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Expert recommendations on the utilization of sodium-glucose cotransporter 2 inhibitors for patients with type 2 diabetes in primary medical institutions

The Basic Group of Diabetes Branch of Jiangsu Medical Association, Endocrinology Committee of Jiangsu Primary Health Association, Endocrinology Committee of Jiangsu Geriatric Medicine Society, Diabetes Prevention and Control Committee of Jiangsu Preventive Medicine Association, Geriatric Division of Nanjing Diabetes Communication Society

(Writer: LIANG Beibei, ZHI Junna)

Corresponding authors: TANG Wei, E-mail: drtangwei@njmu.edu.cn;

BI Yan, E-mail: biyan@nju.edu.cn

Abstract: Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) are increasingly utilized in the treatment of type 2 diabetes, especially for their efficacy in weight reduction and improvement of cardiovascular and renal outcomes, and are progressively gaining widespread utilization in primary medical and healthcare institutions. During their administration, it is imperative to remain vigilant regarding the potential risks of genitourinary infections, SGLT-2i-related ketoacidosis, hypotension, and acute kidney injury in certain patients. This recommendation systematically and popularly introduces the SGLT-2i concept, classification, hypoglycemic mechanism, indications, contraindications, methods of use, super-label scheme, precautions for combined use of SGLT-2i, adverse reactions and their management, as well as the use of SGLT-2i in special patients, in order to help the doctors in primary medical and healthcare institutions to standardize, reasonably and safely use SGLT-2i and correctly grasp the relevant precautions.

Keywords: Primary medical and healthcare institutions; Type 2 diabetes mellitus; Sodium-glucose cotransporter 2 inhibitors; Standardized use of medication

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In recent years, a series of large clinical trials have confirmed that sodium-glucose transporter-2 inhibitors (SGLT-2i) have heart and kidney protective effects in diabetic patients [1-5]. Both domestic and international guidelines advocate utilizing SGLT-2i in diabetic patients with chronic kidney disease (CKD), heart failure (HF), atherosclerotic cardiovascular disease (ASCVD), as well as high-risk populations. Presently, the therapeutic advantages of SGLT-2i have been expanded to non-diabetic individuals as an innovative approach for CKD and HF. Nevertheless, numerous issues warrant attention regarding their utilization within primary healthcare settings; lack of familiarity with drug indications, apprehensions about adverse reactions, and clinical inertia pose potential barriers. This expert recommendation aims to furnish primary care physicians with clinical guidance on appropriate SGLT-2i usage for optimizing patient outcomes.

1. What is the SGLT and SGLT-2i?

The kidneys play a crucial role in glucose metabolism, as filtering glucose through the glomeruli and reabsorbing it in the proximal convoluted tubules. Over a century ago, it was observed that urine glucose concentration correlates positively with blood glucose, leading to the concept of "kidney glucose threshold", which is influenced by genetic mutations or drugs. Research has revealed that renal glucose reabsorption is primarily mediated by sodium-glucose cotransporters (SGLTs), with SGLT-1 and SGLT-2 playing key roles in regulating sodium and glucose reabsorption. SGLT-2, located at the beginning of the proximal curved tubule of the kidney (segment S1), is responsible for reabsorbing approximately 97% of urinary glucose in healthy individuals. The natural product phlorizin was among the earliest SGLT inhibitors, while newer hypoglycemic agents such as SGLT-2i are now commonly used for type 2 diabetes mellitus (T2DM). In recent years, dual inhibitors targeting both SGLT-1 and SGLT-2 have been developed to enhance hypoglycemic efficacy. It's worth noting that all SGLT-2i can also inhibit SGLT-1; however, their selective inhibition ratio varies——for example, canagliflozin is -250:1 and empagliflozin is -2,500:1.

2. What are the varieties and categories of SGLT-2i?

SGLT-2i is listed in five types, including up to Glenn net, net, Craig, Glenn net, net atto Glenn, and constant Glenn net **[Table 1]**. In addition, it has a good Glenn net, net of lattice column, and constant Glenn net with metformin in different dosage proportions of compound preparations **[Table 2]**.

Tab. 1 Varieties, specifications and usage of SGLT-2i

Representative drugs	Selectivity of SGLT-2 / SGLT-1	Dose per tablet (mg)	Usage and dosage
Empagliflozin	2,700	10/25	Once daily, in the morning Control blood sugar: 10mg to 25 mg CKD and HF: 10mg
Dapagliflozin	1,200	5/10	Once daily, in the morning Control blood sugar: 5mg-10 mg CKD and HF: 10mg
Canagliflozin	160-410	100	Once daily, before the first meal 100mg-300mg
Ertugliflozin	2,200	5	Once daily, in the morning 5mg
Henagliflozin	1824	5/10	Once daily, in the morning 5mg-10mg

Tab. 2 Compound preparations containing SGLT-2i and their usage and dosage

Representative drugs	Dose per tablet (mg)	Usage and Dosage
Metformin empagliflozin tablets (I)	Metformin 500 mg and empagliflozin 5mg	Twice daily, with food and gradually increase the dose, but do not exceed the maximum recommended daily dose (metformin 2,000 mg and empagliflozin 25 mg)
Metformin empagliflozin tablets (III)	Metformin 850 mg and empagliflozin 5mg	
Metformin empagliflozin tablets (IV)	Metformin 850 mg and empagliflozin 12.5 mg	
Metformin empagliflozin tablets (V)	Metformin 1,000 mg and empagliflozin 5 mg	
Metformin empagliflozin tablets (VI)	Metformin 1,000mg and empagliflozin 12.5 mg	
Dapagliflozin metformin sustained-release tablets (I)	Dapagliflozin 5 mg and metformin 500 mg Dapagliflozin 10 mg and metformin 1,000 mg	With a meal in the morning or evening, once daily. According to the efficacy and tolerability dose adjustment, but should not be more than the daily maximum recommended dose (Dapagliflozin 10 mg and metformin hydrochloride 2,000 mg)
Dapagliflozin metformin sustained-release tablets (II)	Dapagliflozin 2.5 mg and metformin 1,000 mg	
Dapagliflozin metformin sustained-release tablets (III)	Dapagliflozin 5 mg and metformin 1,000 mg	
Dapagliflozin metformin sustained-release tablets (IV)	Dapagliflozin 10 mg and metformin 500 mg	
Henagliflozin metformin sustained-release tablets (I)	Henagliflozin 5 mg and metformin 500 mg	Usually with a meal in the morning and once daily. According to patients now use treatment, individual decision starting dose, but should not exceed the maximum recommended dose constant (henagliflozin 10 mg and 2,000 mg metformin hydrochloride)
Henagliflozin metformin sustained-release tablets (II)	Henagliflozin 5 mg and metformin 1,000 mg	

3. What is the mechanism of decreasing blood glucose by SGLT-2i?

The glycoside ligand of SGLT-2i competes with glucose for binding to the kidney SGLT-2 receptor, thereby inhibiting its activity. This leads to a reduction in glucose reabsorption by proximal renal tubule epithelial cells, lowering of the renal glucose threshold, an increase in urinary glucose excretion, and consequently a decrease in blood glucose levels. Therefore, the hypoglycemic effect of SGLT-2i is not dependent on improvements in islet β cell function or insulin sensitivity.

4. What are the indications for SGLT-2i?

Domestic indications for SGLT-2i: Used to improve blood glucose control in T2DM patients based on diet control and exercise and used in combination with metformin, while empagliflozin, dapagliflozin, and canagliflozin can be prescribed as monotherapy. Canagliflozin and empagliflozin may be used with sulfonylureas, whereas henagliflozin can be used in triple combination with metformin and retagliptin. Dapagliflozin and empagliflozin are suitable for use with insulin. Additionally, dapagliflozin and empagliflozin have been approved for treating CKD and HF **[Table 3]**.

Tab.3 Indications of SGLT-2i

Indications		Dapagliflozin	Canagliflozin	Empagliflozin	Ertugliflozin	Henagliflozin
Indications for decreasing blood glucose	Single agent	√	—	√	—	√
	Combined with metformin	√	√	√	√	√
	Combined with metformin and sulfonylurea	—	√	√	—	—
	Combined with insulin	√	—	√	—	—
Indications for disease treatment	T2DM	√	√	√	√	√
	HF	√	—	√	—	—
	CKD[a]	√	—	√	—	—

Note：[a]: DKA, diabetic ketoacidosis.

5. What are the contraindications for SGLT-2i?

According to the instructions for SGLT-2i, contraindications include: (1) Individuals with a history of severe hypersensitivity to the active ingredient or any excipient of the drug, such as allergic reactions or angioedema; (2) Patients with type 1 diabetes mellitus (T1DM); (3) Patients with DKA; (4) Due to insufficient safety and efficacy data, individuals under 18 years of age are prohibited from using it; (5) Lactating patients who are breastfeeding; (6) Pregnancy: henagliflozin and ertugliflozin are contraindicated in pregnant patients. Dapagliflozin, empagliflozin, and canagliflozin are not recommended in the second and third trimesters of pregnancy; (7) Patients with renal insufficiency: canagliflozin, henagliflozin, and ertugliflozin are contraindicated in those with severe renal impairment [estimated glomerular filtration rate (eGFR) below 30 mL/(min • 1.73m$^{2)}$] and patients on dialysis receiving empagliflozin and dapagliflozin; (8) Hepatic insufficiency: dapagliflozin, canagliflozin, ertugliflozin, and empagliflozin are not recommended for patients with severe hepatic insufficiency. Henagliflozin is recommended to be reduced to 5 mg daily in patients with moderate to severe hepatic insufficiency.

6. Is SGLT-2i taken before or after a meal?

High-fat diet has a specific impact on the pharmacokinetics of SGLT-2i, leading to decreased plasma peak drug concentration (Cmax) and area under the curve (AUC). However, this effect is not clinically significant, allowing for administration on fasting or postprandial status. SGLT-2i reduce glucose reabsorption by inhibiting the action of SGLT-2 and/or SGLT-1, thereby decreasing the renal glucose threshold and promoting urinary glucose excretion to reduce blood glucose level. Canagliflozin inhibits both SGLT-2 and SGLT-1. Given its potential to reduce postprandial blood glucose fluctuations through delayed intestinal glucose absorption, it can be taken before the first meal of the day.

7. What precautions should take when engaging in physical activity while using SGLT-2i?

When using SGLT-2i, especially in combination with insulin and oral insulin secretagogues, the exercise plan should be tailored to the patient's age and condition to minimize the risk of inadvertent injuries such as hypoglycemia, hypotension, and falls. In case of hypoglycemia during exercise, cease exercising immediately and consume carbohydrate-containing foods. If experiencing fatigue, weakness, dizziness, angina pectoris-like pain or discomfort, discontinue exercise promptly to prevent falls and seek medical attention if necessary.

8. What is the effect of decreasing blood glucose of SGLT-2i?

According to different baseline HbA1c levels, SGLT-2i monotherapy can effectively reduce HbA1c by 0.5% to 1.2%[6], and the extent of reduction is associated with both the baseline value and the dosage of SGLT-2i. A meta-analysis revealed that in adult patients with T2DM treated with Dapagliflozin at doses of 5 mg and 10 mg, HbA1c decreased by 0.6% and 0.7%, respectively, while fasting blood glucose (FBG) decreased by 1.1 mmol/L and 1.4 mmol/L. HbA1c decreased by 0.8% and 0.9% with the administration of canagliflozin at doses of 100 mg and 300 mg, respectively. Treatment with empagliflozin at doses of 10 mg and 25 mg decreased HbA1c by 0.6% and 0.7%, respectively[7]. ertugliflozin at a dose of 5 mg reduced HbA1c by 0.7%, while patients with high baseline HbA1c (⩾ 9%) experienced a reduction of 1.6%[8]. The use of henagliflozin at doses of 5 mg and 10 mg led to reductions in HbA1c levels by approximately 0.91% and 0.94%, respectively, with more significant decreases observed in patients with high baseline HbA1c (⩾8.5%)[9].

9. What is the role of SGLT-2i for cardiovascular benefits?

In patients with T2DM and ASCVD, the use of SGLT-2i supported by evidence-based data can significantly reduce the risk of 3-point major adverse

cardiac events (3P-MACE) including cardiovascular death, myocardial infarction, and stroke. EMPA-REG Outcomes [5] demonstrated that Empagliflozin led to a significant reduction in 3P-MACE risk (-14%) and cardiovascular mortality risk (-38%). CANVAS study indicated that canagliflozin reduced the risk of 3P-MACE (-14%) and cardiovascular death (-13%) [10]. In CREDENCE study, Canagliflozin was associated with a significant decrease in 3P-MACE risk (-20%) and cardiovascular mortality risk (-22%) [11]. Studies of DECLARE-TIMI 58 showed an overall reduction in 3P-MACE risk (-7%) as well as a decrease in mortality from cardiovascular causes (-2%). Additionally, the DAPA-HF study confirmed that Dapagliflozin significantly lowered the risk of mortality from cardiovascular causes by -18% [12].

10. What is the impact of SGLT-2i on improving cardiac function?

SGLT-2i can reduce cardiovascular events related to HF in both diabetic and non-diabetic patients. The improvement in cardiac function is typically observed 2-4 weeks after treatment initiation and continues to increase over time [13-15]. SGLT-2i demonstrates efficacy across all stages of HF (acute, recently worsening, and chronic). It is consistently beneficial for HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Currently, dapagliflozin and empagliflozin have received independent indications for the treatment of HF. For T2DM patients with cardiovascular disease or high cardiovascular risk, SGLT-2 is recommended to reduce the risk of hospitalization due to HF if there are no contraindications; they should be initiated after hemodynamic stabilization in patients with acute HF or exacerbation. When used for treating HF, patients should be treated with the target dose of SGLT-2i[16], and it is not recommended to exceed this target dose **[Table 1]**

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11. What is the impact of SGLT-2i on renal preservation?

SGLT-2i can enhance renal composite endpoint, delay eGFR decline, and reduce urinary albumin, independent of lowing glucose effect. CREDENCE study demonstrated that Canagliflozin significantly decreased the risk of hard renal endpoints (end-stage renal disease, doubling of serum creatinine, renal or cardiovascular death) by 30% and albuminuria by 32% [11]. DAPA-CKD study indicated that Dapagliflozin reduced albuminuria by 29% and lowered the risk of the primary endpoint (eGFR decline ⩾ 50%, progression to end-stage renal disease, cardio-renal death) by 39%[17], as well as the nephron-specific composite endpoint (eGFR decline ⩾ 50%, progression to end-stage renal disease, renal death) by 44%. EMPA-KIDNEY study revealed that empagliflozin significantly decreased the risk of renal endpoint events (end-stage renal disease, persistent eGFR decline to <10 mL/(min • 1.73m^2), renal death, or persistent eGFR decline of ⩾ 40% after randomization) by 29% [18].

12. What are the off-label combination glucose-lowering regimens involving SGLT-2?

Off-label combined hypoglycemic regimens include: (1) metformin combined with dipeptidyl peptidase four inhibitors (DPP-4i) and SGLT-2i as a triple regimen (dapagliflozin-approved indication) [19]. (2) For T2DM patients with ASCVD or high ASVCD risk, HF, or CKD, SGLT-2i and GLP-1RA can be combined [20]. Additionally, clinical studies are exploring the combination of SGLT-2i with thiazolidinediones and α-glucosidase inhibitors

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13. What precautions should be taken when combining SGLT-2i?

(1) Pharmacokinetic interactions: SGLT-2i is mainly metabolised by uridine diphosphate glucuronosyltransferase (UGT), and dapagliflozin, canagliflozin, ertugliflozin, and henagliflozin are rarely metabolised by the cytochrome P450 (CYP450) enzyme, and are at a low risk of pharmacokinetic interactions with other drugs. 300 mg of canagliflozin increases the Cmax of digoxin by up to 36%, and digoxin blood levels should be closely monitored when used in combination. When used in combination with rifampicin, the AUC of carglitazone and hengrezin decreased, with the effect of reduced glucose-lowering efficacy. (2) Pharmacodynamic interactions: the risk of hypoglycaemia is higher with the combination of canagliflozin (100 mg and 300 mg) with insulin and sulphonylureas, and careful monitoring of blood glucose levels is required [21]. Diabetic states can lead to renal cortical hypoxia as well as hypoxic kidney injury, and SGLT-2i may exacerbate cortical-medullary junction ischaemia and hypoxia, further increasing the risk of ischaemic injury to the renal medulla when combined with NSAIDs or contrast agents. To reduce the risk of contrast nephropathy, the use of SGLT-2i should be delayed until 2 weeks after the completion of iodine-containing contrast examinations [22]. The combination of SGLT-2i with diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin I receptor blockers (ARBs) warrants caution against the possibility of acute renal damage.

14. What are the common adverse effects of SGLT-2i?

(1) Reproductive and urinary system infections: including female vulvar and vaginal fungal infections, as well as male balanitis. Urinary system infection is characterized by frequent urination, nocturnal urination, polyuria, urination discomfort, pyelonephritis, and even sepsis.

Severely infected individuals may develop perineal

necrotizing fasciitis (Fournier's gangrene), a rare but life-threatening condition.

(2) Diabetic ketosis and ketoacidosis: The risk of developing ketosis and ketoacidosis is higher after surgery, infection, excessive weight loss, low-carbohydrate diet or low total calorie intake, impaired islet β cell function, reduction or withdrawal of exogenous insulin, and alcohol abuse.

(3) Reduced blood volume: manifested by thirst, dehydration, postural or symptomatic hypotension; acute transient serum creatinine increase, and eGFR decrease.

(4) Hypoglycemia: When used in combination with insulin, insulin analogues, or secretagogues (sulfonylureas and glinides), it may lead to hypoglycemia.

(5) Risk of lower limb amputation: The effect of SGLT-2i on the risk of lower limb amputation remains unclear. The CANVAS study observed an increased risk of toe and mid-foot amputation; however, no statistical difference was found in other studies.

(6) Osteoporosis and fracture risk: In the CANVAS study, bone mineral density decreased, and fracture risk increased in the canagliflozin group.

(7) Risk of sarcopenia: Studies have indicated that SGLT-2i can result in weight loss and muscle mass reduction[23], but the results from EMPA-ELDERLY study suggest that englaglizin does not affect muscle mass or strength in patients[24].

(8) Other adverse reactions: Rare hypersensitivity phenomena such as rash, angioedema, urticaria, etc.

15. How to manage reproductive and urinary tract infections?

Considering the benefits of SGLT-2i, it is generally unnecessary to discontinue the medication in cases of mild urinary tract infection. Close monitoring can be implemented alongside anti-infective treatment[10]. However, suspension of SGLT-2i is recommended for moderate to severe genitourinary infections. Management of urinary tract infections should emphasize increased fluid intake, promotion of urination, and completion of a full course of appropriate anti-infective therapy. Bacteriuria should be reassessed 2 to 6 weeks after completion of antimicrobial treatment. Selection of antibiotics for diabetic patients with urinary tract infections should take into account renal function and other relevant factors based on urine culture and drug susceptibility. Fungal infection should be treated with antifungal treatment, washing the genitals with soda water, as well as local application of Miconazole cream and clotrimazole ointment locally. Female genital fungal infections may necessitate Miconazole suppository use and a consultant gynecologist if necessary[25]. In suspected cases of Fournier's gangrene, immediate administration of broad-spectrum antibiotics and surgical debridement is essential. Discontinuation of SGLT-2i is recommended while promptly referring the patient to a superior hospital[26].

16. What are etiology and management principles of diabetic ketoacidosis induced by SGLT-2i?

The DKA induced by SGLT-2i is categorized into hyperglycemic DKA (blood glucose≥13.9 mmol/L) and non-hyperglycemic ketoacidosis (euDKA, blood glucose<13.9 mmol/L), about 70% of which was euDKA. Common triggers for DKA during SGLT-2 inhibitor use include stress, infection, inadequate carbohydrate intake, substantial (>20%) reducing insulin dose in a short period of time, heavy alcohol consumption, and perioperative states [26-27]. The management principles for euDKA encompass appropriate fluid replacement, insulin supplementation, correction of acidosis (bicarbonate administration when arterial blood pH<6.9), maintenance of electrolyte balance, removal of precipitating factors and prevention of complications, timely discontinuation of SGLT-2i and initiation of alternative glucose-lowering regimens.

17. How to adjust the treatment plan in patients with renal insufficiency?

From a clinical perspective, the selection of appropriate SGLT-2i treatment should be based on the cardiac and renal status of patients (Table 4). To achieve cardio-renal protection, some experts recommend that T2DM patients with eGFR≥20 mL/ (min•1.73m^2) should give preference to Dapagliflozin and Empagliflozin [28]. According to the guidelines, treatment with Empagliflozin can be initiated when eGFR is ≥20 mL/(min•1.73m^2); Dapagliflozin may initiated at eGFR ≥25 mL/(min•1.73m^2); and Henagliflozin may be considered at eGFR ≥30 mL/(min•1.73m^2). During the course of treatment, patients experiencing persistent decline in eGFR should undergo more frequent renal function assessments and timely adjustments to the dose and type of SGLT-2i.

It is important to recognize that SGLT-2i are linked to an elevated risk of acute kidney injury (AKI) in patients with hypovolemia. AKI should be suspected when individuals with T2DM exhibit a sustained increase in serum creatinine (50% or more), a rapid reduction in urine volume [< 0.5 mL/(kg•h)], or over 25% decrease in eGFR in the short term. In such cases, it is recommended not to initiate SGLT-2i. If a patient is already taking SGLT-2i, they should generally discontinue immediately and be referred to a superior hospital for further management and assessment. When patients are in the recovery stage of renal function (with urea nitrogen and serum creatinine levels tending to normalize and eGFR≥45 mL/ (min•1.73m^2), re-administration of SGLT-2i at the initial dosage may be considered, while closely monitoring changes in renal function.

Tab. 4 Summary of application of SGLT-2i in patients with different eGFR

Representative drugs	Initial dose	Recommended dose	Maximum dose	Appropriate patients	eGFR [ml/(min•1.73m²)]	Dose adjustment
Canagliflozin	100 mg, once daily	100 mg-300 mg, once daily	300 mg, once daily	Glycemic control in T2DM	≥ 60 45-59 < 45 < 30	No dose adjustment ≤100 mg Not recommended Prohibition
Dapagliflozin	5 mg, once daily	5 mg to 10 mg, once daily	10 mg, once daily	Glycemic control in T2DM	≥ 45 < 45	No dose adjustment Not recommended
	10 mg once daily	10 mg, once daily	10 mg, once daily	HF or CKD	≥ 25 < 30 non-Dialysis Dialysis	No dose adjustment Not recommended to start treatment, no dose adjustment if it has been taken Prohibition
Empagliflozin	10 mgmg, once daily	10-25 mg, once daily	25 mg, once daily	Glycemic control in T2DM	≥ 30 < 30	No dose adjustment Not recommended
	10 mg, once daily	10 mg, once daily	10 mg, once daily	HF or CKD	≥ 20 < 20 Dialysis	No dose adjustment Not recommended to start Prohibition
Ertugliflozin	5 mg, once daily	5 mg, once daily	5 mg, once daily	Glycemic control in T2DM	≥ 45 < 45 < 30	No dose adjustment Not recommended disable
Henagliflozin	5 mgmg, once daily	5 mg-10 mg, once daily	10 mg, once daily	Glycemic control in T2DM	≥ 30 < 30	No dose adjustment Prohibition

18. How to use SGLT-2i in patients with hepatic insufficiency?

Several clinical trials have examined the use of SGLT-2i in individuals with varying degrees of liver impairment as per Child-Pugh classification. These findings suggest that liver function should be assessed before and during treatment in T2DM patients, and SGLT-2i may be suitable for those with mild-to-moderate liver dysfunction. Henagliflozin is not recommended for patients with severe hepatic insufficiency, except that its use may be reduced to 5 mg/day[30-31]. Evidence indicates that SGLT-2i can also ameliorate liver enzymes in T2DM patients with non-alcoholic fatty liver disease (NAFLD), leading to reductions in liver inflammation, steatosis, and fibrosis[32].

19. Is hypoglycemia a common occurrence with SGLT-2i?

The use of SGLT-2i alone is not associated with an increased risk of hypoglycemia[33]. However, when combined with insulin, the risk of hypoglycemia is heightened, particularly in elderly and non-obese patients[34]. Additionally, combining SGLT-2i with sulfonylureas raises the risk of hypoglycemia, and the severity of hypoglycemia is closely linked to the dosage of sulfonylureas[35]. It is recommended to discontinue or reduce the dosage of insulin and sulfonylureas when adding SGLT-2i. Limited data are available on the risk of hypoglycemia associated with combining SGLT-2i and glinides. On the other hand, combining SGLT-2i with metformin, DPP-4i, thiazolidinediones, and GLP-1RA has a favorable effect on decreasing blood sugar levels without increasing the risk of hypoglycemia.

20. Can patients with hypotension safely use SGLT-2i?

SGLT-2i have a certain antihypertensive effect, and the standard dosage can reduce systolic blood pressure by 3.6 mmHg -6.3 mmHg and diastolic blood pressure by 2.6 mmHg-3.9 mmHg. However, due to their osmotic diuretic effects, SGLT-2i may exacerbate existing hypovolemia. Therefore, SGLT-2i are contraindicated for T2DM patients with symptomatic hypotension or systolic blood pressure<95 mmHg. Additionally, in T2DM patients with a longer duration, SGLT-2i may increase the risk of postural hypotension in diabetic autonomic neuropathy [36].

21. Can SGLT-2i be used in patients with low body weight?

The use of SGLT-2i can lead to weight reduction in patients, primarily through the promotion of urinary glucose excretion and osmotic diuretic effects. Regardless of normal body mas index (BMI), overweight, or obese T2DM patients, using SGLT-2i may experience dose-dependent weight loss of 1.3kg-1.9kg[37-38]. It is important to carefully assess the nutritional status of patients when considering the use of SGLT-2i in those with low body weight.

22. Is SGLT-2i appropriate for patients with sarcopenia and concomitant excessive abdominal circumference?

SGLT-2i may induce changes in body composition, primarily reducing fat content. The impact on sarcopenia in diabetic patients has yielded conflicting findings. While several studies have indicated a higher risk of developing sarcopenia with long-term use of SGLT-2i, others have suggested that Dapagliflozin and Canagliflozin treatments do not affect muscle mass[39-40]. Patients with sarcopenia using SGLT-2i should engage in appropriate exercise and maintain a balanced diet, and monitor muscle mass.

23. Is it appropriate for individuals who have experienced a stroke to use SGLT-2i?

The use of SGLT-2i in stroke patients remains inconclusive. A meta-analysis indicated that while SGLT-2i did not have a significant effect on overall stroke risk, there was a variation in stroke risk across different baseline GFR subgroups. Specifically, the subgroup with the lowest GFR [< 45 mL/(min•1.73m^2)] experienced a 50% reduction in stroke risk. Other studies have suggested that SGLT-2i may reduce the risk of hemorrhagic stroke by 50%, but do not significantly affect ischemic stroke[41]. In addition, the use of SGLT-2i reduced the risk of ischemic stroke in diabetic patients with atrial fibrillation by 20%. However, reports of adverse drug events indicated a significantly higher incidence of adverse events associated with SGLT-2i in ischemic stroke and lacunar infarction, but not in hemorrhagic stroke[42].

24. Can SGLT-2i be used in patients with lower extremity ischemic disease?

In patients with atherosclerotic diseases of the lower extremities, acute arterial embolism, peripheral arterial spasm, deep venous thrombosis of the lower extremities, and varicose veins of the lower extremities, cautious use of SGLT-2i is advised after assessing the risks and benefits. SGLT-2i is not recommended in patients with severe lower limb ischemia, such as resting ankle-brachial index (ABI)<0.40 or ankle arterial pressure (AP)<50 mmHg or toe artery pressure (TP)<30 mmHg, or in patients with ischemic ulcer or gangrene and ischemic resting pain due to the risk of amputation.

25. Can patients with diabetic foot use SGLT-2i?

Caution is necessary when considering the use of SGLT-2i in individuals with chronic refractory foot ulcers, a history of amputation, and a high risk of amputation. The CANVAS study has shown an increased risk of lower limb amputation with Canagliflozin use. Toe and midfoot amputations are most commonly reported, with some patients undergoing multiple major amputations involving both lower limbs[43-44]. Other studies have not definitively established an association between SGLT-2i treatment and lower limb amputation in diabetic patients. Close monitoring and informed awareness of associated risks are essential for individuals with diabetic foot ulcers receiving SGLT-2i.

26 Can SGLT-2i be used in patients with osteoporosis?

The impact of SGLT-2i on fracture risk and bone mineral metabolism is still controversial. While some studies have linked Canagliflozin to an elevated fracture risk. Kohan reported a higher incidence of fracture in patients using Dapagliflozin[45], Whereas Mcmurray found no significant change in fracture risk among patients using Dapagliflozin[12]. The Empagliflozin study did not show a significant association with fracture risk[46]. When considering the use of SGLT-2i, it is important to comprehensively assess the potential for fractures and take patients' bone mineral density and specific SGLT-2i drugs into account. It is recommended to consider the patient's bone mineral density and selecting the specific SGLT-2i medication. It should be employed cautiously in individuals with a high susceptibility to fractures.

27. Can patients with prostate hyperplasia use SGLT-2i?

The expression of SGLT-2 is upregulated in prostate cancer tissues and facilitates glucose transport *in vitro*. Canagliflozin can partially inhibit SGLT-1, delaying the progression of prostate hyperplasia, inhibiting the proliferation and survival of human prostate cancer cells and tumors, and rendering them more sensitive to radiation therapy[47]. Men with diabetes who initially used SGLT-2i experienced a higher incidence of polyuria and nocturia. Patients with prostatic hyperplasia, particularly those with chronic urinary retention, are at significantly increased risk for urinary tract infections. Male patients with chronic urinary retention are prone to develop overflow incontinence, renal function impairment, bladder distension, hydronephrosis, etc. Therefore, the use of SGLT-2i is not recommended for diabetic patients with urinary retention.

28 Can SGLT-2i be utilized in patients with T1DM?

SGLT-2i is not approved for the treatment of T1DM in China, and is also not recommended. Studies conducted abroad have indicated that combining SGLT-2i with insulin can lead to improvements in HbA1c, reduction in postprandial glucose variability, increased time spent within the target glucose range[48], decreased insulin dosage, and weight reduction in T1DM patients without an elevated risk of hypoglycemia [49]. However, there is an increased risk of developing DKA.

29. Is it necessary to discontinue SGLT-2i during the perioperative period?

The potential for an increased incidence of perioperative AKI associated with their use is a controversy. Perioperative patients should refrain from using SGLT-2i in cases of hypovolemia or shock. Gilbert[50] suggested that perioperative patients who continued SGLT-2i treatment were less likely to develop AKI. The half-life of SGLT-2i is prolonged in the presence of kidney damage, potentially leading to acute, chronic kidney failure[51]. To minimize the risk of euDKA, it is recommended to discontinue the medication 3-4 days before surgery[52]. Immediate discontinuation of SGLT-2i is advised for patients undergoing emergency surgery, and resumption post-surgery depends on individual circumstances. SGLT-2i is typically administered to patients undergoing local anesthesia and body surface surgery. Patients undergoing epidural anesthesia, without involvement of digestive tract reconstruction, may continue using SGLT-2i after resuming normal bowel function and diet. SGLT-2i should be resumed after returning to a regular diet for patients undergoing general anesthesia. It should be used after the patient has resumed a regular diet after gastrointestinal surgery. It should be used after full recovery for those undergoing genitourinary system surgery. SGLT-2i should be reinitiated in patients undergoing catheterization following catheter removal and upon exclusion of infection, bleeding, and other related conditions.

30. Can pregnant and lactating diabetic patients safely use SGLT-2i?

SGLT-2i are classified as category C drugs during pregnancy. Limited data from current studies on the use of SGLT-2i in pregnant women do not allow for a determination of the risk of major birth defects and miscarriage associated with these medications. Therefore, it is not recommended to use SGLT-2i in pregnant women with hyperglycemia. The secretion of SGLT-2i in human milk has unknown impact on breastfed infants and milk production. Therefore, the use of SGLT-2i during lactation is not recommended.

31. Can children with diabetes use SGLT-2i?

The safety and efficacy of all marketed SGLT-2i in children under 18 years of age have not been established, so the use of SGLT-2i in children with diabetes is not recommended.

32. Can SGLT-2i be used in patients with severe infectious stage diabetes?

Currently, there is a lack of clinical data supporting the use of SGLT-2i in individuals with severe infections.

Writing consultant (Sort by stroke order of the last name)
Ma Xianghua (Department of Endocrinology, the First Affiliated Hospital of Nanjing Medical University); LIU Chao (Department of Endocrinology, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine); YANG Tao (Department of Endocrinology, the First Affiliated Hospital of Nanjing Medical University)

Members of the writing team (Sort by stroke order of the last name)
LIANG Beibei (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University). ZHI JunNa ((Department of pharmacy, Geriatric Hospital Affiliated to Nanjing Medical University)

Member of the sort (Sort by stroke order of the last name)
MA Jingdi (Department of Endocrinology, Xinyi People's Hospital); WANG Aiping (Department of Endocrinology, Nanjing JunXie Hospital); WANG Ping (Department of Endocrinology, Nanjing Gaochun People's Hospital); WANG Xueqin (Department of Endocrinology, Nantong First People's Hospital); MAO Li (Department of Endocrinology, Huaian First People's Hospital) ; YE Xinhua (Department of Endocrinology, Changzhou Second People's Hospital); BI Yan (Department of Endocrinology, Endocrine and Metabolic Disease Medical Center, Affiliated Drum Tower Hospital, Medical School, Nanjing University); ZHU Ping (Department of Endocrinology, Huaian Chuzhou Hospital of Traditional Chinese Medicine); ZHU Jian (Department of Endocrinology, Affiliated Hospital of Jiangnan University); LIU Dongmei (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University). LIU Yanmei (Department of Endocrinology, Yancheng First People's Hospital); LIU Xinliang (Department of Endocrinology, Xuyi People's Hospital); XU Lan (Department of Endocrinology, Wuxi People's Hospital); SUN Xinjuan (Department of Endocrinology, Nanjing JunXie Hospital); WU Haidi (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University). YANG Bingquan (Department of Endocrinology, Southeast University Zhongda Hospital); YANG Shufang (Department of Endocrinology, The Affiliated Taizhou People's Hospital of Nanjing Medical University); WU Xinhua (Department of Endocrinology, Huaian hospital); SONG Jinfang (Department of Clinical Pharmacy, Affiliated Hospital of Jiangnan University); CHEN Zhengfang (Department of Endocrinology, Changshu Hospital Affiliated to Soochow University, Changshu NO.1 People's Hospital); FAN Hongqi (Department of Endocrinology, the First Affiliated Hospital of Nanjing Medical University); ZHAO Qing (Department of Endocrinology, Lianshui People's Hospital); HU Ji (Department of Endocrinology, the Second Hospital Affiliated to Soochow University); YU Yun (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University); SHI Bimin (Department of Endocrinology, the First Affiliated Hospital of Soochow University); LOU Qinglin (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University). YUAN Guoyue (Department of Endocrinology, Affiliated Hospital of Jiangsu University); GU Yunjuan (Department of Endocrinology, Affiliated Hospital of Nantong University; LING Hongwei (Department of Endocrinology, Affiliated Hospital of Xuzhou Medical University); TANGA Wei (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University); ZAI Guotian (Department of Endocrinology, Nanjing Jiangbei hospital); CUI Siyuan (Department of Endocrinology, Jiangnan University Medical Center); LIANG Beibei (Department of Endocrinology, Geriatric Hospital Affiliated to Nanjing Medical University); GE Zhijuan (Department of Endocrinology, Endocrine and Metabolic Disease Medical Center, Affiliated Drum Tower Hospital, Medical School, Nanjing University). JIANG Xiaohong (Department of Endocrinology, Changzhou First People's Hospital); ZHI Junna (Department of pharmacy, Geriatric Hospital Affiliated to Nanjing Medical University); JIAO Xuehua (Department of Endocrinology, Suzhou Ninth Hospital Affiliated to Soochow University)

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·指南与共识·

基层 2 型糖尿病患者钠—葡萄糖共转运体 2 抑制剂使用专家建议

江苏省医学会糖尿病学分会基层学组,江苏省基层卫生协会内分泌专业委员会,
江苏省老年医学学会老年内分泌专业委员会,江苏省预防医学会糖尿病预防与控制专业委员会,
南京糖尿病并发症研究会老年分会
(执笔:梁贝贝,　智俊娜)

摘要:钠-葡萄糖共转运体 2 抑制剂(SGLT-2i)目前越来越多地用于 2 型糖尿病患者的治疗,尤其是对于减轻体重和改善心血管和肾脏结局方面具有独特优势,也逐渐在基层医疗机构中广泛应用。在使用过程中,需警惕部分患者可能出现的生殖、泌尿道感染、SGLT-2i 相关酮症酸中毒、低血压以及急性肾损伤风险。本建议系统通俗地介绍 SGLT-2i 的概念、类别、降糖机制、适应证、禁忌证、用法、超说明书方案、合并用药注意事项、不良反应及处理以及特殊患者的使用等,以帮助基层医疗机构医生规范、合理、安全使用 SGLT-2i,正确掌握相关注意事项。

关键词:基层医疗机构;2 型糖尿病;钠-葡萄糖共转运体 2 抑制剂;规范用药
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Expert recommendations on the utilization of sodium-glucose cotransporter 2 inhibitors for patients with type 2 diabetes in primary medical institutions

The Basic Group of Diabetes Branch of Jiangsu Medical Association, Endocrinology Committee of Jiangsu Primary Health Association, Endocrinology Committee of Jiangsu Geriatric Medicine Society, Diabetes Prevention and Control Committee of Jiangsu Preventive Medicine Association, Geriatric Division of Nanjing Diabetes Communication Society
(Writer: LIANG Beibei, ZHI Junna)
Corresponding authors: *TANG Wei*, *E-mail*: *drtangwei@njmu.edu.cn*; *BI Yan*, *E-mail*: *biyan@nju.edu.cn*

Abstract: Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) are increasingly utilized in the treatment of type 2 diabetes, especially for their efficacy in weight reduction and improvement of cardiovascular and renal outcomes, and are progressively gaining widespread utilization in primary medical and healthcare institutions. During their administration, it is imperative to remain vigilant regarding the potential risks of genitourinary infections, SGLT-2i-related ketoacidosis, hypotension, and acute kidney injury in certain patients. This recommendation systematically and popularly introduces the SGLT-2i concept, classification, hypoglycemic mechanism, indications, contraindications, methods of use, super-label scheme, precautions for combined use of SGLT-2i, adverse reactions and their management, as well as the use of SGLT-2i in special patients, in order to help the doctors in primary medical and healthcare institutions to standardize, reasonably and safely use SGLT-2i and correctly grasp the relevant precautions.

Keywords: Primary medical and healthcare institutions; Type 2 diabetes mellitus; Sodium-glucose cotransporter 2 inhibitors; Standardized use of medication
Fund program: Social Development Project of Jiangsu Provincial Key Research and Development Plan (BE2023774)

近年来,一系列大型临床试验证实钠—葡萄糖转运蛋白-2 抑制剂(sodium-glucose cotransporter 2 inhibitors, SGLT-2i)对糖尿病患者具有心脏和肾脏保护作用[1-5]。国内外指南建议,在糖尿病合并慢性肾脏病(CKD)、心力衰竭(HF)和动脉粥样硬化性心血管疾病(ASCVD)及高危人群中推荐使用 SGLT-2i。目前,SGLT-2i 的益处已扩展到非糖尿病患者,作为 CKD 和 HF 治疗的新方法。然而,在基层医疗机构使用中仍存在许多值得重视的问题,对该类药物适应证不熟悉以及对

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通信作者:唐伟, E-mail: drtangwei@njmu.edu.cn; 毕艳, E-mail: biyan@nju.edu.cn
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不良反应的担心和临床惰性成为潜在障碍。本项专家建议旨在为基层医生正确使用 SGLT-2i 并让更多患者获益提供临床指导。

1　什么是 SGLT 和 SGLT-2i?

葡萄糖代谢过程中,肾脏发挥着重要作用,葡萄糖经肾小球滤过,并在肾近曲小管重吸收。大约一个世纪前,人们认识到尿糖浓度与血糖浓度呈正相关,并定义了“肾糖阈”概念,即尿液中出现葡萄糖时的血糖浓度,这一阈值可受到遗传突变或药物的影响而改变。研究发现,肾脏重吸收葡萄糖主要由钠—葡萄糖共转运体(SGLTs)介导。SGLTs 家族目前已知有 6 个亚型,其中 SGLT-1 和 SGLT-2 在调节钠和葡萄糖的重吸收和转运中起到关键作用。SGLT-2 主要位于肾近曲小管起始端(S1 段),负责重新吸收健康个体约 97%的尿葡萄糖。最早被发现的 SGLTs 抑制物是天然产物根皮苷(phlorizin),新型降糖药物 SGLT-2i 现已成为治疗 2 型糖尿病(type 2 diabetes mellitus, T2DM)的常用药物。近年来,SGLT-1 和 SGLT-1/2 双抑制剂也被研发出来,用以提高降糖功效。事实上,所有 SGLT-2i 也能够抑制 SGLT-1,但对 SGLT-2 和 SGLT-1 的选择性抑制比例不同,比如卡格列净为~250∶1,恩格列净为~2 500∶1。

2　SGLT-2i 有哪些品种和类别?

我国上市的 SGLT-2i 现有 5 种,包括达格列净、恩格列净、卡格列净、艾托格列净和恒格列净(表 1)。此外,已有恩格列净、达格列净和恒格列净与二甲双胍以不同剂量比例组成的复方制剂(表 2)。

3　SGLT-2i 降糖机制是什么?

SGLT-2i 的糖苷配基与葡萄糖竞争性结合肾脏 SGLT-2,从而抑制其活性,减少近端肾小管上皮细胞对葡萄糖的重吸收,降低肾糖阈,增加尿葡萄糖的排泄,从而降低血中葡萄糖的水平。因此,SGLT-2i 的降糖作用不依赖于胰岛 β 细胞功能和胰岛素敏感性的改善。

4　SGLT-2i 的适应证是什么?

国内 SGLT-2i 适应证:在饮食控制和运动基础上,用于改善 T2DM 患者的血糖控制。SGLT-2i 均可和二甲双胍联用,恩格列净、达格列净及恒格列净可单药使用。卡格列净和恩格列净可与磺脲类联合应用。恒格列净可与二甲双胍和瑞格列汀三药联合应用。达格列净和恩格列净可与胰岛素联合应用。此外,达格列净和恩格列净获批用于 CKD 和 HF 适应证(表 3)。

5　SGLT-2i 的禁忌证是什么?

依据 SGLT-2i 说明书,禁忌证包括:(1) 对药物活性成分或任何辅料有严重超敏反应史者禁用,如过敏反应或血管性水肿;(2) 1 型糖尿病(T1DM)患者;(3) 糖尿病酮症酸中毒(DKA)患者;(4) 因缺乏用药的安全性和有效性数据,18 岁以下儿童禁用;(5) 采用母乳喂养的哺乳期患者;(6) 妊娠期:恒格列净与艾托格列净禁用于妊娠期患者,达格列净、恩格列净与卡格列净在妊娠中期和晚期不推荐使用;(7) 肾功能不全患者:卡格列净、恒格列净与艾托格列净在重度肾损害[估算的肾小球滤过率(eGFR) 低于 30 mL/(min · 1.73m^2)]禁用,恩格列净和达格列净透析患者禁用。(8) 肝功能不全:达格列净、卡格列净、艾托格列净与恩格列净不推荐重度肝功能不全患者使用;恒格列净在中重度肝功能不全患者建议减量至每日 5 mg 使用。

6　SGLT-2i 餐前还是餐后服用?

高脂饮食对 SGLT-2i 药代动力学具有一定影响,血浆药物峰浓度(C_{max})和曲线下面积(AUC)均有所下降,但不具有临床意义,因此空腹或进食后服用均可。SGLT-2i 通过抑制 SGLT-2 和/或 SGLT-1 的作用减少葡萄糖重吸收,降低肾糖阈而促进尿葡萄糖排泄,从而降低血液循环中葡萄糖水平。卡格列净同时抑制 SGLT-2 和 SGLT-1。考虑到肠道葡萄糖吸收的延缓可能会降低餐后血糖波动,可在每天第一餐餐前服用。

7　应用 SGLT-2i 时运动需要注意什么?

在使用 SGLT-2i 尤其是联合胰岛素和口服胰岛素促泌剂时,依据患者的年龄和病情适时调整运动计划,避免低血糖、低血压及跌倒等意外伤害事件的发生。运动过程中若出现低血糖,应立即停止运动并进食含碳水化合物的食物。若出现疲乏、无力、头晕、心前区隐痛或不适等,应立即停止运动,防止摔伤,必要时及时就医。

表 1　SGLT-2i 品种、规格及用法用量

Tab. 1　Varieties, specifications and usage of SGLT-2i

代表药物	SGLT-2/SGLT-1 选择性	每片剂量(mg)	用法用量
恩格列净(Empagliflozin)	2 700	10/25	1 次/d,早晨服用控制血糖:10~25 mg,CKD 和 HF 适应证:10 mg
达格列净(Dapagliflozin)	1 200	5/10	1 次/d,早晨服用控制血糖:5~10 mg,CKD 和 HF 适应证:10 mg
卡格列净(Canagliflozin)	160~410	100	1 次/d,第一餐前服用 100~300 mg
艾托格列净(Ertugliflozin)	2 200	5	1 次/d,早晨服用 5 mg
恒格列净(Henagliflozin)	1 824	5/10	1 次/d,早晨服用 5~10 mg

表 2　含有 SGLT-2i 的复方制剂及用法用量

Tab. 2　Compound preparations containing SGLT-2i and their usage and dosage

代表药物	每片剂量(mg)	用法用量
二甲双胍恩格列净片(Ⅰ)	二甲双胍 500 mg 与恩格列净 5 mg	每日 2 次随餐服用,逐渐递增剂量,但是不可以超出每日推荐的最大剂量(二甲双胍 2 000 mg 和恩格列净 25 mg)
二甲双胍恩格列净片(Ⅲ)	二甲双胍 850 mg 与恩格列净 5 mg	
二甲双胍恩格列净片(Ⅳ)	二甲双胍 850 mg 与恩格列净 12.5 mg	
二甲双胍恩格列净片(Ⅴ)	二甲双胍 1 000 mg 与恩格列净 5 mg	
二甲双胍恩格列净片(Ⅵ)	二甲双胍 1 000 mg 与恩格列净 12.5 mg	
达格列净二甲双胍缓释片(Ⅰ)	达格列净 5 mg 和二甲双胍 500 mg 达格列净 10 mg 和二甲双胍 1 000 mg	早晨或晚上随餐服用,每日 1 次。根据疗效和耐受性调整剂量,但不应超过每日最大推荐剂量达格列净 10 mg 和盐酸二甲双胍 2 000 mg
达格列净二甲双胍缓释片(Ⅱ)	达格列净 2.5 mg 和二甲双胍 1 000 mg	
达格列净二甲双胍缓释片(Ⅲ)	达格列净 5 mg 和二甲双胍 1 000 mg	
达格列净二甲双胍缓释片(Ⅳ)	达格列净 10 mg 和二甲双胍 500 mg	
恒格列净二甲双胍缓释片(Ⅰ)	恒格列净 5 mg 和二甲双胍 500 mg	通常早晨随餐服用,每日 1 次。根据患者现在使用的治疗方案,个体化决定起始剂量,但不应超过每日最大推荐剂量恒格列净 10 mg 和盐酸二甲双胍 2 000 mg
恒格列净二甲双胍缓释片(Ⅱ)	恒格列净 5 mg 和二甲双胍 1 000 mg	

表 3　SGLT-2i 适应证

Tab. 3　Indications of SGLT-2i

适应证		达格列净	卡格列净	恩格列净	艾托格列净	恒格列净
降糖方案适应证	单药	√	-	√	-	√
	联合二甲双胍	√	√	√	√	√
	联合二甲双胍及磺脲类	-	√	√	-	-
	联合胰岛素	√	-	√	-	-
疾病治疗适应证	T2DM	√	√	√	√	√
	HF	√	-	√	-	-
	CKD	√	-	√	-	-

8　SGLT-2i 的降糖作用如何?

根据基线 HbA1c 水平不同,SGLT-2i 单药治疗可有效降低糖化血红蛋白(HbA1c)0.5%～1.2%[6],降幅与其基线值及 SGLT-2i 的剂量相关。网络荟萃分析显示成年 T2DM 患者使用达格列净 5 mg、10 mg 治疗后,HbA1c 分别下降 0.6%和0.7%,空腹血糖(FBG)降低 1.1 mmol/L 及 1.4 mmol/L;卡格列净以 100 mg、300 mg 的剂量应用,HbA1c 分别下降0.8%和 0.9%;恩格列净 10 mg、25 mg 治疗,HbA1c 分别下降 0.6%和 0.7%[7]。艾托格列净 5 mg 降低 HbA1c 0.7%,HbA1c 基线高(≥9%)的患者可降低 HbA1c 达 1.6%[8]。恒格列净 5 mg、10 mg治疗可分别降低 HbA1c 0.91%和0.94%, HbA1c 基线高(≥8.5%)的患者 HbA1c 下降更显著[9]。

9　以心脑血管获益为目的,如何应用 SGLT-2i?

伴有 ASCVD 的 T2DM 患者,选择有循证证据的 SGLT-2i,可显著降低三点(心血管死亡、心肌梗死、卒中)主要心脑血管不良事件(3P-MACE)风险。EMPA-REG Outcomes 研究表明,恩格列净显著降低 3P-MACE 风险(-14%)和心血管原因死亡风险(-38%)[5]。CANVAS Program 研究显示,卡格列净降低 3P-MACE 风险(-14%)以及心血管死亡风险(-13%)[10];CREDENCE研究中,卡格列净能够显著降低 3P-MACE 风险(-20%)及心血管死亡风险(-22%)[11]。DECLARE-TIMI 58研究显示,达格列净降低 3P-MACE 风险(-7%)及心血管原因死亡风险(-2%);DAPA-HF 研究证实达格列净显著降低心血管原因死亡风险(-18%)[12]。

10　以心功能获益为目的,如何应用 SGLT-2i?

SGLT-2i 可以降低糖尿病患者和非糖尿病患者以 HF 为主的心血管事件,改善心功能作用约在治疗 2～4 周后出现,且随时间延长而增大[13-15]。SGLT-2i 可改善 HF 所有阶段(急性、近期恶化和慢性)的预后,这种获益在射血分数降低的心衰(HFrEF)和射血分数保留的心衰(HFpEF)中是一致的。目前,达格列净和恩格列净已获得治疗 HF 的独立适应证。对于合并心血管疾病或心血管高危风险的 T2DM 患者,无禁忌证情况下,推荐使用 SGLT-2i 降低因 HF 住院风险,需在急性 HF 或 HF 恶化患者血流动力学稳定后启用。以 HF 治疗为目的时,患者使用 SGLT-2i 的目标剂量(详见表 1)[16],不推荐超目标剂量治疗 HF。

11　以肾保护为目的,如何应用 SGLT-2i?

SGLT-2i 可改善肾脏复合终点、延缓 eGFR 的下降及降低尿白蛋白,具有独立于降糖之外的肾脏保护作用。CREDENCE研究显示,卡格列净显著降低肾脏复合硬终点(终末期肾病、血清肌酐倍增、肾脏或心血管死亡)风险 30%,降低白蛋白尿达 32%[11]。DAPA-CKD 研究结果提示,达格列净降低白蛋白尿 29%及主要终点(eGFR 下降≥50%,进展至终末期肾病,心肾死亡)风险 39%,肾脏特异性复合终点(eGFR 下降≥50%,进展至终末期肾病,肾性死亡)风险 44%[17]。EMPA-KIDNEY研究显示,恩格列净显著降低肾脏终点事件(终末期肾病、eGFR 持续下降至<10 mL/(min · 1.73 m^2)、肾性死亡或随机分组后 eGFR 持续下降≥40%)风险 29%[18]。

12　SGLT-2i 超说明书联合降糖方案有哪些?

超说明书联合降糖方案包括:(1) 二甲双胍联合二肽基肽酶 4 抑制剂(DPP-4i)及 SGLT-2i 三联方案(恒格列净已获批适应证)[19]。(2) 合并 ASCVD 或高 ASVCD 风险、HF 或 CKD 的 T2DM 患者,可联合使用 SGLT-2i 与 GLP-1 受体激动剂(GLP-

1RA)[20]。此外,还有 SGLT-2i 与噻唑烷二酮以及 α 糖苷酶抑制剂等联合应用的临床研究。

13　SGLT-2i 合并用药的注意事项有哪些?

(1) 药动学相互作用:SGLT-2i 主要通过尿苷二磷酸葡萄糖醛酸转移酶(UGT)代谢,达格列净、卡格列净、艾托格列净和恒格列净极少经细胞色素 P450 酶(CYP450 酶)代谢,与其他药物发生药动学的相互作用的风险较小。卡格列净 300 mg 可增加地高辛的 C_{max}达 36%,合并使用时应密切监测地高辛的血药浓度。与利福平合并使用时,卡格列净和恒格列净的 AUC 降低,有降糖疗效下降的影响。(2) 药效学相互作用:卡格列净(100 mg 和 300 mg)与胰岛素和磺脲类药物联合使用发生低血糖的风险更高,需注意血糖水平监测[21]。糖尿病状态可导致肾皮质缺氧以及缺氧型肾损伤,SGLT-2i 可能会加重皮质髓质交界处缺血缺氧,合并使用非甾体抗炎药(NSAIDs)或者造影剂时会进一步增加肾髓质缺血性损伤的风险。为减少造影剂肾病的风险,SGLT-2i 的使用应延迟至含碘造影剂检查完成后 2 周[22]。SGLT-2i 联用利尿剂、血管紧张素转换酶抑制剂(ACEI)及血管紧张素 1 型受体阻断剂(ARB)时,需警惕出现急性肾损伤(AKI)的可能。

14　SGLT-2i 常见不良反应有哪些?

(1) 生殖、泌尿系统感染:包括女性外阴、阴道真菌感染和男性龟头炎。泌尿系统感染表现为尿频、夜尿、多尿、排尿不适、肾盂肾炎甚至脓毒血症。严重感染者可出现会阴坏死性筋膜炎(福尼尔坏疽,Fournier's gangrene),后者罕见但可危及生命。(2) 糖尿病酮症及酮症酸中毒:在术后、感染、过度减重、低碳水化合物饮食或总热量摄入过少、胰岛 β 细胞功能受损、减少或停用外源性胰岛素以及酗酒等,发生酮症及酮症酸中毒的风险更高。(3) 血容量减少:表现为口渴、脱水、体位性或症状性低血压、急性一过性血清肌酐升高和 eGFR 降低。(4) 低血糖:SGLT-2i 与胰岛素、胰岛素类似物或促泌剂(包括磺脲类、格列奈类)联用时可能出现。(5) 下肢截肢风险:SGLT-2i 对下肢截肢风险的影响尚不明确。CANVAS 研究中观察到卡格列净组患者脚趾及足中部的截肢风险上升,但在其他研究中并无统计学差异[10]。(6) 骨质疏松及骨折风险:CANVAS 研究中,卡格列净组患者骨密度降低及骨折风险上升[10]。(7) 肌少症风险:研究显示 SGLT-2i 可引起体重下降和肌肉量的减少[23]。但 EMPA-ELDERLY 研究结果提示,恩格列净不影响患者肌肉质量或力量[24]。(8) 其他不良反应:少见超敏现象,如皮疹、血管性水肿、荨麻疹等。

15　出现生殖、泌尿道感染如何处理?

考虑到 SGLT-2i 的获益,轻度尿路感染多数情况下无需停药,可边抗感染治疗边观察[10]。中重度泌尿生殖感染,建议暂停 SGLT-2i。尿路感染治疗时注意多饮水、促排尿,足量、足疗程抗感染治疗。抗感染药物治疗结束后 2~6 周复查菌尿情况。根据尿培养和药敏结果用药,糖尿病合并尿路感染选用抗菌药物还需考虑肾功能等情况。真菌感染应行抗真菌治疗,苏打水清洗生殖器,咪康唑乳膏、克霉唑软膏局部涂抹。女性生殖道真菌感染可使用咪康唑栓剂,必要时请妇科会诊[25]。当发现疑似 Fourniers 坏疽病例,应立即开始使用广谱抗生素和外科清创术治疗,停用 SGLT-2i,及时转诊至上级医院[26]。

16　SGLT-2i 引发 DKA 的原因和处置原则?

SGLT-2i 引发的 DKA 分为:高血糖性 DKA(血糖 ≥ 13.9 mmoL/L)和非高血糖性酮症酸中毒(euDKA,血糖 < 13.9 mmoL/L),约 70% 为 euDKA。使用 SGLT-2i 期间发生 DKA 的常见诱因包括出现应激、感染、碳水化合物摄入过少、胰岛素剂量短时间内减量过多(>20%)、大量饮酒及围手术期等状态[27-28]。euDKA 的治疗原则包括足量补液、补充胰岛素、纠正酸中毒(动脉血 pH<6.9 时应输注碳酸氢盐)、维持电解质平衡、去除诱因和防治并发症,及时停用 SGLT-2i 并换用其他降糖方案。

17　肾功能不全的患者,如何调整治疗方案?

临床上需结合患者心肾功能状态,选择合适的 SGLT-2i 治疗(表 4)。为实现心肾保护作用,有专家建议对 eGFR ≥ 20 mL/(min · 1.73 m^2)的 T2DM 患者优先选择达格列净和恩格列净[29]。根据说明书,恩格列净在 eGFR ≥ 20 mL/(min · 1.73 m^2)时可起始使用;达格列净在 eGFR ≥ 25 mL/(min · 1.73 m^2)时可起始使用;恒格列净在 eGFR ≥ 30 mL/(min · 1.73 m^2)可起始使用。在治疗过程中,eGFR 持续下降的患者需增加肾功能检查次数,并及时调整 SGLT-2i 剂量和种类。

需注意在低血容量情况下,SGLT-2i 有增加 AKI 的风险,当 T2DM 患者在短期内出现血肌酐持续升高(升高 50%或以上)、尿量迅速减少[<0.5 mL/(kg · h)]或eGFR下降超过25%时,应警惕 AKI 的可能,此时不建议启用 SGLT-2i。若患者正在用 SGLT-2i,原则上应立即停用,并转诊至上级医院治疗和评估。待患者处于肾功能恢复期(尿素氮、血肌酐水平趋于正常及 eGFR≥45 mL/(min · 1.73 m^2)时,考虑按起始剂量重新使用 SGLT-2i,同时密切监测肾功能变化。

18　肝功能不全的患者,如何使用 SGLT-2i?

多项临床试验研究基于 Child-Pugh 分类法分析了 SGLT-2i 在不同程度肝损伤人群中的应用,建议在 T2DM 患者用药前和用药期间评估肝功能,轻中度肝功能不全患者可以选择 SGLT-2i 类药物;重度肝功能不全的患者,恒格列净可减至 5mg/日使用外,其他均不推荐[30-31]。有证据表明,SGLT-2i 还可以改善伴有非酒精性脂肪肝(NAFLD)的 T2DM 患者的肝酶,减轻肝脏炎症、脂肪变性和纤维化[32]。

19　使用 SGLT-2i 容易发生低血糖吗?

SGLT-2i 单药使用不易出现低血糖[33],当联合胰岛素治疗时会增加发生低血糖的风险,在老年与非肥胖患者中发生低血糖的风险更高[34]。SGLT-2i 联合使用磺脲类降糖药物也

表 4　SGLT-2i 在不同 eGFR 患者中的应用总结

Tab. 4　Summary of application of SGLT-2i in patients with different eGFR

代表名称	起始剂量	推荐剂量	最大剂量	治疗对象	eGFR[mL/(min · 1.73 m^2)]	调整剂量
卡格列净 Canagliflozin	100 mg,1 次/d	100~300 mg, 1 次/d	300 mg, 1 次/d	用于 T2DM 血糖控制	60 或以上	无需调整剂量
					45 至 59	剂量≤100 mg
					45 以下	不推荐使用
					30 以下	禁用
达格列净 Dapagliflozin	5 mg,1 次/d	5~10 mg, 1 次/d	10 mg, 1 次/d	用于 T2DM 血糖控制	45 或以上	无需调整剂量
					45 以下	不推荐使用
	10 mg,1 次/d	10 mg,1 次/d	10 mg,1 次/d	HF 或 CKD	25 或以上	无需调整剂量
					25 以下不合并透析	不推荐起始治疗,若已服用无需调整剂量
					透析	禁用
恩格列净 Empagliflozin	10 mg,1 次/d	10~25 mg, 1 次/d	25 mg, 1 次/d	用于 T2DM 血糖控制	30 或以上	无需调整剂量
					30 以下	不推荐使用
	10 mg,1 次/d	10 mg,1 次/d	10 mg,1 次/d	HF 或 CKD	20 或以上	无需调整剂量
					20 以下	不建议开始使用
					透析	禁用
艾托格列净 Ertugliflozin	5 mg,1 次/d	5 mg,1 次/d	5 mg,1 次/d	用于 T2DM 血糖控制	45 或以上	无需调整剂量
					45 以下	不推荐使用
					30 以下	禁用
恒格列净 Henagliflozin	5 mg,1 次/d	5~10 mg,1 次/d	10 mg, 1 次/d	用于 T2DM 血糖控制	30 或以上	无需调整剂量
					30 以下	禁用

会增加低血糖风险,且低血糖的严重程度与磺脲类降糖药物的剂量密切相关[35]。在加用 SGLT-2i 时应酌情停用或减少胰岛素和磺脲类药物的剂量。SGLT-2i 联合使用格列奈类降糖药物发生低血糖风险的研究鲜有报道。SGLT-2i 联合二甲双胍、DPP-4i、噻唑烷二酮类和胰高糖素肽 1 受体激动剂(GLP-1RA)具有较好的降糖作用,低血糖风险并不增加。

20　低血压患者可以使用 SGLT-2i 吗?

SGLT-2i 具有一定降压作用,常规剂量 SGLT-2i 能够降低收缩压 3.6~6.3 mmHg/舒张压 2.6~3.9 mmHg。SGLT-2i 能够产生渗透性利尿作用,可能加重原有血容量不足的状态。因此,SGLT-2i 禁用于症状性低血压或收缩压<95 mmHg 的 T2DM 患者。对于病程较长的 T2DM 患者,SGLT-2i 可能增加糖尿病自主神经病变患者发生体位性低血压风险[36]。

21　低体重患者可以使用 SGLT-2i 吗?

SGLT-2i 使用能够减轻患者体重,主要是通过促进尿糖排出和渗透性利尿作用。无论正常身体质量指数(BMI),还是超重以及肥胖的 T2DM 患者使用 SGLT-2i 药物后均可出现体重下降 1.3~1.9 kg,且呈剂量依赖性[37-38]。在低体重患者中使用 SGLT-2i 时应注意评估患者的营养状态。

22　肌少症合并腹围超标适合用 SGLT-2i 吗?

SGLT-2i 会引起人体成分的变化,主要是降低脂肪含量,是否会增加糖尿病患者肌少症,研究结论不一。多项研究显示长期使用 SGLT-2i 可导致肌少症的发病率增加。但也有研究显示,达格列净和卡格列净治疗不影响肌肉量[39-40]。肌少症患者在使用 SGLT-2i 过程中,应适当运动及平衡膳食,监测肌肉质量。

23　脑卒中患者可以使用 SGLT-2i 吗?

SGLT-2i 类药物对于糖尿病合并脑卒中患者是否获益尚无定论。荟萃分析显示,SGLT-2i 对脑卒中风险无显著影响,但不同基线肾小球滤过率亚组脑卒中风险有差异,肾小球滤过率最低的亚组[<45 mL/(min · 1.73m^2)]中脑卒中风险降低 50%;在不同类型卒中方面 SGLT-2i 可使出血性卒中发生风险降低 50%,但对缺血性卒中风险无显著影响[41]。此外,应用 SGLT-2i 使糖尿病合并心房颤动患者缺血性卒中风险降低 20%。而药物不良事件报告显示,SGLT-2i 与缺血性卒中和腔隙性梗死的不良事件报告显著升高相关,而出血性卒中无显著升高[42]。

24　下肢缺血性疾病患者可以使用 SGLT-2i 吗?

有下肢动脉粥样硬化性病变,以及急性动脉栓塞、周围动脉痉挛、下肢深静脉血栓形成和下肢静脉曲张患者,建议评估风险与获益后谨慎使用 SGLT-2i。严重下肢缺血患者,即静息踝肱指数(ABI)<0.40 或踝动脉压(AP)<50 mmHg 或趾动脉压(TP)<30 mmHg,或缺血性溃疡或坏疽、缺血性静息痛的患者,因存在截肢风险,不推荐使用 SGLT-2i。

25　糖尿病足病患者可以使用 SGLT-2i 吗?

在有慢性难治性足溃疡、截肢史和截肢高风险的人群中使用 SGLT-2i 需要谨慎。CANVAS 研究中指出,使用卡格列净治疗会增加下肢截肢风险,足趾和中足截肢最常见,少数患者出现多次大截肢,甚至累及双下肢[43-44]。其他研究中尚未证实 SGLT-2i 治疗是否与患者下肢截肢有关。在糖尿病足溃疡人群中使用 SGLT-2i,需密切观察,并告知相关风险。

26　骨质疏松症患者可以使用 SGLT-2i 吗?

SGLT-2i 对骨折风险以及骨和矿物质代谢的影响目前仍存在争议。多项研究发现卡格列净会导致骨折风险增加。Kohan 等[45] 发现达格列净增加骨折发生率,但 McMurray 等[12] 研究显示使用达格列净的患者骨折风险无明显变化。恩格列净研究显示与骨折风险之间无明显关联[46]。在应用 SGLT-2i 类药物时应该全面评估患者骨折的发生风险,建议综合考虑患者骨密度以及具体 SGLT-2i 药物,在高骨折风险人群中应谨慎使用。

27　前列腺增生患者可以使用 SGLT-2i 吗?

SGLT-2 在前列腺癌组织中表达增加,具有体外转运葡萄糖的功能。卡格列净具有部分抑制 SGLT-1 的作用,延缓前列腺增生的进展,且可抑制人类前列腺癌细胞和肿瘤的增殖和存活,并使其对放射治疗敏感[47]。初次使用 SGLT-2i 的男性糖尿病患者,发生尿频和夜尿增多的几率高。前列腺增生尤其伴慢性尿潴留患者,泌尿道感染风险明显增加。男性慢性尿潴留患者容易出现溢出性尿失禁、肾功能损害、膀胱紧张、肾积水等,故在糖尿病尿潴留患者中不推荐使用 SGLT-2i。

28　T1DM 患者可以使用 SGLT-2i 吗?

SGLT-2i 在国内尚未获批用于治疗 T1DM,不推荐使用 SGLT-2i。国外研究提示,SGLT-2i 联合胰岛素能在不增加低血糖风险的情况下,改善 T1DM 患者的 HbA1c、降低餐后血糖漂移的幅度、增加葡萄糖的目标范围内时间[48]、减少胰岛素使用剂量,并减轻体重[49],但 DKA 的发生风险有增加。

29　围手术期是否需要停用 SGLT-2i?

围手术期患者均需避免在血容量不足甚至休克状态下使用 SGLT-2i,如果使用,可导致围手术期 AKI 发生率增加,但存在一定争议。Gilbert 等[50] 认为继续接受 SGLT-2i 治疗的围手术期患者,AKI 发生的可能性降低;SGLT-2i 的半衰期在存在肾损害时会延长,并可能引发急性—慢性肾衰竭[51]。为了最大限度减少 euDKA 发生的可能性,建议术前 3~4 d 停药[52]。对于急诊手术患者,建议立即停用 SGLT-2i,术后恢复用药的时机需要视具体情况而定;局麻体表手术患者,正常使用 SGLT-2i;硬膜外麻醉手术患者,如不涉及到消化道重建,恢复排气及正常饮食后可继续使用 SGLT-2i;全麻手术患者,待正常饮食后恢复使用 SGLT-2i;胃肠道手术患者,待恢复正常饮食后使用;泌尿生殖系统手术患者,需完全恢复后启用;行导尿术患者,需在拔除尿管并排除感染、出血等情况后恢复使用。

30　妊娠及哺乳期糖尿病患者能使用 SGLT-2i 吗?

SGLT-2i 属于妊娠期 C 类用药。目前妊娠妇女使用 SGLT-2i 的研究数据有限,不能够确定与 SGLT-2i 相关的重大出生缺陷及流产风险,因此不建议在妊娠期高血糖孕妇中使用 SGLT-2i。SGLT-2i 是否随人类乳汁分泌、对母乳喂养婴儿的影响或对乳汁分泌的影响尚不清楚,不建议在哺乳期使用 SGLT-2i。

31　儿童糖尿病患者可以使用 SGLT-2i 吗?

目前所有上市的 SGLT-2i 在 18 岁以下儿童患者中的安全性和疗效均尚未确定,故不建议在儿童糖尿病患者中使用 SGLT-2i。

32　重症感染期糖尿病患者可以使用 SGLT-2i 吗?

目前尚无 SGLT-2i 在重症感染人群中使用的临床数据,暂不推荐在此类人群中使用。

编写顾问(按姓氏笔画排序)

马向华(南京医科大学第一附属医院内分泌科),刘超(南京中医药大学附属中西医结合医院内分泌科),杨涛(南京医科大学第一附属医院内分泌科)

编写组成员(按姓氏笔画排序)

马敬弟(新沂市人民医院内分泌科),王爱萍(东部战区空军医院内分泌科),王萍(南京市高淳人民医院内分泌科),王雪琴(南通市第一人民医院内分泌科),毛莉(淮安市第一人民医院内分泌科),叶新华(常州市第二人民医院内分泌科),毕艳(南京大学医学院附属鼓楼医院内分泌科),朱平(淮安市楚州中医院内分泌科),朱剑(江南大学附属医院内分泌科),刘冬梅(南京医科大学附属老年医院内分泌科),刘艳梅(盐城市第一人民医院内分泌科),刘新亮(盱眙县人民医院内分泌科),许岚(无锡市人民医院内分泌科),孙新娟(东部战区空军医院内分泌科),巫海娣(南京医科大学附属老年医院内分泌科),杨兵全(东南大学附属中大医院内分泌科),杨淑芳(南京医科大学附属泰州人民医院内分泌科),吴新华(淮安市淮安医院内分泌科),宋金方(江南大学附属医院临床药学科),陈正方(常熟市第一人民医院内分泌科),范红旗(南京医科大学第一附属医院内分泌科),赵清(涟水县人民医院内分泌科),胡吉(苏州大学附属第二医院内分泌科),俞匀(南京医科大学附属老年医院内分泌科),施毕旻(苏州大学附属第一医院内分泌科),娄青林(南京医科大学附属老年医院内分泌科),袁国跃(江苏大学附属医院内分泌科),顾云娟(南通大学附属医院内分泌科,凌宏威(徐州医科大学附属医院内分泌科),唐伟(南京医科大学附属老年医院内分泌科),宰国田(南京江北医院内分泌科),崔思远(无锡市人民医院内分泌科),梁贝贝(南京医科大学附属老年医院内分泌科),葛智娟(南京大学医学院附属鼓楼医院内分泌科),蒋晓红(常州市第一人民医院内分泌科),智俊娜(南京医科大学附属老年医院药剂科),焦雪花(苏州大学附属苏州九院内分泌科)

执笔(按姓氏笔画排序)

梁贝贝(南京医科大学附属老年医院内分泌科),智俊娜(南京医科大学附属老年医院药学部)

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