

REVIEW ARTICLE

Cardiovascular and Renal Outcomes of Incretin-based Therapies: A Review of Recent Clinical Trials

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Abstract: Background: To report the cardiovascular and renal effects of incretin-based therapies.

Methods: The studies of clinical trials on incretin-based therapy published in medical journals from the years 2010 to 2017 were comprehensively searched using MEDLINE and EMBASE with no language restriction. The studies were reviewed and the cardiovascular and renal risks reported were recorded.

Results: Incretin-based therapeutics represent novel and promising anti-diabetes drugs, the direct cardiovascular actions which may translate into demonstrable clinical benefits on cardiovascular outcomes. Furthermore, incretin-based therapies do not adversely affect renal function.

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1. INTRODUCTION

Incretin-based therapies are a novel class of antidiabetic medications increasingly used in the treatment of hyperglycemia in patients with type 2 diabetes. The Canadian Diabetes Association (CDA) 2013 clinical practice guidelines, a position statement of the American Diabetes Association (ADA-EASD), and a consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology (ACCE/ACE) recommend incretin-based therapies, dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, as an option for add-on therapy to first-line therapy with metformin or other antidiabetic medications. However, there is limited evidence about the relative clinical effectiveness and safety of incretin-based therapies in patients with diabetes and CKD [1]. Incretin-based therapies were amongst the first T2D treatments for which detailed evaluation of long-term CV safety was encouraged under the 2008 FDA guidance [2]. Incretin-based therapies are based on the gut-derived

incretin hormone glucagon-like peptide (GLP)-1. GLP-1 is released by intestinal L-cells on food ingestion and regulates glucose homeostasis by influencing pancreatic islet-cell function, including glucose-dependent stimulation of insulin and suppression of glucagon secretion. GLP-1 receptor agonists have been associated with resting heart rate acceleration (mean increase of 2-4 bpm), an established risk factor for cardiovascular and all-cause mortality.

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in people with diabetes and therefore managing cardiovascular (CV) risk is a critical component of diabetes care. As incretin-based therapies are recent effective additions to the glucose-lowering treatment armamentarium for type 2 diabetes mellitus (T2D), understanding their CV safety profiles is of great importance [2].

According to Petrie [2], data from animal models and pilot clinical studies have indicated that native GLP-1 may have cardioprotective effects in the setting of ischemia, or following ischemic injury. Moreover, studies using the technique of brachial artery flow-mediated vasodilation during GLP-1 infusion in people with T2D and stable coronary artery disease suggest that GLP-1 may improve endothelial function in some individuals with T2D. It should be mentioned that people with T2D who are overweight or obese,

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are hypertensive or have dyslipidaemia are at increased risk of adverse CV events. Incretin-based therapies have been shown to have an impact on these CV risk factors; however, differences in these effects between DPP-4 inhibitors and GLP-1 receptor agonists have been noted. These differences may arise from differences in the mechanism of action, or levels of GLP-1 receptor activation produced by these individual drug classes.

Additionally, substantial resting heart rate elevation is associated with increased CV mortality, and drugs that prolong cardiac repolarisation carry a risk of provoking adverse CV events.

The purpose of this review is to report the cardiovascular and renal effects of incretin-based therapies found in recent clinical trials.

2. METHODS

A search was conducted in MEDLINE (*via* PubMed) and EMBASE for articles from years 2010-2017. The search strategy was based on free text terms, using keywords such as incretin-based therapies, hormones, diabetes, cardiovascular and renal outcomes. Study type was restricted to clinical trials, controlled clinical trials and randomized trials.

The articles that were included in the study were selected using the PRISMA approach. Sixty-seven records were iden-

tified through the database and other sources searched. After removal of the duplicates, thirty-five records were screened, from which fifteen were excluded mainly because they were only abstracts. The number of full-text articles that were assessed for eligibility was narrowed down to twelve but fortunately, none of them was excluded. The inclusion process can be shown in the flow chart Fig. (1).

3. RESULTS

A 2.5 mg dose of saxagliptin once daily was found to offer sustained efficacy and good tolerability for patients with T2DM and renal impairment [3]. That was the conclusion of a 52-week study assessing the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus (T2DM) and renal impairment. Researchers found that the decrease in HbA1c was greater with saxagliptin than placebo in patients with renal impairment rated as moderate or severe, but similar to placebo for those with end-stage renal disease (ESRD). Additionally, reductions in fasting plasma glucose (FPG) were numerically greater with saxagliptin in patients with moderate or severe renal impairment. Generally, saxagliptin was well tolerated; similar proportions of patients in the saxagliptin and placebo groups reported hypoglycaemic events (28% and 29%, respectively).

It has also been showed that, in patients with type 2 diabetes and severe RI, linagliptin provides clinically meaning-

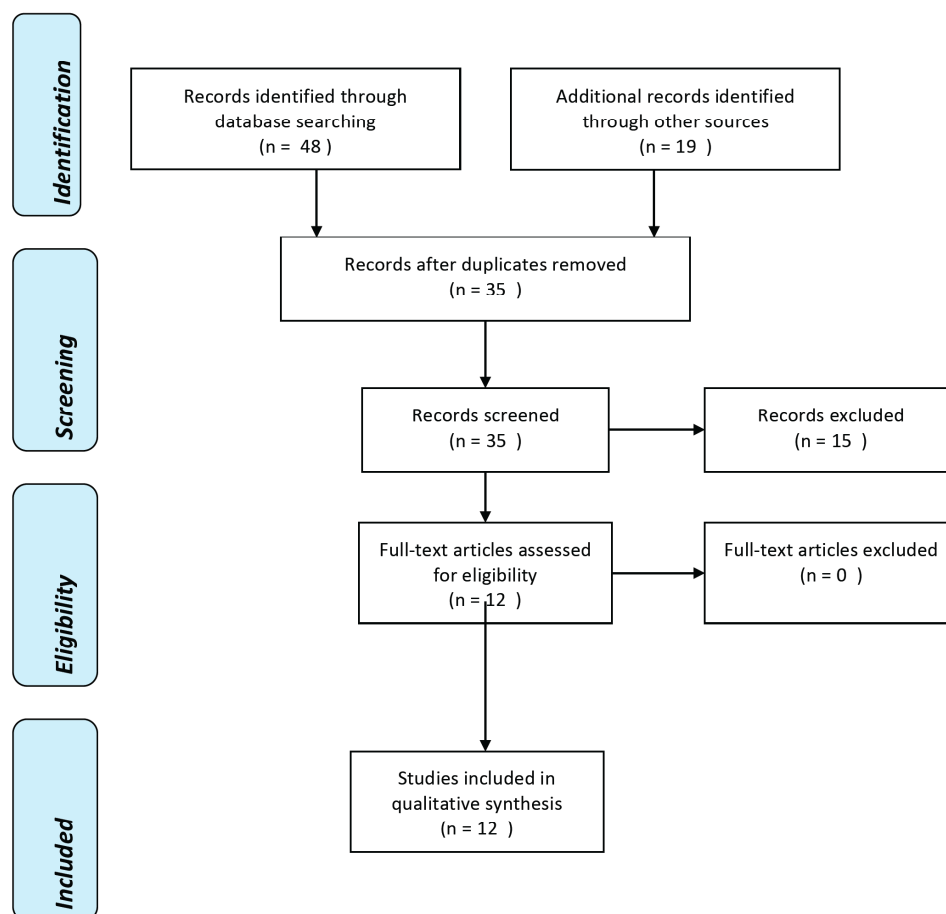


Fig. (1). PRISMA flow chart of study selection. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

ful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure [4]. The researchers conducted a 1-year, double-blind study of 133 patients with type 2 diabetes and severe renal impairment (RI) and assessed long-term efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin. They found that HbA1c decreased by 20.76% with linagliptin and 20.15% with placebo. In addition, HbA1c improvements were sustained with linagliptin (20.71%) over placebo (0.01%) at 1 year. Overall adverse event incidence was similar over 1 year (94.1 vs. 92.3%). Incidence of severe hypoglycemia with linagliptin and placebo was comparably low (three patients per group). Finally, linagliptin and placebo had little effect on renal function and no drug-related renal failure occurred. Similar results were found for vildagliptin [5]. It was shown that, in patients with T2DM and moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo during 1-year observation. Furthermore, relative to placebo, a clinically significant decrease in A1C was maintained throughout 1-year treatment with vildagliptin. It was a double-blind, randomized, 52-week clinical trial comparing safety and efficacy of vildagliptin (50 mg qd, $n = 216$) and placebo ($n = 153$) in patients with T2DM and moderate or severe RI. The study population comprised of 122 and 89 patients with moderate RI and 94 and 64 patients with severe RI. After 1 year, the between-treatment difference in adjusted mean change in A1C was $-0.4 \pm 0.2\%$ ($p = 0.005$) in moderate RI (baseline = 7.8%) and $-0.7 \pm 0.2\%$ ($p < 0.0001$) in severe RI (baseline = 7.6%). In patients with moderate RI, similar proportions of patients experienced any adverse event (AE) (84 vs. 85%), any serious adverse event (SAE) (21 vs. 19%), any AE leading to discontinuation (5% vs. 6%) and death (1% vs. 0%) with vildagliptin and placebo, respectively. This was also true for patients with severe RI: AEs (85% vs. 88%), SAEs (25% vs. 25%), AEs leading to discontinuation (10% vs. 6%) and death (3% vs. 2%). Idorn *et al.* [6] found that plasma liraglutide concentrations increase during treatment in patients with type 2 diabetes and ESRD, who experience more gastrointestinal (GI) side effects. They conducted a double-blind, randomized trial in order to evaluate parameters related to the safety and efficacy of liraglutide in patients with type 2 diabetes and dialysis-dependent ESRD. Twenty patients with ESRD and 20 control subjects completed the study period. According to their results, dose-corrected plasma trough liraglutide concentration at the final visit was increased by 49% (95% CI 6-109, $p = 0.02$) in patients with ESRD. Initial and temporary nausea and vomiting occurred more frequently among liraglutide-treated patients with ESRD and glycemic control tended to improve during the study period in both liraglutide-treated groups.

Another study by Davies *et al.* [7] showed that liraglutide did not affect renal function and demonstrated better glycemic control, with no increase in hypoglycemia risk but with higher withdrawals due to GI adverse events than placebo in patients with type 2 diabetes and moderate renal impairment. This 26-week, double-blind trial was conducted to establish the efficacy and safety of liraglutide as an add-on to existing glucose-lowering medications in patients with inadequately controlled type 2 diabetes and moderate renal impairment. They found that fasting plasma glucose decreased more with

liraglutide (21.22 mmol/L) than with placebo (20.57 mmol/L; $p = 0.036$). No changes in renal function were observed (eGFR relative ratio to baseline: 21% liraglutide, +1% placebo; estimated treatment ratio (ETR) 0.98; $p = 0.36$). The most common adverse events were gastrointestinal adverse effects.

Furthermore, it seems that DPP-4 inhibition with saxagliptin does not affect the rate of ischemic events, though the rate of hospitalization for heart failure may be increased [8]. Although saxagliptin has been shown to improve glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes. This finding originates from SAVOR-TIMI 53, a multicenter, randomized, double-blind, placebo-controlled, phase 4 trial. The trial lasted from May 2010 through December 2011 and a total of 16,492 patients took part. The total observation time was 16,884 person-years in the saxagliptin group and 16,761 person-years in the placebo group. The DPP-4 inhibitor saxagliptin neither reduced nor increased the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke, when added to the standard of care in patients at high risk for cardiovascular events, thus meeting the criterion for noninferiority to placebo but not providing any cardioprotective benefit. Saxagliptin was associated with significantly improved glycemic control and reduced the development and progression of microalbuminuria; however, it increased the risk of hospitalization for heart failure and the risk of hypoglycemic events [14]. In a randomised, double-blind, parallel-group, multinational phase 3 study, patients over 70 years with type 2 diabetes, receiving metformin, sulfonylureas, or basal insulin, or combinations of these drugs were enrolled in order to assess the effectiveness of linagliptin [9]. Overall safety and tolerability were much the same between the linagliptin and placebo groups; 75.9% of patients in both groups had an adverse event, but no deaths occurred. Serious adverse events occurred in 8.6% (14) of patients in the linagliptin group and 6.3% (five) patients in the placebo group; none were deemed related to study drug. The most common adverse event in both groups was hypoglycaemia, but did not differ between groups. Therefore, it was proven that, in elderly patients with type 2 diabetes, linagliptin was efficacious in lowering glucose with a safety profile similar to placebo.

Another group of researchers studied the efficacy and safety of sitagliptin and glipizide monotherapy in patients with type 2 diabetes and ESRD on dialysis therapy. It was a 54-week, randomized, double-blind, parallel-arm study in which 129 patients 30 years or older participated [10]. According to their results, treatment with sitagliptin or glipizide led to a significant ($p < 0.001$) reduction in HbA1c level from baseline at week 54 and both treatments led to reductions in FPG level. Both treatments generally were well tolerated over and incidences of overall adverse events and discontinuation due to adverse events were similar between groups. The proportion of patients reporting adverse events of symptomatic hypoglycemia was numerically, but not significantly ($p = 0.3$), lower in the sitagliptin group (6.3%). However, no patient in the sitagliptin group had a severe episode of hypoglycemia, whereas 7.7% of patients in the glipizide group experienced at least one. For gastrointestinal adverse events, there were no significant between-group dif-

ferences for adverse events of diarrhea, nausea, vomiting and abdominal pain ($p > 0.05$ for all). The conclusion was that treatment with sitagliptin or glipizide monotherapy can be effective and well tolerated in patients with type 2 diabetes and ESRD who receive dialysis.

The efficacy and safety of sitagliptin with glipizide was also studied in patients with T2DM and moderate-to-severe chronic renal insufficiency and inadequate glycemic control [11]. The trial lasted 54 weeks and at week 54, treatment with sitagliptin was found to be noninferior to treatment with glipizide in A1C change from baseline. However, there was a lower incidence of symptomatic hypoglycemia adverse events with sitagliptin vs. glipizide (6.2 and 17.0%, respectively; $p = 0.001$) and a decrease in body weight with sitagliptin (20.6 kg) vs. an increase (1.2 kg) with glipizide (difference, 21.8 kg; $p < 0.001$). The incidence of gastrointestinal AEs was low with both treatments. In conclusion, in patients with T2DM and chronic renal insufficiency, sitagliptin and glipizide provided similar A1C-lowering efficacy. Sitagliptin was generally well-tolerated, with a lower risk of hypoglycemia and weight loss vs. weight gain, relative to glipizide. The EXAMINE study assessed cardiovascular outcomes with alogliptin, a new inhibitor of dipeptidyl peptidase 4 (DPP-4), as compared with placebo in patients with type 2 diabetes who had had a recent acute coronary syndrome [12]. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary endpoint of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in which a total of 5380 patients underwent treatment and were followed for up to 40 months (median, 18 months). The alogliptin and placebo groups did not differ significantly with respect to the incidence of serious adverse events (33.6% and 35.5%, respectively; $p = 0.14$) and the incidence of hypoglycemia was similar in the two study groups. The incidences of acute and chronic pancreatitis were similar in the two groups; no cases were fatal. Overall, researchers concluded that, among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.

A recent study by Tonneijck *et al.* [13] aimed to investigate the acute renal effects of the glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide in type 2 diabetes patients. They conducted a randomized, double-blind, placebo-controlled trial at the Diabetes Center VU University Medical Center (VUMC) and the final analyses included 52 patients. The authors demonstrated that acute intravenous administration of exenatide does not affect gold-standard-measured glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in these patients. In addition, they showed that exenatide does not influence filtration fraction (FF), glomerular hydrostatic pressure (P_{GLO}) or vascular resistance of the efferent (R_E) renal arteriole while it acutely increases vascular resistance of the afferent (R_A) renal arteriole. Absolute sodium excretion, fractional electrolyte excretion of sodium (FE_{Na}) and potassium (FE_K) increase, while urea (FE_U), urinary flow and free water clearance decrease. Finally, they demonstrate that exenatide does not affect

plasma renin concentration (PRC) or urinary markers of renal damage following acute administration.

A double-blind trial by Marso *et al.* [14] investigated the cardiovascular effect of liraglutide on type 2 diabetes. In the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), a total of 9340 patients participated with a median follow-up of 3.8 years. The primary outcome was the death of cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke. The trial demonstrated that liraglutide was superior to placebo with respect to the primary endpoint (time to the first major adverse cardiovascular event [MACE]). The participants were patients with T2DM who had an HbA1c $\geq 7.0\%$ at screening (no upper limit) and had never taken any antidiabetic drug or were treated with one or more oral antidiabetic drugs (OADs) and/or neutral protamine Hagedorn (NPH) insulin, long-acting insulin, or premixed insulin. They also had to be at high risk for cardiovascular events with either established cardiovascular disease or chronic kidney disease and age ≥ 50 years, or with at least one cardiovascular risk factor and age ≥ 60 years. According to the results, liraglutide reduced the estimated risk of MACE, expanded MACE, cardiovascular death and all-cause death compared with placebo.

4. DISCUSSION

This review included recent articles upon clinical trials of incretin-based therapies. From the analysis, it was showed that incretin-based therapies demonstrate a trend towards a lower risk of cardiovascular disease compared to placebo or other antihyperglycemic agents, although the difference was not statistically significant.

From the incretin-based therapies studied, saxagliptin offers sustained efficacy and good tolerability for patients with T2DM and renal impairment. In addition, saxagliptin does not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure may be increased.

Linagliptin provided clinically meaningful improvements in glycemic control, in patients with type 2 diabetes and severe RI, with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure. In elderly patients with type 2 diabetes, linagliptin was efficacious in lowering glucose with a safety profile similar to placebo.

In patients with T2DM and moderate or severe RI, vildagliptin had a safety profile similar to placebo.

Plasma liraglutide concentrations increased during treatment in patients with type 2 diabetes and ESRD, who experienced more gastrointestinal side effects. Furthermore, liraglutide did not affect renal function and demonstrated better glycemic control, with no increase in hypoglycemia risk but with higher withdrawals due to GI adverse events than placebo in patients with type 2 diabetes and moderate renal impairment. However, as far as the cardiovascular effects are concerned, liraglutide decreases the risk of death.

Treatment with sitagliptin or glipizide monotherapy was effective and well tolerated in patients with type 2 diabetes

and ESRD who were receiving dialysis and in patients with T2DM and chronic renal insufficiency, sitagliptin and glipizide provided similar A1C-lowering efficacy. Sitagliptin was generally well-tolerated, with a lower risk of hypoglycemia and weight loss vs. weight gain, relative to glipizide.

Among patients with type 2 diabetes who had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.

Finally, exenatide infusion does not acutely affect renal haemodynamics in overweight type 2 diabetes patients at normal filtration levels. Furthermore, acute GLP-1RA administration increases proximal sodium excretion in these patients.

CONCLUSION

Overall, it can be concluded that incretin-based therapies are effective and well-tolerated. Furthermore, they can lower the risk of cardiovascular disease and they do not adversely affect renal function. Therefore, they can be a safe choice in the treatment of patients with T2DM.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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