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Review Article

GLP-1 Receptor Agonists and Cardiac Outcome Trials in Patients with Type 2 Diabetes

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Abstract

Type 2 diabetes is a common and chronic condition with a rapidly growing prevalence. Cardiovascular events are the main reason for death in type 2 diabetes, hence prevention and treatments of cardiovascular disease should be the main point of concern in diabetes. Glucagon-like peptide-1 receptor agonists not only reduce the risks contributing to cardiovascular events such as glycaemia, body weight, dyslipidaemia, and hypertension but also improve the endothelial function, ischemia, and heart failure. Recent clinical trials on cardiovascular events have been performed with GLP-1 agonists. In these trials, liraglutide and semaglutide have revealed to be superior in cardiovascular outcomes. The mechanisms of showing cardiovascular benefits by liraglutide and semaglutide are still not known but it is recommended for these benefits to use these therapeutic regimes routinely in the clinical practice [1].

Keywords: Type 2 Diabetes; Pharmacology; GLP-1

Introduction

Pharmacology of GLP-1 agonists

GLP-1 agonists have many potential advantages in type 2 diabetes. Intravenous administration of exogenous GLP-1 in type 2 diabetics reduces the plasma glucose levels to the normal concentration, this occurs also in people who did not have an adequate response to oral anti-diabetic agents.

Some benefits of exogenous GLP-1 observed in type 2 diabetic patients include:

- Reducing glucagon levels
- Increasing insulin sensitivity
- Reducing HBA1C levels
- Reducing gastric emptying
- Increasing satiety levels
- Reducing free fatty acid levels
- Reducing weight [2].

Figure 1: GLP-1 agonists outcomes on the cardiovascular system (cited from https://www.sciencedirect.com/science/article/pii/S1109966618304081) [3].

Generic name	Dose	Administration before the meal required?	Available dose forms
Exenatide	Twice daily	Required	5-µg pen, 29-30-31 gauge pen needles
Lixisenatide	Once- daily	Required	50 µg/mL in 3-mL prefilled pen; 100 µg/mL in 3-mL pre-filled pen
Liraglutide	Once- daily	Not Required	Multi- dose pen
Exenatide QW	Once weekly	Not Required	Single dose 2mg vial and 2mg pen
Albiglutide	Once weekly	Not Required	Single- dose 30 and 50 mg pens
Dulaglutide	Once weekly	Not Required	Single pen dose or prefilled syringe
Semaglutide	Once weekly	Not Required	Single- dose 0.25 , 0.5 and 1mg pens

Table 1: Available GLP-1 Agonists in the United States for the Management of Type 2 Diabetes [2].

Cardiovascular outcomes trials completed with GLP-1 agonists till date include:

- Lixisenatide: ELIXA trial
- Exenatide QW: EXSCEL trial
- Liraglutide: LEADER trial
- Semaglutide: SUSTAIN-6 trial
- Albiglutide: Harmony outcomes
- Dulaglutide: REWIND trial
- Semaglutide: PIONEER 6 trial [4].

ELIXA trial

The first cardiovascular outcome trial (CVOT) for the GLP-1 agonists investigated the effect of Lixisenatide in acute coronary syndrome (ELIXA). In patients with high cardiovascular risk or recent cardiovascular event that required admission, once-daily Lixisenatide on the top of other anti-diabetic drugs for 25 months was not inferior to placebo for the endpoints of cardiovascular death, heart failure hospitalization, unstable angina, revascularization, non-fatal myocardial infarction and non-fatal stroke. Lixisenatide use was associated with reduction in HBA1C levels and showed neutral effects on body weight. Safety endpoints revealed a similar risk for overall rates of adverse effects in Lixisenatide group compared to placebo.

This study proved the cardiovascular safety of Lixisenatide over a long period time [5].

EXSCEL trial

Heart failure and other cardiovascular disease are priorities in the management of type 2 diabetes mellitus, and GLP-1 agonists can achieve a beneficial effect on them. EXSCEL trial provides only a weak evidence of a differential effect on vascular outcomes by baseline heart failure status, but the analysis of recurrent heart failure events provides important additional support for an effect of Exenatide on heart failure. A formal evaluation of the combined effects of GLP-1 agonists and SGLT2 inhibitors is warranted given the likely additive benefits of reduced mortality, morbidity and heart failure in type 2 diabetics [6].

The GLP-1 agonist cardiovascular outcome trials have shown a renal protection of GLP-1 agonists besides the cardiovascular protective effects [7].

LEADER trial

This study evaluated the effect of Liraglutide on cerebrovascular disease, myocardial infarction, and death in type 2 diabetic individuals. LEADER trial revealed that Liraglutide lowered the main cardiovascular risks compared to placebo. Fewer patients in liraglutide group experienced a suboptimal glycemic control or the need for other anti-diabetic medications for glycemic control. Patients in the Liraglutide group had better glucose levels over time than the placebo group. The glycemic level deteriorated in both placebo and Liraglutide group during five years, but the deterioration occurred more rapidly in the placebo group [8].

SUSTAIN-6 trial

The trial performed on 2735 individuals with previous cardiovascular or renal disease, or both conditions. The primary outcomes were fewer in Semaglutide users compared to placebo, however, more subjects discontinued the treatment due to gastrointestinal side effects. In type 2 diabetic patients and cardiovascular risk factors, total numbers of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death were remarkably less in patients receiving Semaglutide, hence this trial confirmed the non-inferiority of Semaglutide [9].

PIONEER-6 trial

In this trial on 137 subjects with type 2 diabetes, all-cause mortality reduced remarkably with oral Semaglutide with a risk reduction of 21 percent.

Semaglutide in both trials was associated with a beneficial effect on hypertension, weight loss, and glycemic control. The mean pulse rate was increased in both trials with Semaglutide [10].

Results of the SUSTAIN 6 and PIONEER 6 trials revealed that Semaglutide has a cardiovascular risk reduction in patients who had the same REWIND trial criteria, revealing that cardiovascular effects of Semaglutide may extend to both primary and secondary prevention in type 2 diabetic people, compatible with the results for Dulaglutide in REWIND trial [11].

Harmony outcomes trial

Published in 2018 with participants of 40 years or above and type 2 diabetes with one of the criteria of cerebrovascular, cardiovascular, or peripheral arterial disease. Albiglutide use showed a major reduction in non-fatal or fatal myocardial infarctions. This trial did not evaluate the micro vascular outcomes like retinopathy or renal dysfunction. Serious side effects, hypoglycaemia rates, pancreatitis, pancreatic neoplasms, and thyroid cancer rates remained the same in both groups. This was a short term trial in high-risk individuals with high HgA1c levels compared to other cardiovascular clinical trials.

Rewind trial

This study was a superiority trial for the cardiovascular outcomes of GLP1-agonists on individuals of 50 years old and above with diabetes and either cardiovascular risk factors or established cardiac events. Primary cardiovascular outcomes happened in statistically less number of patients in Dulaglutide group compared to placebo. Also Non-fatal stroke and renal outcomes were remarkably less in the Dulaglutide group compared to placebo. The rate of retinopathy outcomes or serious side effects such as hypoglycaemia, pancreatitis, pancreatic tumors, or thyroid cancer rates remained the same in both groups.

This study differed from other clinical trials with GLP1-agonists. This was a longer duration trial with lower risk subjects, and lower initial HgA1c levels [12].

GLP-1 agonists are an important category of drugs for the management of patients with type 2 diabetes with the ability to improve HBA1C levels and weight also carrying minimal risk of hypoglycaemia. Moreover, seven cardiovascular outcomes trials in the past few years with short- acting Exenatide, intermediate-acting Liraglutide, Lixisenatide, and long- acting Dulaglutide, Exenatide, and Semaglutide have shown non-inferiority for the cardiovascular events, and mostly superiority of these class of medications. These outcomes have changed the guidelines on type 2 diabetes treatment [12].

Conclusion

GLP-1 agonists are effective additions to the management of type 2 diabetes as mono or combined therapy with or without insulin. Six subcutaneous GLP-1 agonists are available in the Europe and USA with many resemblances and some special characteristics. Stimulating the GLP-1 receptors increases insulin levels and suppresses glucagon excretion in a glucose-based pattern, hence improves the clinical outcomes associated with glycaemic control and weight management. These drugs also have proved the non-inferiority and sometimes superiority for the major cardiovascular outcomes. GLP-1 agonists are tolerated well, with gastrointestinal complaints being the most common side effects, and carry a minimal risk of hypoglycaemia. GLP-1 agonist administration needs to be tailored and individualized for every diabetic patient [13].

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