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Anti-atherogenic effect and cardiovascular benefit of GLP-1 receptor agonists

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Abstract

Obesity is now becoming the most important Risk Factor (RF) for Cardiovascular (CV) diseases throughout the population level. It directly leads to the onset and development of CV diseases and increases cardiovascular mortality independently of other RFs. GLP-1 receptor agonists elegantly interfere with physiological mechanisms regulating food intake. Specifically, liraglutide regulates appetite by increasing feelings of satiety and fullness while reducing feelings of hunger and the desire to consume additional food. In addition, it reduces the risk of diabetes development and has antiatherogenic effects. The SCALE Obesity and Prediabetes Study demonstrated a 9.2 % average decrease in body weight compared to the baseline value after 56 weeks of treatment, while the risk of developing type 2 diabetes mellitus was reduced by 80% over a 3-year period. Significant weight loss leads to reduced risk of hypertension, arrhythmias (including atrial fibrillation), coronary artery disease, and heart failure. In the case of already-developed CV diseases, weight reduction will allow a reduction in the extent of pharmacotherapy and hospitalization, and it will bring improvement to the patient's quality of life and prognosis. In the LEADER study, liraglutide significantly reduced the incidence of major adverse cardiovascular episodes by 13 %, HR 0.87 (p = 0.005). GLP-1 receptor agonists reduce CV episodes, including the risk of hospitalization for heart failure, not only in patients with clinical CV disease, but also in patients with increased CV risk without clinically apparent CV disease.

Introduction

Overweight and obesity are currently among the most important risk factors: an increase in BMI of 5 kg/m^2 leads to a 30% increase in overall mortality and a 40% increase in vascular mortality for coronary heart disease, cerebrovascular diseases, and other vascular diseases.

Weight reduction in patients with Cardiovascular (CV) diseases and concurrent overweight or obesity brings a fundamental improvement in health and prognosis of such diseases, a proven reduction in mortality and morbidity, and is associated with a reduction in pharmacotherapy and the number of hospitalizations, therefore, it is also economically effective [1-3].

With the current growing trend in population, obesity also becomes a population Risk Factor (RF) that is more significant than smoking, and a leading cause of preventable diseases.

From this point of view, the availability of a new effective anti-obesity medication is very welcome, in particular, liraglutide

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elegantly interferes with the physiological mechanisms regulating food intake. In addition, it reduces the risk of developing diabetes and has anti-atherogenic effects.

Obesity and cardiovascular risk

Obesity parameters are not included in the latest ESC recommendations for the calculation of CV risk because they would no longer increase the accuracy of the SCORE2 estimation. Although obesity increases the level of individual risk factors such as dyslipidaemia and hypertension, which are already included in the SCORE2 system, it also directly leads to the development of CV diseases and increases cardiovascular mortality independently of other RFs.

In addition to the direct effect of pericardial fat on epicardial arteries, obesity significantly affects coronary microvasculature, a key regulator of coronary flow (endothelial dysfunction, subclinical inflammation, remodelling of small arteries). Obesity itself strongly supports the emergence and development of left ventricular diastolic dysfunction and heart failure even in the absence of other diseases.

Concomitant myocardial fibrosis on ECG is manifested by prolonged time intervals, development of tachycardia, extrasystole, and atrial fibrillation.

Obesity is associated with greater prevalence of coronary atherosclerosis, especially in men.

In a large clinical study including more than 100,000 patients [4], obesity was the strongest NSTEMI RF in younger subjects, followed by smoking. The higher the BMI, the lower the age at which the MI was formed (both STEMI and NSTEMI).

Current knowledge highlights the importance of abdominal obesity as a serious risk factor independent of BMI. Even individuals with normal BMI weight, but with increased waist circumference as a manifestation of abdominal obesity, are in the band of increased cardiometabolic risk and increased mortality.

Extensive meta-analyses show that the relative risk of fatal and non-fatal CV disease, adjusted for age, gender and smoking, continuously increases with each centimetre by a multiple of 1.05 in females and 1.02 in males [5]. Thus, with an increase of 10 cm, a 1.5-fold increase in the risk for women can be expected.

Weight reduction of 10 kg in obese patients with hypertension is associated with a reduction in systolic blood pressure of 10-40 mmHg on average and diastolic blood pressure of 10-20 mmHg on average.

General knowledge on the effects of GLP-1 receptor agonists in the treatment of obesity with a focus on liraglutide

GLP-1 is a physiological regulator of appetite and food intake, it works in areas of the brain that are involved in regulating appetite. Liraglutide is an analogue of human GLP-1, it is synthesized as the body's own incretin hormone GLP-1 (97% homology in the composition of amino acids). It reduces body weight in humans GLP-1 is a physiological regulator of appetite and food intake, it works in areas of the brain that are involved in regulating appetite. Liraglutide is an analogue of human GLP-1, it is synthesized as the body's own incretion hormone GLP-1 (97% homology in the composition of amino acids). It reduces body weight in humans mainly through fat loss along with relative loss of total body fat, which is higher than the loss of subcutaneous fat. Liraglutide controls appetite by enhancing satiety and satisfaction, while alleviating hunger and appetite to consume more food, ultimately leading to reduced food intake. Liraglutide does not increase energy expenditure compared to placebo. In terms of laboratory results, treatment will be shown by decreased fasting glucose, improved lipidogram, decreased hsCRP, and decreased adiponectin levels.

The most important results were presented in a series of publications under the SCALE programme [6-12]. In the SCALE Obesity and Pre-Diabetes study, including its 3-year extension, the following was demonstrated:

- 9.2% average decrease in body weight from baseline after 56 weeks of treatment,
- categorical weight loss ≥5%, ≥10%, and ≥15%, achieved by 63.2%, 33.1%, and 14.4% of patients, respectively,
- sustained weight loss over 3 years of treatment,
- an average waist circumference reduction of 8.2 cm,
- decrease of blood pressure levels,
- 80 % reduction in the risk of developing type 2 diabetes mellitus over 3 years.

Throughout the SCALE trial programme, liraglutide treatment was accompanied by regular guidance on lifestyle focused on at least 150 minutes of physical activity per week and dietary guidance to reduce energy intake by 500 kcal/day. The high safety level of the treatment allowed to indicate the treatment from the age of 12 years.

Cardioprotective and anti-atherogenic effects of GLP-1 receptor agonists with a focus on liraglutide

Significant weight loss leads to reduced risk of hypertension, arrhythmias (including atrial fibrillation), ischaemic heart disease, and heart failure. In already developed CV diseases, weight reduction will allow to reduce the scope of pharmacotherapy, hospitalization, and improve the quality of life and prognosis of the patient. In addition, GLP-1 receptor agonists generally reduce cardiovascular risk by acting directly on the vascular wall endothelium, the effect being likely mediated by anti-atherosclerotic mechanisms [13-15].

GLP-1 receptors are expressed in many tissues, including the gastrointestinal tract. Their activation leads to a decrease in intestinal permeability and a decrease in the concentration of triacylglycerols and postprandial lipaemia, which in turn reduces inflammation and lipid deposition in the vascular wall.

Liraglutide and also semaglutide play a specific role in anti-inflammatory processes, which makes one consider potential prevention of atherosclerotic plaque formation. The long-term anti-atherosclerotic effect mediated by GLP-1 receptor agonists is independent of changes in body weight and glucose levels.

The LEADER study (The Liraglutide Effects and Action in Diabetes Evaluation of Cardiovascular Outcome Results) included a cohort of 9,340 patients with inadequately controlled type 2 diabetes [16]. The vast majority of them had already been diagnosed with cardiovascular disease. Patients were randomised to receive either liraglutide at a daily dose of up to 1.8 mg (4,668 patients) or placebo (4,672 patients), both in addition to standard therapy, for a study duration of 54 months, in 10% for more than 54 months.

Liraglutide significantly reduced the incidence of major adverse cardiac events (primary endpoint, MACE) versus placebo with a 13% risk reduction, HR 0.87 (p = 0.005). GLP-1 receptor agonists have also been shown to reduce CV events, including the risk of hospitalization for heart failure, not only in patients with clinical CV disease, but also in patients with elevated CV risk without clinically apparent CV disease [17].

Conclusion

At a time of a growing obesity epidemic in the population, GLP-1 receptor agonist medicinal products based on the influence of physiological mechanisms regulating food intake may have significant benefits in the treatment of both obesity and CV diseases and for increased CV risk.

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