

SGLT2 Inhibitors: Star Hypoglycemic Agents

On May 14, Henagliflozin, a SGLT2 inhibitor independently developed by Hengrui Pharma was officially launched. This is the first independently developed SGLT2 inhibitor in China. [SGLT2 inhibitors](#) are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. Now, the SGLT2 inhibitor has once again been shown to the public, which makes us wonder what the charm of this magical target that constantly bringing "blockbusters"?

SGLT2 inhibitors --- the statins of the 21st century

In 1835, French chemist C. Petersen isolated Phlorizin (originally used in malaria treatment) from the root bark of apple trees. Later, studies confirmed that injection of phloridzin can reduce blood sugar concentration in diabetic animals.

But it wasn't until 1996 that researchers at Kyoto University and Tanuba Seiygyu developed the first chemically synthesized SGLT2 inhibitor. In 2012, the European EMA approved **the first SGLT2 inhibitor, Dapagliflozin** for marketing.

Subsequent studies have proved that SGLT2 inhibitors are not only a hypoglycemic drug, but also effective in the treatment of type 2 diabetes, heart failure with or without type 2 diabetes and diabetic nephropathy. Eugene Braunwald once called [SGLT2 inhibitors "statins of the 21st century"](#) in his review article.

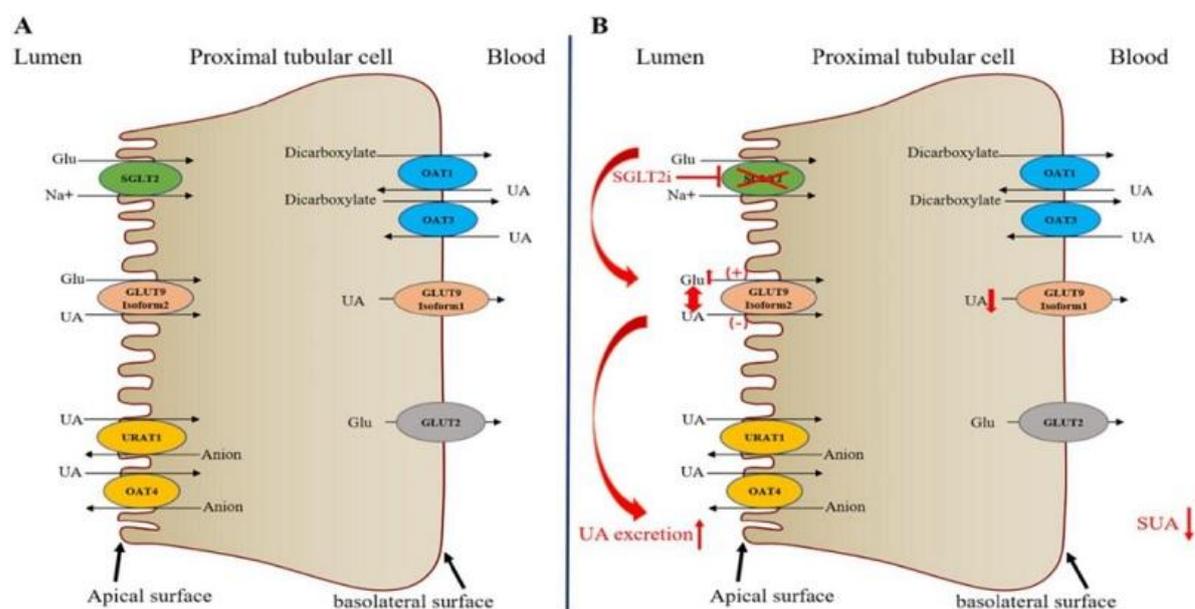


Figure 1 Mechanism of action of SGLT2 inhibitors
(Image source: Reference 2)

SGLT2, full name is Sodium-glucose Cotransporter-2, which is distributed in the renal tubules and plays the role of reabsorbing the glucose in the original urine back into the blood. When SGLT2 is inhibited, the reabsorption of glucose by the renal tubules will be inhibited, and the urine sugar will increase, thereby reducing blood sugar.

Notably, SGLT2 inhibitors are safe because their hypoglycemic effect is independent of insulin and fasting increases compensatory hepatic endogenous glucose production.

In addition to hypoglycemic effects, [SGLT2 inhibitors](#) have these effects:

1. Cardiovascular protection

A number of studies have shown that SGLT2 inhibitors have cardioprotective effects and can be used in the treatment of heart failure. They can not only improve the prognosis of patients, but also reduce the hospitalization rate and mortality rate, and have certain effects on heart failure with or without diabetes. In addition, it can improve atherosclerosis, myocardial energy metabolism and anti-fibrosis.

2. Antihypertensive effect

Clinical data show that SGLT2 inhibitors can reduce systolic blood pressure to varying degrees, and the reduction is significantly dose-dependent. For example, in the clinical trial of canagliflozin, systolic blood pressure decreased between 2.6-5.7mmHg at the 100mg dose and 3.5-7.9mmHg at the 300mg dose compared to the placebo group.

The mechanism of action is on the one hand to reduce blood pressure through urinary sodium excretion, and on the other hand to improve vascular cell function and reduce arteriosclerosis by reducing inflammatory response and oxidative stress. Surprisingly, SGLT2 inhibitors can reduce blood pressure without causing hyponatremia.

3. Weight loss

SGLT2 inhibitors reduce energy through the action of urine sugar, and at the same time induce browning of white adipose tissue. Since there are two main types of fat in humans, namely white fat and brown fat, the former stores energy and the latter produces heat and consumes energy, thus increase the

quantity of brown fat, can increase energy consumption, improve metabolism, achieve the effect of weight loss.

4. Decreased uric acid

SGLT2 inhibitors can lead to increased excretion of uric acid and decrease uric acid in the body. However, compared with classical uric acid lowering drugs, the effect is relatively weak, so it is more promising to be applied to patients with asymptomatic hyperuricemia or diabetes complicated with hyperuricemia.

5. Liver protection

SGLT2 inhibitors can protect the liver by altering the glucose-fatty acid cycle, increasing the utilization and oxidation of fatty acids in skeletal muscle, adipose tissue and the liver, thereby reducing the accumulation of fatty acids in the liver. Clinical data show that SGLT2 inhibitors can prevent and treat nonalcoholic fatty liver disease to a certain extent.

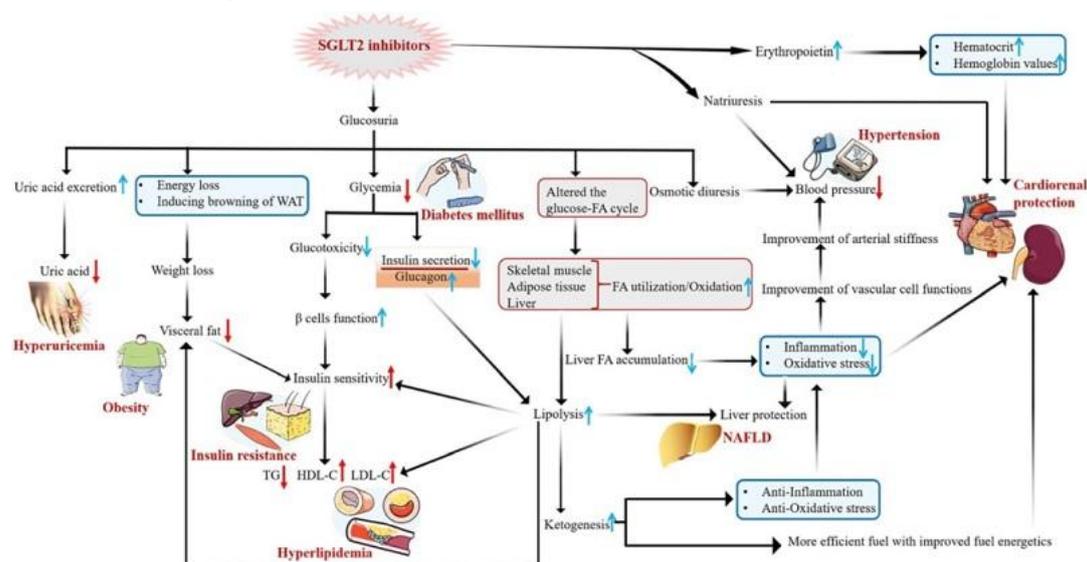


Figure 2 Pharmacological action of SGLT2 inhibitor
(Image source: Reference 2)

What are the types of SGLT2 inhibitors?

At present, there are eight SGLT2 inhibitors that have been listed in the world, namely Canagliflozin, [Dapagliflozin](#), [Empagliflozin](#), Ipragliflozin, Luseogliflozin, Tofogliflozin, Sotagliflozin, Ertugliflozin. Among them, the FDA approved Canagliflozin, Dapagliflozin and Empagliflozin, and the Japanese Ministry of Health, Labour and Welfare approved the listing of Ipragliflozin, Luseogliflozin, and Tofogliflozin.

Currently, there are five SGLT2 inhibitors widely used in the [treatment of diabetes](#) in the United States and Europe, namely: Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin and Sotagliflozin.

In China, the main ones listed are [Canagliflozin](#), Dapagliflozin, Empagliflozin and Ertugliflozin.

Dapagliflozin is the world's first SGLT2 inhibitor approved for the treatment of type 2 diabetes. It was first approved by the European EMA in 2012. In addition to lowering blood sugar, Dapagliflozin can significantly reduce the incidence of heart failure patients, it has a certain preventive effect on heart failure and proteinuria in diabetic and non-diabetic patients.

Canagliflozin was the first SGLT2 inhibitor approved by the FDA in 2013 to improve glycemic control in adults with type 2 diabetes.

Empagliflozin is currently the best-selling SGLT2 inhibitor, with global sales of \$6.14 billion in 2021. Empagliflozin is also the first type 2 diabetes drug to include data on cardiovascular mortality risk reduction in labelling in multiple countries. In China, the indication of Empagliflozin tablets for the treatment of adult patients with heart failure with preserved ejection fraction has been included in the priority review list by CDE, and approval is just around the corner.

The first independently developed SGLT2 inhibitor has been approved in China

The research and development of [SGLT2 inhibitors](#) in China is also booming. Henagliflozin Proline Tablets, a class 1 new drug independently developed by Hengrui Pharma, was approved by the NMPA at the end of last year for improving blood sugar control in adults with type 2 diabetes. On May 14, the drug was officially launched commercially in China.

In addition to Hengrui Pharma's listed Henagliflozin, there are also Sihuan Pharm's Janagliflozin and HEC Pharm's Rongliflozin in Phase III clinical trials. Among them, Janagliflozin has been declared for listing, and Rongliflozin is also expected to complete Phase III clinical trials and submit a listing application in 2022.

Conclusion

Since existing SGLT2 inhibitors can not only lower blood sugar, but also have the advantages of reducing heart failure, protecting kidneys, and reducing

body weight, making them occupy an increasingly important position and market share in the [treatment of diabetes](#), with promising prospects.

However, it is precisely because of the excellent therapeutic performance of SGLT2 inhibitors that the research enthusiasm remains high, resulting in more and more similar drugs currently on the market, limited development space, and difficulty in breaking through patents. In view of such problems, computer-aided drug design can be fully used to accelerate the design and screening of compounds in the process of preclinical research, and more and better lead compounds can be found by means of molecular docking and virtual screening to facilitate the development of new drugs for SGLT2 inhibitors.

[Huateng Pharma](#) is expert in manufacturing and development of [pharmaceutical intermediates](#) in its ultra-modern state of art facilities. We can provide pharmaceutical intermediates of hypoglycemic drug, such as [Canagliflozin intermediates](#), [Dapagliflozin intermediates](#) and [Empagliflozin intermediates](#) with commercial scale production.

References:

- [1]. [SGLT2 inhibitors: the statins of the 21st century](#)
- [2]. [Characteristics and molecular mechanisms through which SGLT2 inhibitors improve metabolic diseases: A mechanism review](#)