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The new type 2 diabetes mellitus therapy: comparison between the two classes of drugs GLPR (glucagon-like peptide receptor) agonists and SGLT2 (sodium-glucose cotransporter 2) inhibitors

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Type 2 diabetes mellitus represents one of the most common chronic-degenerative diseases in modern society and is the cause of innumerable micro- and macrovascular complications that weigh on the national health system. Until a few years ago, there was no anti-diabetic drug that, in addition to lowering blood sugar, had an impact on cardiovascular risk in these patients. In this report, we will analyse the characteristics, contraindications, and evidence in favour of the use of two innovative categories of molecules that aim, for the first time in history, at controlling blood sugar levels and simultaneously lower cardiovascular risk in diabetics individuals: the glucagon-like peptide receptor agonists and the sodium–glucose cotransporter 2 inhibitors.

Introduction

Type 2 diabetes mellitus represents one of the most common chronic degenerative diseases in modern society. According to an estimate by the International Diabetes Federation (IDF), in 2015, diabetic subjects in the world amounted to 415 million, a figure destined to increase up to 642 million in 2040.[1] This figure is particularly worrying considering the impact that this pathology has on heart, kidney, retinal, and vascular diseases. It is estimated that 15% of people with diabetes suffer from coronary artery disease; 22% of retinopathy which can cause blindness; 38% have chronic kidney disease, and 3% have vascular diseases that can lead to amputation.[2]

From these data it can be seen that optimal control of the disease is of fundamental importance for the adequate prevention of its multiple complications; hence the need for innovative therapies with cutting-edge drugs. Among these, two classes of molecules that have emerged in the last 10 years stand out: GLP1-agonists and SGLT2 inhibitors.

GLP1-agonists

Gastric inhibitory polypeptide and glucagon-like peptide 1 (GLP1) represent the main molecules belonging to the class of incretins, a group of hormones secreted by intestinal L and K cells in response to the ingestion of a meal. GLP1 exerts its action by binding to its receptor which is expressed in different tissues, including pancreatic β cells: here, GLP1 stimulates the release of glucose-dependent insulin. In addition, GLP1 suppresses the release of glucagon from pancreatic α cells, probably due to the local release of somatostatin by δ cells.[3] GLP1 also promotes the slowing down of gastric emptying and the induction of a sense of satiety.[3] Studies conducted on rodents and *in vitro* have also shown an activity of inhibition of apoptosis and an enhancement of regenerative capacity in favour of pancreatic β cells[3] (*Figure 1*).

The half-life of GLP1 is 2–3 min because it is rapidly inactivated by the enzyme Dipeptidyl Peptidase 4 (DPP4) and subsequently excreted via the kidneys, making the molecule unsuitable for pharmacological use. To allow effective therapeutic use, the synthesis of GLP1-R receptor agonists

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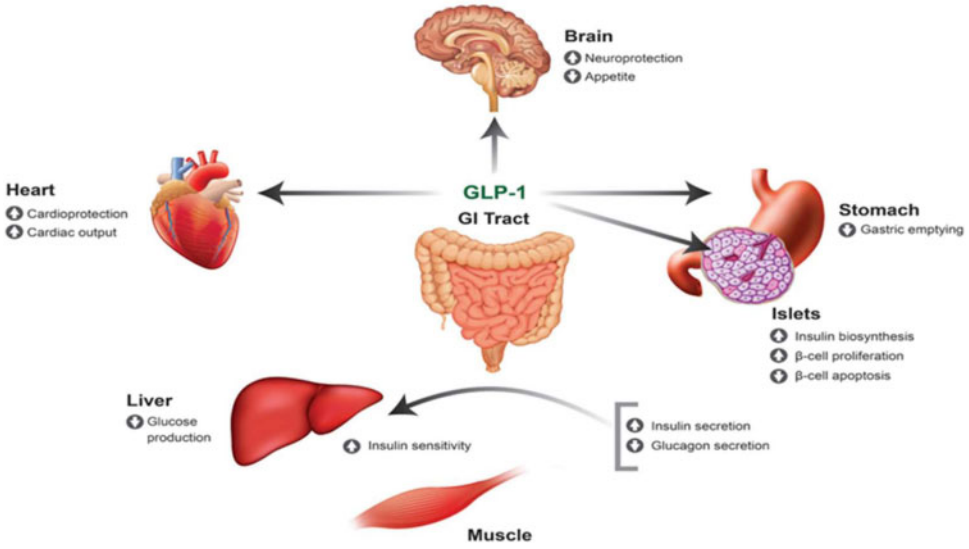

Figure 1 GLP-1 acts through innumerable both intra and extra-pancreatic mechanisms, as shown in the figure. C. Thomopoulos, MD. Antidiabetic drugs as a cardiovascular shield: from skepticism to euphoria. 2019.

resistant to the action of the DPP4 enzyme and consequently with a longer half-life was necessary: the first compound is represented by Exenatide, a synthetic analogue of GLP1 exendin-4 agonist isolated in the saliva of the reptile Heloderma suspectum.[3] It is characterized by the presence of an amino acid variation that guarantees its resistance to the action of DPP4, prolonging its half-life up to 2.4 h.[4] However, since the peptide is also subject to renal clearance, the resistance to cleavage by DPP4 can extend its half-life only to a limited extent. By directly binding the GLP1-agonist with plasma albumin or inducing its binding through the introduction of fatty acid chains, its elimination can be prevented by glomerular filtration: this is the case of the Liraglutide and Albiglutide molecules, respectively equipped with a half-life 13 and 120 h. Another similar method consists in combining the molecule with the Fc fragment of an IgG4 as in the case of Dulaglutide.[4]

We can divide the various GLP1 agonists into short-acting and long-acting based on the half-life.

Short acting

Short-acting GLP1-RAs are usually administered before a meal, typically before breakfast and dinner as in the case of Exenatide or only at breakfast as in the case of Lixisenatide.[5] These molecules exert a modest action on blood glucose levels and insulin secretion under fasting conditions. However, the rapid increase in plasma concentrations following their administration, combined with the reduced development of tachyphylaxis, results in a substantial prolongation of gastric emptying, and a consequent delay in intestinal glucose absorption, which accounts for the marked reduction in post-prandial glucose which characterizes this group of molecules.[5] Another consequence of the delayed gastric emptying is the post-prandial reduction of the blood levels of triglycerides and fatty acids.

Long acting

Recent studies show that long half-life molecules are associated with a reduction in levels of glycated haemoglobin of ~1.5%, a greater value than agents with reduced half-lives,[5] metformin, and sulphonylureas.[6] Long-acting agents do not have a substantial effect on gastric motility, probably due to the rapid development of tachyphylaxis; as a consequence, they will not impact post-prandial blood sugar levels as much as short-acting molecules. However, unlike the latter, the plasma concentrations of long-acting GLP-1RAs remain consistently high over time between one administration and the next; this results in better glycaemic control during fasting periods, including at night and in the morning.

A peculiarity that these molecules have in common is represented by the reduction of body weight, an action mediated by the effects that GLP1-RAs exert on the central nervous system and especially at the hypothalamic level.

Side effects and contraindications

The main side effects are represented by the appearance of nausea and vomiting.[3] It is important to note that, while the nausea secondary to the administration of these molecules tends to decrease after 4–8 weeks of treatment, the weight loss remains stable over time.[3]

GLP1-RAs had initially been associated with a higher incidence of pancreatitis, pancreatic cancer and cholelithiasis. Recent studies have shown that there is no increased risk of pancreatitis or pancreatic cancer associated with the use of these molecules; however, there is an increase in the incidence of cholelithiasis.[7]

GLP1-RAs have been associated with an increase in the incidence of medullary thyroid carcinoma in rodents; although this association has not been highlighted in humans, the use of these drugs should be avoided in patients with a history of medullary thyroid carcinoma or MEN2.

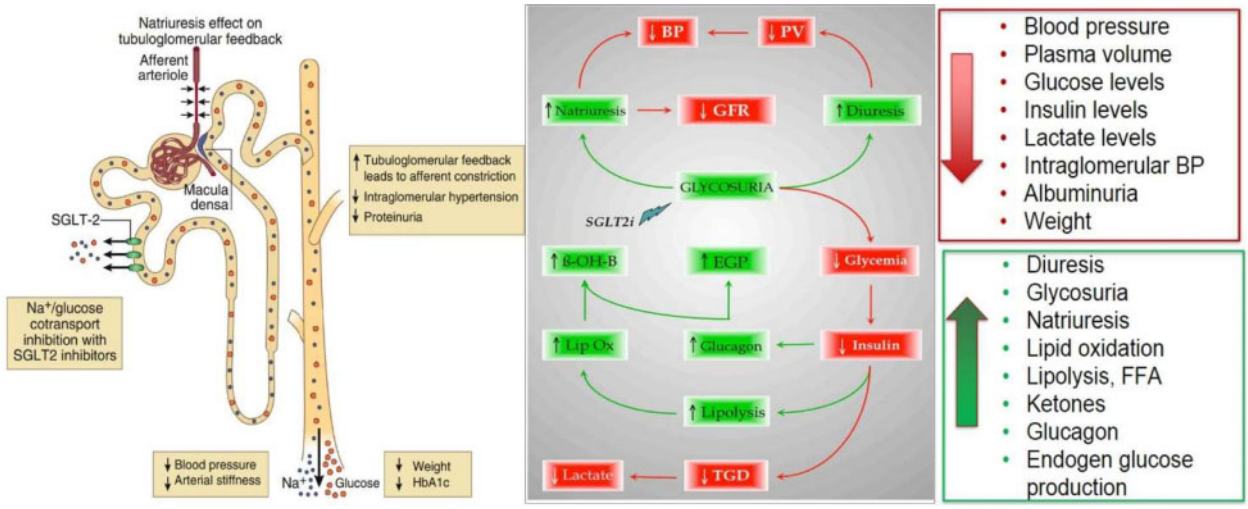

Figure 2 Mechanism of action of SGLT2i. C. Thomopoulos, MD. Antidiabetic drugs as a cardiovascular shield: from skepticism to euphoria. 2019.

SGLT2 inhibitors

The kidney filters around 180 L of plasma every day. In an individual with plasma glucose concentrations equal to 90–100 mg/dL this corresponds to a concentration of glucose reaching the nephron equal to 162–180 g/day, an amount that will be completely reabsorbed at the level of the proximal convoluted tubule. This is made possible by the presence, at this level, of sodium-glucose co-transporters (SGLTs). Of these, the responsible for the reabsorption of 90% of filtered glucose is represented by SGLT2, expressed only in the kidney at the level of the S1 tract of the proximal convoluted tubule. The remaining 10% of filtered glucose is reabsorbed by SGLT1, a co-transporter located in the S3 section of the proximal tubule and in the intestine.[8]

Under normal conditions all the filtered glucose is reabsorbed through the aforementioned mechanisms; as a consequence, glucose is not normally found in the urine. The blood glucose limit value beyond which glycosuria begins to occur in healthy subjects is 180 mg/dL. Several studies have shown that a chronic increase in plasma glucose concentration is accompanied by an up-regulation of SGLT2, as occurs in diabetics; this leads to an increase in tubular glucose transport capacity which translates into greater reabsorption and a reduction in glycosuria,[8] with consequent increase in blood glucose.

The SGLT2 inhibitor drugs have their effect by selective blocking of these transporters by preventing tubular reabsorption of glucose and promoting renal excretion (*Figure 2*).

Currently, three molecules belonging to this class have been approved by the EMA: Canagliflozin, Dapagliflozin, and Empagliflozin. It has been shown that their use is associated with a reduction in glycated haemoglobin values of about 1%, a value that can be superimposed on that of sulphonylureas.[6] Unlike the latter, however, the risk of hypoglycaemia is zero.[9] The use of this type of molecule has several other advantages: being SGLT2 expressed only in the renal tubular epithelium, SGLT2i have a very selective action. In particular, Dapagliflozin has a selectivity for SGLT2 1400 times greater than for SGLT1, while Empagliflozin 5000 times.[9]

Another feature of the SGLT2i is represented by weight loss: the increase in urinary glucose excretion favours a negative energy balance of about 200–300 kcal/day.

Most clinical trials with SGLT2i in diabetic subjects demonstrated a significant weight loss in treated patients compared to control or placebo-treated patients.[9] It also appears that these molecules have a favourable effect on the lipid profile and functionality of pancreatic β cells.[10]

Side effects and contraindications

Adequate renal function is required for the intrinsic mechanism of action of these drugs: they must not be started if the glomerular filtrate is $<$60 mL/min and must be suspended if the glomerular filtrate drops to values below 45 mL/min.[6]

Urinary tract infections and specifically mycotic infections represent the main complication associated with the use of these drugs, especially in female subjects. These infections, usually mild, do not affect the continuation of therapy.[9]

A consequence of the mechanism of action of SGLT2i is the increase in diuresis and natriuresis: this entails a greater risk of volume depletion and consequent hypotension, especially in the elderly in therapy with diuretics.[9]

It should be noted that there was a slight increase in minor foot amputations with the use of Canagliflozin[6]; the use of this molecule should be avoided in patients at risk for amputation. Screening using the ABI index prior to initiating SGLT2i therapy may be useful in all those patients with peripheral vascular disease.

Canagliflozin is also associated with a slight but statistically significant increase in bone fractures; therefore, it should be used with caution in patients with osteoporosis.

Finally, a rare but possible complication is represented by diabetic ketoacidosis.

Table 1 The reason behind the cardiovascular benefits of this class of drugs seems to be linked to a reduction in the events related to atherothrombotic phenomena, although the mechanism of action has not yet been clarified

	ELIXA	LEADER	SUSTAIN-6	EXSCEL	REWIND	HARMONY-OUTCOMES	PIONEER-6
GLP-1 agonist and comparator	Lixisenatide vs. placebo	Liraglutide vs. placebo	Semaglutide[a] vs. placebo	Exenatide ER[a] vs. placebo	Dulaglutide[a] vs. placebo	Albiglutide[a] vs. placebo	Semaglutide[b] vs. placebo
Number of patients	6068	9340	3297	14 752	3183	9463	3183
Main inclusion criteria	Recent ACS (<3 months)	Established CVD	Established CVD, HF, or CKD (Stage 3 or above)	No CV criteria specified			
Primary outcome	4P-MACE	4P-MACE	3P-MACE	3P-MACE	3P-MACE	3P-MACE	3P-MACE
Main secondary outcome	Expanded primary	Expanded primary	Expanded primary	All-cause mortality; HHF; hospitalization for ACS	All-cause mortality; HHF; hospitalization for ACS	Expanded primary; HHF	Expanded composite outcome
Median follow-up	2.1 years	3.8 years	2.1 years	3.2 years	1.4 years	1.5 years	1.4 years

C. Thomopoulos, MD. Antidiabetic drugs as a cardiovascular shield: from skepticism to euphoria. 2019.
[a]Weekly injection.
[b]Oral administration once a day.

When and why to use these drugs?

Until a few years ago, no anti-diabetic drug had shown clear benefits on reducing cardiovascular risk and macrovascular complications. This paradigm has been overcome by the EMPA-REG and LEADER clinical trials, which have opened the door to a new era of anti-diabetic therapy in subjects with high/very high cardiovascular risk or with known cardiovascular disease.

According to the latest ADA 2019 guidelines, the first-choice drug in the diabetic patient remains metformin. GLP1-RAs and SGLT2i are indicated as addition to metformin in all patients who do not reach the optimal target of glycated haemoglobin and have known cardiovascular disease or chronic kidney disease. According to the ESC 201911 guidelines, the GLP1-RAs and SGLT2i can be considered both as first-line drugs in patients not on drug therapy and with a known cardiovascular disease or a high/very high cardiovascular risk, and as an addition to metformin in patients who do not reach optimal levels of glycated haemoglobin and which present a known cardiovascular disease or high/very high cardiovascular risk. Currently, of GLP1-RAs only Liraglutide and of SGLT2i only Empagliflozin have FDA approval for use in patients with type 2 diabetes with high/very high cardiovascular risk or known cardiovascular disease.[12]

What evidence on GLP1-RAs?

The LEADER study conducted on patients with high cardiovascular risk and mainly in secondary prevention (81% of patients) has shown that the use of Liraglutide compared to placebo leads to a significant reduction in global mortality and cardiovascular events by 15% and 22%, and a non-statistically significant reduction in AMI (acute myocardial infarction) and non-fatal strokes.[11] Secondary analysis also demonstrated a reduction in the progression of chronic kidney disease. In the SUSTAIN-6 study, the use of Semaglutide demonstrated a 26% greater reduction in cardiovascular events, in particular a significant 39% reduction in non-fatal strokes compared to placebo. A 22% reduction in major cardiovascular events and a significant 25% reduction in AMI compared to placebo has also been documented following the use of Albiglutide in the HARMONY OUTCOMES[11] study. *Table 1* lists the main trials performed with these drugs.

What evidence about SGLT2i?

In the EMPA-REG OUTCOME study, the use of Empagliflozin in a population of long-term diabetics with known cardiovascular disease reduced the primary composite endpoint (death from cardiovascular events, non-fatal IMA, non-fatal stroke) by 14% in comparison with placebo.[11] This is mainly due to a 38%, as well as highly significant, reduction in death from cardiovascular events. Empagliflozin reduced overall mortality by 32% ($P < 0.00001$) and reduced hospitalization for heart failure by 35%. Importantly, these benefits have been observed in patients with and without known heart failure. In the CANVAS study, the use of Canagliflozin demonstrated a significant 33% reduction in hospitalization rates for heart failure and improved renal outcomes, while not impacting global mortality or mortality due to cardiovascular events.[11] Dapagliflozin, used in the DECLARE TIMI-58 study, reduced secondary renal

Table 2

	EMPA-REG OUTCOMES	CANVAS	DECLARE TIMI-38	CREDENCE
SGLT2 inhibitors and comparator	Empagliflozin vs. placebo	Canagliflozin vs. placebo	Dapagliflozin vs. placebo	Canagliflozin vs. placebo
Number of patients	7020	10 142	17 160	4401
Main inclusion criteria	CVD (clinical or sub-clinical)	High CV risk	High CV risk	CKD (GFR $>$ 30)
Primary outcome	3P-MACE	3P-MACE	3P-MACE	Composite renal + CVD
Main secondary outcomes	Primary expanded	HHF; any-cause death	Any-cause death; composite renal outcome	3P-MACE; HHF
Median follow-up	3.1 years	3.6 years	4.2 years	2.6 years

Thomopoulos C. Antidiabetic drugs as a cardiovascular shield: from skepticism to euphoria. 2019.

composite outcome and hospitalization for heart failure in patients with and without reduced ejection fraction.[13] In particular, a reduction in overall mortality and cardiovascular events was observed but only in patients with ejection fraction $<$45%. The ejection fraction could therefore be an important parameter to identify all patients who could benefit most from the use of SGLT2i.[13] *Table 2* lists the main trials performed with these drugs.

GLP1-RAs and SGLT2i in comparison

As demonstrated in the DECLARE-TIMI-58 study, SGLT2i seem to have a predominant effect on patients with heart failure with reduced ejection fraction, reducing the number of hospitalizations and mortality. It is important to underline how, in every study involving this class of molecules, the positive effects such as the reduction of mortality began to become evident only after a few weeks from the beginning of the treatment.[11] This seems to be linked to mainly non-metabolic phenomena, therefore, not related to the reduction of the progression of atherosclerosis. In fact, the following mechanisms could play a role: the osmotic diuresis that these drugs induces, reducing the left ventricular preload, could lead to an improvement in cardiac function; as well as weight loss due to negative calorie balance; and the reduction of blood pressure due to the loss of fluids. In addition to the cardiovascular benefits, improvements in kidney function have been observed, possibly due to a decrease in intra-glomerular pressure as a consequence of the reduction in plasma volume.[13]

The effects of GLP1-RAs, unlike SGLT2i, do not manifest themselves for several months.[11] This explains the probable metabolic effect which involves a reduction of atherosclerotic and inflammatory phenomena. As a consequence, GLP1-RAs seem to be the most appropriate choice in the case of a diabetic patient without a history of heart failure but at risk for AMI or stroke.[13] On the contrary, in patients with heart failure SGLT2i are preferable.[13]

Conclusions

The GLP1-RAs and the SGLT2i represent two unprecedented classes of drugs, since they are the first to bring a concrete benefit on cardiovascular risk and to reduce the levels of glycated haemoglobin in diabetic subjects. Further studies are needed to identify more specifically the subjects who will benefit most from the use of these molecules.

Conflict of interest: none declared.

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