Lancet Diabetes Endocrinol 2020; 8: 392-406. https://doi.org/10.1016/s2213-8587(20)30074-7.
25.Tentolouris A, Eleftheriadou I, Athanasakis K, et al. Prevalence of diabetes mellitus as well as cardiac and other main comorbidities in a representative sample of the adult Greek population in comparison with the general population. Hell J Cardiol 2020; 61: 15-22. https://doi.org/10.1016/j.hjc.2018.04.008.
26.Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015; 373: 1720-32. https://doi.org/10.1056/nejmoa1504347.
27.Skliros NP, Vlachopoulos C, Tousoulis D. Tousoulis Treatment of diabetes: Crossing to the other side. Hellenic J Cardiol 2016; 57: 304-10. https://doi.org/10.1016/j.hjc.2016.07.002.
28.Peterson SC, Barry AR. Effect of Glucagon-like Peptide-1 Receptor Agonists on All-cause Mortality and Cardiovascular Outcomes: A Meta-analysis. Curr Diabetes Rev 2018; 14: 273-79. https://doi.org/10.2174/1573399813666170414101450.
29.Sattar N, Lee MM, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021; 9: 653-662. https://doi.org/10.1016/s2213-8587(21)00203-5.
30.Malhotra K, Katsanos AH, Lambadiari V, et al. GLP-1 receptor agonists in diabetes for stroke prevention: a systematic review and meta-analysis. J Neurol 2020; 267: 2117-2222. https://doi.org/10.1007/s00415-020-09813-4.
31.Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019; 7: 776-85. https://doi.org/10.1016/s2213-8587(19)30249-9.
32.Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017; 377: 1228-39. https://doi.org/10.1056/nejmoa1612917.
33.Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016; 375: 1834-44. https://doi.org/10.1056/nejmoa1607141.