

New Data on Cardiovascular Effects of Glucagon-Like Peptide-1 Receptor Agonists



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ion: March 03, 2017; **Published:** April 17, 2017

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Abstract

Cardiovascular disease (CV) is the leading cause of morbidity and mortality in patients with type 2 diabetes. Glucagon-like peptide-1 receptor agonists are new agents that are very promising because they affect many cardiovascular risk factors, apart from improving the glycemic control. Based on the published LEADER and SUSTAIN-6 trials liraglutide and semaglutide have shown cardiovascular benefit and could be reasonable options as second line agents for patients with CV disease. Lixisenatide have been evaluated in one CV safety trial and has neutral effects on CV outcomes. Individuals without CV disease can be treated with any of the other classes of anti-diabetic medication. However, in patients with established CV disease medications with proven CV benefit should be preferred.

Keywords: Cardiovascular disease; Type 2 diabetes mellitus; Glucagon-like peptide-1 receptor agonists

Abbreviations: CV: Cardiovascular; UKPDS: UK Prospective Diabetes Study; MI: Myocardial Infarction; ACCORD: Action To Control Cardiovascular Risk in Diabetes Study Group; HbA1c: Glycated Hemoglobin; FDA: Food and Drug Administration; EMA: European Medicines Agency; GLP: Glucagon-Like Peptide; SGLT: Sodium-Glucose Co-Transporters; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; HF: Heart Failure; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome results; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; EXSCEL: Exenatide Study of Cardiovascular Events Lowering Trial; FREEDOM-CVO: Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated with ITCA 650; REWIND: Researching Cardiovascular Events with Weekly Incretin in Diabetes

Introduction

Diabetes mellitus is a metabolic disorder that is characterized by hyperglycemia. Cardiovascular disease (CV) is the leading cause of morbidity and mortality in patients with diabetes and hyperglycemia is the link between them [1-3]. The worldwide rise of incidents of type 2 diabetes is following the increase of the obesity and makes the prevention of CV disease a primary target [4-6]. Several studies in the past have shown that better glycemic control is associated with reductions of micro angiopathic complications, but the cardiovascular effect of strict diabetes control using the older anti-diabetic medications was not clear [7,8].

The first study that showed that intensive blood glucose control with sulfonylureas or insulin significantly reduces the risk of microvascular complications, but has no effect on macrovascular outcomes was The UK Prospective Diabetes Study (UKPDS) [7]. However, the 10-year follow-up of the UKPDS demonstrated that intensive blood reduces significantly (by 15%) myocardial infarction (MI) and therefore, provides

macrovascular benefits [8]. On the other hand, the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial reported that although intensive blood glucose control reduced significantly the risk of MI, it resulted in an increase of all-cause mortality [9]. However, in this study the HbA1c target was <6% and the arm with the intensive treatment experienced more hypoglycemic episodes and consequently, had increased risk of CV disease [10,11].

At the same time, a meta-analysis of the CV safety of rosiglitazone was published and reported that patients had increased risk of MI and borderline increased risk of CV death [12]. As a result, the US Food and Drug Administration (FDA) in 2008 [13] and the European Medicines Agency (EMA) in 2012 [14] reported that new anti-diabetic agents have to perform clinical trials in order to evaluate the CV safety and gain approval. These trials do not evaluate the efficacy to the glycemic control, but assess non-inferiority in lowering CV risk, while superiority is a secondary endpoint. Generally, these trials recruit patients who are at high CV risk or have established CV disease in order

to gather a sufficient number of CV events in a timely manner. Consequently, it is not clear if the findings of CV safety trials can be generalized to a healthier diabetic population.

Over the last decades the quiver of anti-diabetic agents has increased significantly and currently we have 9 classes of medications approved for the treatment of type 2 diabetes: metformin, sulphonylureas, meglitinides, thiazolidinediones, alpha glucosidase inhibitors, insulin, dipeptidyl peptidase -4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists and sodium-glucose co-transporters (SGLT-2) inhibitors. The first line agent for the treatment of type 2 diabetes is metformin according to the American Diabetes Association and the European Association for the Study of Diabetes [15]. However, the choice of the second line agent when metformin fails to achieve proper glycemic control is still challenging. We have to keep in mind that the main target of patients with diabetes is the reduction of diabetic complications and not just the reduction of blood glucose.

The aim of this mini-review is to identify the CV risk profile of GLP-1 receptor agonists, based mostly on CV safety trials. We performed a thorough search of MEDLINE and EMBASE between January 1980 and February 2017 using the terms “anti-diabetic agents”, “CV risk”, “GLP-1 receptor agonists”, alone and in combination to retrieve available data.

GLP-1 Agonists

GLP-1 receptor agonists are newer anti-diabetic agents that are administered subcutaneously and act by maintaining the biological actions of endogenous GLP-1. GLP-1 is a gastrointestinal hormone that promotes insulin release in a glucose-dependent manner and inhibits glucagon secretion, thus lowering basal and postprandial blood glucose. GLP-1 agonists, additionally, promote weight loss by enhancing satiety, slow gastric emptying and have been found to lower systolic blood pressure [16]. The main adverse events are gastrointestinal (nausea and vomiting). Due to those favorable effects on several CV risk factors accompanied with low hypoglycemia risk, the results of the GLP-1 receptor agonist CV trial were expected to be exciting.

Lixisenatide was the first GLP-1 receptor agonist that was evaluated about CV safety in The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial. The primary composite outcome was: non-fatal MI, non-fatal stroke, hospitalization for unstable angina and CV death in patients with type 2 diabetes and an acute coronary syndrome (MI or unstable angina) within 180 days before randomization [17]. In the study 6.068 patients were randomized and had a median follow up of 2.1 years. The results showed that treatment with lixisenatide had neutral effect on the composite primary outcome and on hospitalization for HF, which was a secondary outcome.

The second trial was the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome results

(LEADER). Treatment with liraglutide showed superiority of an anti-diabetic agent for the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke [18]. A total of 9.340 patients with type 2 diabetes at high risk of CV disease were recruited. One arm was receiving placebo and the other was receiving liraglutide. The median follow up was 3.8 years. Fewer patients in the liraglutide group experienced any component of the primary endpoint compared with patients in the placebo group (13% reduction of the primary composite endpoint), including a significantly 22% lower risk of CV death, a non-significant 12% lower risk of non-fatal MI and a non-significant 11% lower risk of non-fatal stroke. Furthermore, treatment with liraglutide was also associated with a 15% lower risk of death from any cause, while hospitalization for HF did not differ between the two treatment arms of the trial.

Treatment with liraglutide was associated with greater weight loss as expected. Liraglutide was also associated with a lower rate of incidence nephropathy, which was a secondary outcome and was defined as new onset microalbuminuria, doubling of serum creatinine, need for continuous renal-replacement therapy or death from renal disease. On the other hand, the incidence of retinopathy was non-significantly higher in the liraglutide treatment group. The main adverse events of liraglutide were gastrointestinal disorders and increases in heart rate. Hypoglycemia was more common in participants receiving placebo, while acute gallstone disease was more common in patients receiving liraglutide. Acute pancreatitis, pancreatic cancer and medullary thyroid carcinoma and did not differ between the two treatment groups.

The positive effect of liraglutide to the CVD was mainly attributed to modification of various CV risk factors such as weight reduction and lowering of systolic blood pressure, apart from the glucose lowering effect. However, the authors were not able to explain the different results of the LEADER and the ELIXA trials and it is not clear yet if the reduction of CV morbidity and mortality is drug specific for liraglutide or a class effect of GLP-1 agonists. It should be taken into account that only subjects with acute coronary syndrome in the previous three months were recruited in the ELIXA study, while in the LEADER trial subjects with established CV disease or subjects at high risk for CV disease were recruited.

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) was the CV safety trial of one weekly semaglutide and was published recently. The trial consisted of 3.297 patients with type 2 diabetes and established CV disease, chronic HF, chronic kidney disease of stage 3 or higher or an age of 60 years or more with at least one CVD risk factor. The median follow up period was 2.1 years [19]. Patients in the semaglutide treatment arm had a 26% lower rate of the primary composite endpoint (i.e. CV death, non-fatal MI or non-fatal stroke) compared with those on placebo. The overall benefit was driven mostly by a

39% reduction in the occurrence of non-fatal stroke, since the 26% reduction in the occurrence of MI was not significant and the rates of CV death were similar between the two treatment groups.

Treatment with semaglutide was not associated with lower risk of death from any cause or hospitalization for HF, but was associated with a 36% lower risk of new or worsening nephropathy. However, diabetic retinopathy complications, such as need for retinal photocoagulation or intravitreal medications, vitreous hemorrhage and onset of diabetes related blindness, were more common in patients receiving semaglutide. Mean heart rate was slightly but significantly higher in the semaglutide groups compared with the placebo group, but treatment with the active agent was associated with lower systolic blood pressure and greater weight loss. The main adverse events of semaglutide were gastrointestinal adverse effects (nausea and vomiting).

We are eagerly expecting within the next years the results of several trials assessing the CV safety of different GLP-1 receptor agonists. The Exenatide Study of Cardiovascular Events Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcome After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus [20] and the Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650 (FREEDOM-CVO) [21] are evaluating the CV safety of exenatide, while The Researching Cardiovascular Events With Weekly Incretin in Diabetes (REWIND) trial [22] is evaluating the CV safety of once weekly dulaglutide.

Conclusion

Altogether, GLP-1 receptor agonists are promising anti diabetic agents that effectively lower HbA1c, weight and systolic blood pressure with low risk of hypoglycemia. Liraglutide and semaglutide are the first GLP-1 analogs that had favorable effects on CV outcomes and seem a reasonable second line treatment in patients that do not reach HbA1c goals with metformin, while lixisenatide has been shown to be neutral in terms of CV safety. However, the exciting findings of the LEADER and the SUSTAIN 6 trials need confirmation by further studies in different study populations in order to have more robust data and with superiority as a primary outcome.

References

1. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades RM, et al. (2015) Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol* 3(2): 105-113.
2. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. (2013) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 34(39): 3035-3087.
3. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 375(9133): 2215-2222.
4. Centers for Disease Control and Prevention (2014) Number (in Millions) of Civilian, Non-Institutionalized Persons with Diagnosed Diabetes, United States, 1980-2014. Diabetes Public Health Resource, USA.
5. Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology, and management *JAMA* 287(19): 2570-2581.
6. Gu K, Cowie CC, Harris MI (1998) Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care* 21(7): 1138-1145.
7. Lancet (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) Group. *Lancet* 352(9131): 837-853.
8. Holman RR, Paul SL, Bethel MA, Matthews DR, Neil HA (2008) 10 years follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359(15): 1577-1589.
9. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, et al. (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358(24): 2545-2559.
10. Chow E, Bernjak A, Williams S, Fawdry RA, Hibbert S, et al. (2014) Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes* 63(5): 1738-1747.
11. Nordin C (2010) The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia* 53(8): 1552-1561.
12. Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356(24): 2457-2471.
13. Final Guidance for Industry: Guidance for Industry: Diabetes Mellitus - Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. U.S. Department of Health and Human Resources; December 2008. European Medicines Agency Guideline on the Investigation of Drug Interactions.
14. American Diabetes Association (2017) Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 40(Suppl 1): S64-S74.
15. Garber AJ (2011) Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 34(supply 2): S279-S284.
16. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, et al. (2015) Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med* 373(23): 2247-2257.
17. Marso SP, Daniels GH, Brown FK, Kristensen P, Mann JF, et al. (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 375: 311-322.
18. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, et al. (2016) Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes *N Engl J Med* 375(19): 1834-1844.
19. AstraZeneca (2017) Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus. *ClinicalTrials*, USA.
20. Intarcia Therapeutics (2017) A Study to Evaluate Cardiovascular Outcomes in Patients With Type 2 Diabetes Treated With ITCA 650. *ClinicalTrials*, USA.
21. Eli Lilly and Company (2017) Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND). *ClinicalTrials.gov*, USA.



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DOI: [10.19080/CRDOJ.2017.2.555577](https://doi.org/10.19080/CRDOJ.2017.2.555577)

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