

Consensus on glycemic management for patients with coronary heart disease and type 2 diabetes

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ABSTRACT The prevalence of patients with coronary heart disease (CHD) and diabetes mellitus is notably high, posing significant residual cardiovascular risks even after routine interventions such as antihypertensive, lipid-lowering, and antithrombotic treatments. Recent studies have demonstrated that certain glucose-lowering medications confer cardiovascular benefits for patients with type 2 diabetes. However, a survey indicates that cardiologists may not be fully acquainted with the optimal screening timing, indicators, and diagnostic criteria for type 2 diabetes, and there is insufficient awareness and a low rate of prescription of novel glucose-lowering medications with proven cardiovascular efficacy, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i). In this context, based on domestic and international guidelines or consensus and the latest evidence-based evidence, this consensus aims to standardize the glycemic management for patients with acute coronary syndrome, chronic coronary syndrome, and perioperative management for percutaneous coronary intervention. It highlights the key points of screening and diagnosis of type 2 diabetes, and the comprehensive management of cardiovascular risk in patients with CHD. The consensus elaborates on the principles and algorithms of glycemic management for CHD patients, without involving acute complications of diabetes, clarifies the clinical practice of glucose-lowering medications with cardiovascular benefits, and promotes the standardized use of these medications in cardiovascular and other related specialty fields. Additionally, it addresses the glucose-lowering treatment to comprehensively reduce cardiovascular risks.

Diabetes stands as a pivotal risk factor and comorbidity for coronary heart disease (CHD). In China, surveys reveal that 45% of acute coronary syndrome (ACS) patients coexist with diabetes,^[1] and this figure is 26.8% for chronic stable CHD.^[2] Furthermore, hyperglycemia is an independent risk factor for all-cause and cardiac death during percutaneous coronary intervention (PCI).^[3] The FOURIER study showed that patients with CHD and diabetes maintain a substantial residual risk despite conventional interventions, including antihypertensive, lipid-lowering, and antithrombotic therapies, highlighting the need for enhanced therapeutic strategies.^[4]

In recent years, novel glucose-lowering medications, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs, such as liraglutide, semaglutide, and dulaglutide) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i, such as empagliflozin, dapagliflozin, and canagliflozin), have demonstrated significant cardiovascular benefits for type 2 diabetes mellitus (T2DM) by further reducing the risk of cardiovascular events. However, a survey in-

volving 342 cardiologists and endocrinologists revealed several challenges in utilizing GLP-1 RAs/SGLT-2i among Chinese patients with atherosclerotic cardiovascular disease (ASCVD) and T2DM, such as underuse and non-standard treatment.^[5] This highlights the need for standardized theoretical guidance and management protocols.

Therefore, the Cardiovascular Subcommittee of Chinese International Exchange and Promotion Association for Medical and Healthcare organized experts in the field of cardiovascular and endocrinology in China, and combined domestic and international guidelines/consensus and the latest evidence-based medicine to jointly formulate the “Expert Consensus on Glycemic Management for Patients with Coronary Artery Diseases and Type 2 Diabetes.” The target physicians of this consensus are cardiologists and related professional physicians, and the target population is patients with CHD, including ACS, chronic coronary syndrome (CCS), and perioperative PCI, with content mainly involving screening, diagnosis, management, and long-term follow-up of T2DM to provide standardized guidance for

glycemic management and comprehensive disease management in patients with CHD and T2DM.

SCREENING AND DIAGNOSIS OF T2DM WITH CHD

Key message

(1) All patients with CHD should undergo screening and evaluation for T2DM.

(2) Fasting plasma glucose (FPG) and glycated hemoglobin (HbA_{1c}) levels are preferred for glycemic screening. The oral glucose tolerance test (OGTT) serves as the confirmatory test when initial screenings with FPG and HbA_{1c} do not conclusively diagnose T2DM.

Screening Timing

For all CHD patients, regardless of whether typical symptoms of diabetes (polydipsia, polyuria, polyphagia, unexplained weight loss) are present or not, glycemic screening (including the time of admission, outpatient visit, and perioperative PCI for ACS patients) should be conducted to determine blood glucose levels and T2DM history. The prevalence of T2DM among patients with CHD markedly exceeds that observed in the general population. A large proportion of cases will be missed if no medical attention is paid to T2DM screening. Patients with ACS, irrespective of pre-existing T2DM, frequently exhibit raised blood glucose levels during hospitalization—a phenomenon often linked to stress hyperglycemia associated with ACS, which correlates with poorer outcomes.

Screening Indicators

FPG and HbA_{1c} are recommended as the primary screening tests for T2DM in patients with CHD. The Oral Glucose Tolerance Test (OGTT) serves as a confirmatory test when initial screenings with FPG

and HbA_{1c} don't conclusively diagnose T2DM.^[6] Pancreatic islets function tests, such as serum insulin or C-peptide, may be performed if available.

Diagnostic Criteria

Currently, the diagnosis of diabetes in China adopts the World Health Organization (WHO) 1999 criteria, prioritizing venous plasma glucose levels, and blood glucose is only used as a supplementary reference. The classification of glucose metabolism status is detailed in [Tables 1](#).^[7] According to the Guideline for the Prevention and Treatment of Type 2 diabetes Mellitus in China (2020 edition), the diagnostic criteria for T2DM are: typical diabetic symptoms (polydipsia, polyuria, polyphagia, unexplained weight loss) combined with a random plasma glucose ≥ 11.1 mmol/L; or a fasting plasma glucose ≥ 7.0 mmol/L; or an OGTT 2h ≥ 11.1 mmol/L; an HbA_{1c} $\geq 6.5\%$.^[7] In asymptomatic subjects, carrying out at least one further test on a subsequent day is essential to establish the diagnosis.^[7]

COMPREHENSIVE CARDIOVASCULAR RISK MANAGEMENT IN CHD PATIENTS WITH CONCOMITANT T2DM

Lifestyle Modification

Key message

Lifestyle intervention is the foundation for comprehensive cardiovascular risk management in CHD patients with concomitant T2DM. It is recommended that all CHD patients with concomitant T2DM improve their lifestyle and long-term adherence, including weight loss, dietary management, exercise management, and smoking cessation.

Weight loss

According to the body mass index (BMI) evalu-

Table 1 Classification of glucose metabolic status (WHO 1999).

Glucose metabolic status	Venous plasma glucose concentration (mmol/L)	
	Fasting	OGTT 2 h
Normal glucose level	< 6.1	< 7.8
Impaired fasting glycemic	$\geq 6.1, < 7.0$	< 7.8
Impaired glucose tolerance	< 7.0	$\geq 7.9, < 11.1$
Diabetes mellitus	≥ 7.0	≥ 11.1

OGTT: oral glucose tolerance test. Impaired fasting glycemic and impaired glucose tolerance are collectively referred to as impaired glucose regulation, also known as pre-diabetes; the lower limit of the normal range for fasting glycemic is usually set at 3.9 mmol/L.



ation standard, a BMI of 24.0-27.9 kg/m² indicates overweight, and ≥ 28.0 kg/m² indicates obesity. Furthermore, the diagnostic criteria for abdominal obesity are waist circumference ≥ 90 cm for men and ≥ 85 cm for women.^[7] It is imperative for individuals who are overweight or obese to initiate and consistently maintain weight loss efforts to achieve a BMI range of 20.0-24.0 kg/m². Conversely, patients with normal weight are advised to prevent weight gain during treatment. The cornerstones of weight management include reducing total calorie intake, adhering to a nutritionally balanced diet, engaging in moderate physical activity, and establishing a regular routine.^[8]

Dietary management

Control total caloric intake to 25-30 kcal/kg body weight. Achieving nutritional balance and moderation is critical, adhering to the daily recommended calorie distribution: 15%-20% from proteins, less than 30% from fats, and 45%-60% from carbohydrates. An ample intake of vitamins, minerals, and dietary fiber is crucial, thus a dietary fiber consumption of 25-30 g/day or 10-14 g/1000 kcal is advised. Sodium intake should not exceed 6 g/day, with patients suffering from hypertension and heart failure requiring more stringent restrictions.

Exercise management

It is recommended that patients with CHD and T2DM engage in aerobic exercise or resistance exercise, and the duration and intensity of the exercise should be individualized according to the patient's situation.^[9] It's worth noting that: (1) a comprehensive medical assessment is essential before initiating an exercise program, paying close attention to identifying any indications and contraindications to tailor an individualized exercise plan; (2) it is crucial to monitor blood glucose before and after exercising to prevent hypoglycemia; and (3) patients with T2DM and obesity are advised to take precautions to minimize the risk of joint pain and discomfort during exercise.

Smoking cessation

For CHD patients with concomitant T2DM, it is

imperative to abstain from active smoking and avoid exposure to secondhand smoke. It is strongly advised that current smokers initiate cessation efforts immediately. For those facing challenges in quitting smoking independently, the endorsement of pharmacological interventions is suggested. This includes options such as nicotine replacement therapy, or bupropion, varenicline treatment.^[6]

Glycemic Management Targets

Key message

- (1) For CCS patients with T2DM, a reasonable HbA_{1c} target is $< 7\%$, and the target value should be dynamically adjusted based on the patient's disease progression and any changes in their health status.
- (2) In the perioperative management of ACS patients with T2DM undergoing PCI, it is crucial to tailor glycemic targets to minimize the risk of hypoglycemia while effectively controlling blood glucose levels.

For CHD patients with concomitant T2DM, the primary objective of glycemic management encompasses not only the reduction of blood glucose levels to meet long-term maintenance targets, but also to diminution of cardiovascular events, associated complications, and mortality risks. HbA_{1c} is the most important indicator for assessing glycemic control status. It is recommended that, for most CHD patients with concomitant T2DM, a reasonable HbA_{1c} target should be $< 7\%$, prioritizing individualized assessment and management as a fundamental principle. Targeting HbA_{1c} levels to intensive glycemia control (such as $< 6.5\%$) may be achieved among T2DM patients with younger age, shorter disease duration, and longer life expectancy if no hypoglycemia or other adverse effects are caused. Otherwise, less stringent HbA_{1c} target should be set (such as tailored to $< 8.5\%$). The HbA_{1c} target needs to be promptly adjusted during treatment, considering the patient's disease progression and changes in their condition, to optimally balance the risks and benefits.^[7]

For ACS or perioperative PCI patients with T2DM, previous studies have failed to show any clinical benefit but increased risk of hypoglycemia when strict glycemic control strategies were adopted,^[10] so less stringent glycemic targets are recommended. The



more severe the condition, the less stringent the target. A fasting or pre-prandial blood glucose of 7.8-10.0 mmol/L is recommended if tolerated by the patient.^[7]

Effect of Glucose-lowering Medications On Cardiovascular Outcomes in T2DM Patients

Key message

(1) Glucose-lowering medications with proven cardiovascular benefits: selected GLP-1 RAs (liraglutide, semaglutide, and dulaglutide) and selected SGLT-2i (empagliflozin, dapagliflozin, and canagliflozin).

(2) Glucose-lowering agents with potential cardiovascular benefits: metformin and pioglitazone.

(3) Glucose-lowering medications with cardiovascular safety but uncertain cardiovascular benefits: dipeptidyl-peptidase-4 inhibitors (DPP-4i), sulfonylureas (glimepiride, gliclazide), insulin glargine or insulin degludec, alpha-glucosidase inhibitors (acarbose), and other GLP-1 RAs (lixisenatide, exenatide).

(4) Glucose-lowering medications with unevaluated cardiovascular safety: other insulins and other sulfonylureas.

Glucose-lowering medications with proven cardiovascular benefits

In recent years, a series of randomized controlled clinical studies have demonstrated that GLP-1 RAs (liraglutide, semaglutide, and dulaglutide) and SGLT-2i (empagliflozin, dapagliflozin, and canagliflozin) can significantly improve cardiovascular outcomes and exhibit a favorable safety profile in patients with T2DM.

GLP-1 RAs exerts their function by binding to GLP-1 receptors, thereby activating adenylyl cyclase. This activation triggers an increase in glucose-dependent insulin secretion, inhibits glucagon secretion, enhances glucose uptake in muscle tissue, reduces hepatic glucose output, and delays gastric emptying, collectively contributing to their glucose-lowering effects. Concurrently, GLP-1 RAs have multiple anti-atherosclerotic mechanisms, including reducing small dense low-density lipoprotein and oxidative stress, decreasing macrophages and foam cells, improving endothelial function, and exerting anti-inflammatory, anti-platelet, and plaque-

stabilizing effects.^[11] Among GLP-1 RAs approved for use domestically, liraglutide, semaglutide, and dulaglutide have demonstrated cardiovascular protective effects. The LEADER study found that, during a median follow-up of 3.8 years, liraglutide treatment significantly reduced the risk of major adverse cardiovascular events (MACE; including the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) by 13% and the risk of cardiovascular death by 22%.^[12] Moreover, subgroup and *post-hoc* analyses of the LEADER trial revealed that the cardiovascular benefit of liraglutide was independent of the patient's baseline diabetes duration, BMI, blood pressure, lipid profile, number of diseased vessels, number of microvascular complications, statin therapy, metformin therapy, cardiac functional status, and occurrence of hypoglycemia.^[12,13] The SUSTAIN-6 study demonstrated that once-weekly subcutaneous injection of semaglutide significantly reduced the risk of MACE by 26% and the risk of non-fatal stroke by 39%.^[14] Furthermore, the subgroup and *post-hoc* analyses of the SUSTAIN-6 trial indicated that the cardiovascular benefits of semaglutide were independent of baseline BMI, blood pressure, HbA_{1c}, diabetes duration, number of microvascular complications, renal function, and insulin use, among other factors.^[15] The REWIND study,^[16] in which nearly 70% of patients were at high risk for T2DM combined with ASCVD, reported that dulaglutide significantly reduced the risk of MACE (including the first non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) by 12% during a median follow-up of 5.4 years.

SGLT-2i reduces glucose levels in the circulation primarily by inhibiting the reabsorption of glucose by the proximal tubules of the kidney, lowering the renal threshold for glucose, and promoting the excretion of glucose in urine. The EMPA-REG OUTCOME trial with empagliflozin^[17] and the CANVAS trial with canagliflozin^[18] demonstrated that SGLT-2i significantly reduced the risks of MACE and hospitalization for heart failure. In the DECLARE-TIMI 58 study, no statistically significant reduction in the incidence rate of events for the pri-



mary composite endpoint was observed in the dapagliflozin group. However, a post-hoc analysis of the DECLARE-TIMI 58 trial revealed that dapagliflozin demonstrated a statistically significant reduction in the risk of cardiovascular death or hospitalization for heart failure, primarily driven by the reduction in hospitalization for heart failure.^[19]

Glucose-lowering Medications with Potential Cardiovascular Benefits

Metformin was not required to be tested for cardiovascular outcomes due to its early market launch. However, the UK Prospective Diabetes Study (UK-PDS), several observational studies, and meta-analyses have shown that metformin was associated with a significant reduction in the risk of cardiovascular and all-cause mortality in patients with T2DM, as well as a reliable glucose-lowering effect, favorable safety and tolerability without increasing the risk of hypoglycemia.^[20] The PROactive study evaluated the cardiovascular outcomes of pioglitazone in T2DM patients with ASCVD. The results showed that although the primary composite endpoints didn't reach statistical significance, it reduced the risk of all-cause death, non-fatal myocardial infarction, or stroke by 16%.^[21]

Glucose-lowering Medications with Favorable Cardiovascular Safety but Uncertain Cardiovascular Benefits

Findings of studies investigating dipeptidyl peptidase 4 inhibitors (DPP-4i),^[22-24] sulfonylureas (glimepiride, gliclazide),^[24-26] insulin glargine or insulin degludec,^[27,28] alpha-glucosidase inhibitors (acarbose)^[29] and other GLP-1 RAs (lixisenatide, exenatide)^[30,31] reported that these medications failed to significantly improve cardiovascular outcomes despite exhibiting cardiovascular safety.

Glucose-lowering Medications with Unevaluated Cardiovascular Safety

The cardiovascular safety of short-acting insulins has not been tested yet. Similarly, except for glimepiride and gliclazide, no other sulfonylureas have been evaluated for cardiovascular safety.

Glycemic Management in T2DM Patients with Different Subtypes of CHD

Key message

(1) ACS patients should be tested for HbA_{1c} and closely monitored for blood glucose during hospitalization.

(2) For ACS patients with relatively stable clinic-al conditions, maintaining a regular eating schedule, and having no drug contraindications, the continuation of previously used oral glucose-lowering medications or GLP-1 RAs may be considered after admission. Subcutaneous injection of insulin is recommended in other cases.

(3) For CCS patients with concomitant T2DM, regardless of whether HbA_{1c} target is reached or not, GLP-1 RAs (liraglutide, semaglutide, and dulaglutide) and/or SGLT-2i (empagliflozin, dapagliflozin, and canagliflozin) with proven cardiovascular benefits should be initiated when no specific contraindications exist. For patients with heart failure, SGLT-2i should be preferred. For patients with overweight or obesity, GLP-1 RAs should be preferred.

(4) Insulin is the preferred glucose-lowering choice during the perioperative period of PCI. For patients undergoing elective surgery, other glucose-lowering medications can be adjusted according to the patient's condition when time permits.

(5) Multidisciplinary consultation should be initiated in a timely manner for patients with CHD combined with T2DM who have special conditions (such as pregnancy) or difficulties in diagnosis, treatment, and management.

Basic Principles and Clinical Pathways

ACS patients

The fundamental principle of glycemic management in the acute phase of ACS is to control hyperglycemia while avoiding hypoglycemia. HbA_{1c} should be tested and the blood glucose should be closely monitored during hospitalization to differentiate between diabetes and stress hyperglycemia; pay attention to the detection of urine glucose and urine ketones if the glucose concentration is higher than 13.9 mmol/L.^[7]

The blood glucose levels of ACS patients in the acute phase are influenced by various of factors and vary substantially among individuals. In clinical practice, the choice of treatment regimen should be based on a comprehensive consideration of the indi-



vidual's specific situation. For ACS patients with relatively stable clinical conditions, who maintain a regular eating schedule, and have no drug contraindications, the continuation of previously used oral glucose-lowering medications or GLP-1 RAs may be considered after admission. Subcutaneous injection of insulin is recommended in other cases.^[32]

For patients diagnosed with T2DM without drug contraindications, following achieving hemodynamic stabilization, lifestyle interventions and glucose-lowering medications with proven cardiovascular benefits, such as GLP-1 RA (liraglutide, semaglutide, and dulaglutide) and/or SGLT-2i (empagliflozin, dapagliflozin, and canagliflozin) treatment should be initiated, combined with other glucose-lowering medications based on patients' blood glucose levels, as well as regular blood glucose monitoring to prevent hypoglycemia. For patients who have stress hyperglycemia without a prior T2DM

diagnosis, re-examination of blood glucose and HbA_{1c} two weeks after achieving condition stabilization is recommended to determine the presence of T2DM. Figure 1 summarizes the glycemic management flowchart for ACS patients.

CCS patients

It is recommended that CCS patients with T2DM, irrespective of their HbA_{1c} levels, should initiate treatment with GLP-1 RA (liraglutide, semaglutide, and dulaglutide) and/or SGLT-2i (empagliflozin, dapagliflozin, and canagliflozin) if there are no contraindications, due to their proven cardiovascular benefits. GLP-1 RAs can provide multiple benefits, including lowering blood glucose, promoting weight loss, improving lipid profiles, and reducing blood pressure. If additional glycemic control is needed thereafter, the combination of other glucose-lowering medications may be con-

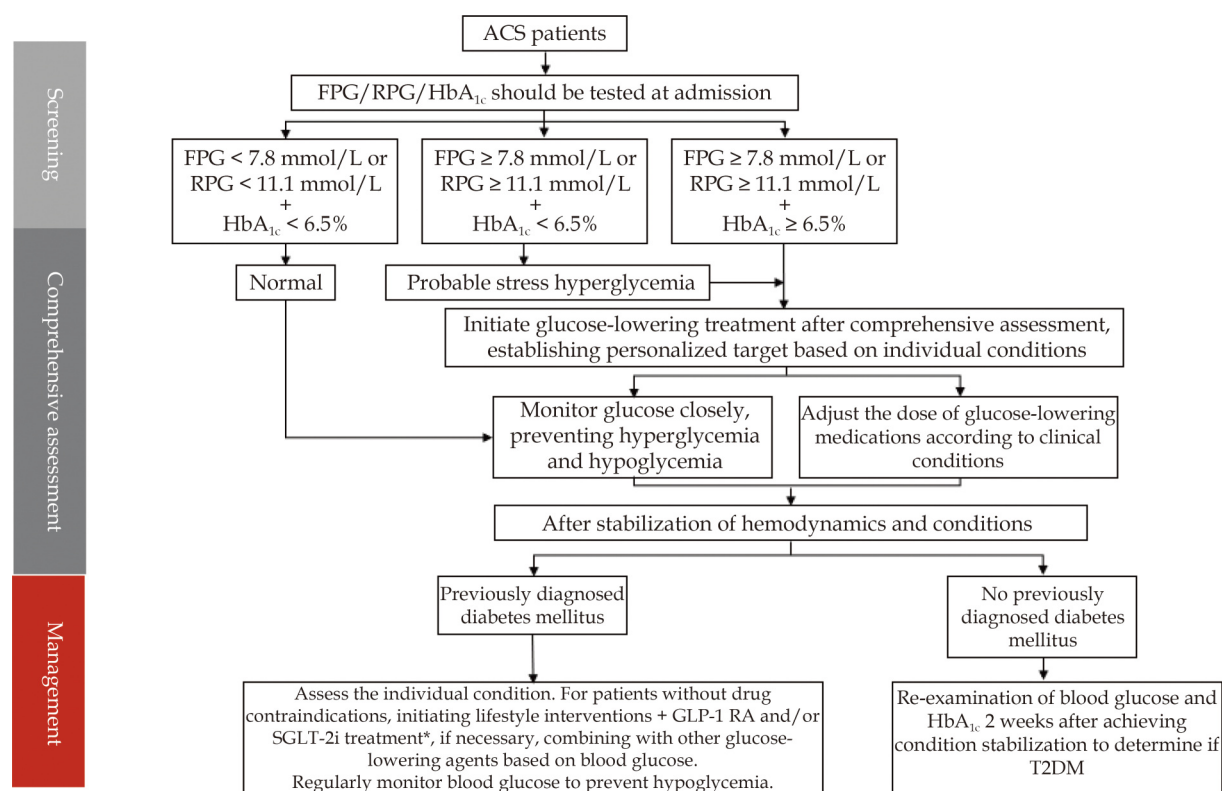


Figure 1 Glycemic management flowchart for ACS patients. *According to the patient's nutritional status and previous medication regimen, the replacement or addition of GLP-1 RAs (liraglutide, semaglutide and dulaglutide) or SGLT-2i (empagliflozin, dapagliflozin, and canagliflozin) with proven cardiovascular benefits was selected individually; If the patient was previously taking DPP-4i, GLP-1 RA should be applied after discontinuation of DPP-4i. ACS: acute coronary syndrome; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated haemoglobin; FPG: fasting plasma glucose; RPG: random plasma glucose; SGLT-2i: sodium-glucose co-transporter-2 inhibitor; DPP-4i: dipeptidyl-peptidase-4 inhibitors.



sidered on an individualized basis after extensive evaluation of drug-specific and patient-specific factors, such as glycemia, comorbidities, weight, risk of hypoglycemia, hepatic and renal function, etc.

Recommendations for glucose-lowering treatment for different patients are as follows: (1) For patients with heart failure, SGLT-2i is preferred, including dapagliflozin, empagliflozin, and canagliflozin, to reduce the risk of hospitalization for heart failure. The addition of GLP-1 RAs may be considered if further glycemic control is required after SGLT-2i treatment.^[6,20] (2) For patients with CKD (defined as structural or functional abnormalities persisting over 3 months), SGLT-2is (such as empagliflozin, dapagliflozin, and canagliflozin) or GLP-1 RAs (such as liraglutide, semaglutide, and dulaglutide) are preferred due to their established cardiac and renal benefits.^[20] (3) For patients with obesity or overweight, GLP-1 RAs are preferred due to their proven weight loss effects.^[20] The weight loss effect

varies across different GLP-1 RAs medications. Studies have shown that treatment with semaglutide 1.0 mg (once-weekly) for 40 weeks reduced body weight by up to 6.5 kg;^[33] liraglutide 1.8 mg (once-daily) treatment for 26 weeks resulted in an average weight loss of 3.5 kg from baseline;^[34] dulaglutide 1.5 mg (once-weekly) monotherapy for 26 weeks led to a weight loss of 1.5 kg from baseline.^[35] According to the Standards of Care in Diabetes – 2024 released by the American Diabetes Association (ADA),^[20] the recommended order of preference based on weight loss effect of GLP-1 RAs is semaglutide, liraglutide, dulaglutide, exenatide and lixisenatide.^[20] The glycemic management flowchart for CCS patients is shown in Figure 2.

Perioperative PCI

In patients undergoing elective PCI who have good glycemic control with oral glucose-lowering medications, there is no need to switch to insulins. If preoperative glycemic control is poor (e.g., FPG > 7.8 mmol/L), a switch to insulin may be considered.

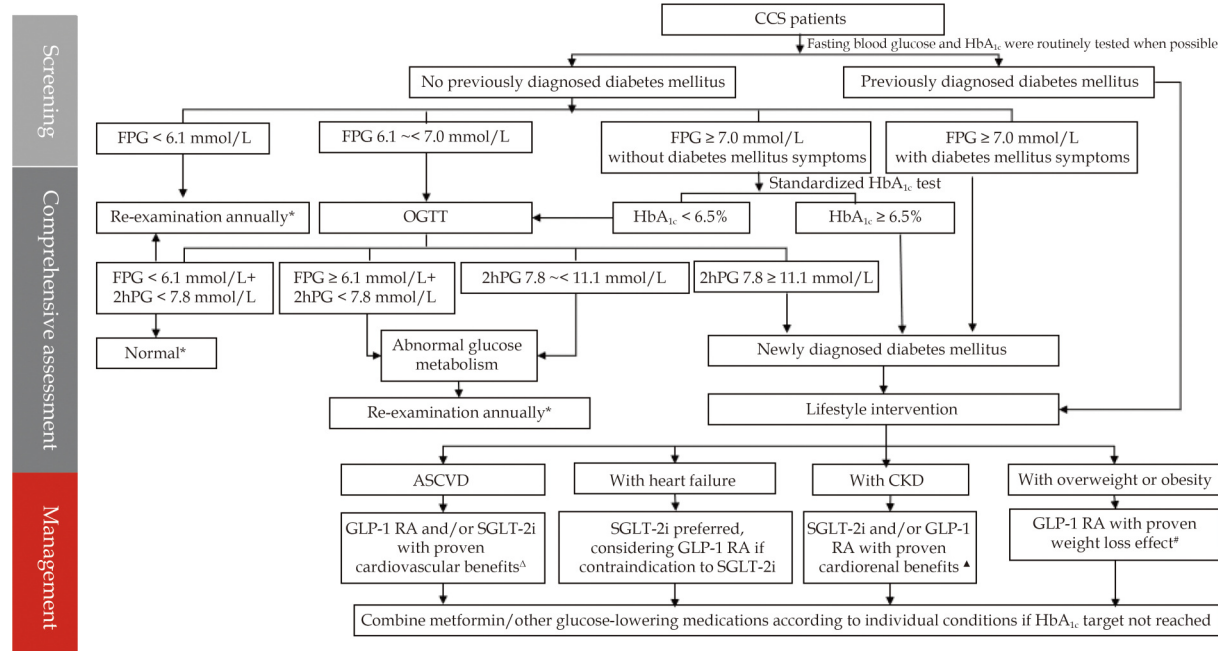


Figure 2 The glycemic management flowchart in CCS patients. *Follow-up protocols will be determined individually based on each patient's situations. [^]GLP-1 RAs (liraglutide, semaglutide and dulaglutide) and SGLT-2is (empagliflozin, dapagliflozin, and canagliflozin) with proven cardiovascular benefit. [^]SGLT-2is (empagliflozin, dapagliflozin, and canagliflozin) or GLP-1 RAs (liraglutide, semaglutide and dulaglutide) with cardio-renal benefits. [^]GLP-1 RAs with proven weight loss effect (including semaglutide, liraglutide and dulaglutide). CCS: chronic coronary syndrome; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; HbA_{1c}: glycated haemoglobin; 2hPG: 2-h postprandial blood glucose; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; SGLT-2i: sodium-glucose co-transporter-2 inhibitors.

Subcutaneous injection of insulin is the preferred regimen for preoperative glycemic control, either basal-prandial insulin (intermediate-/long-acting insulin at bedtime combined with short-/rapid-acting insulin before three meals), premixed insulin subcutaneous injection or insulin pump subcutaneous injection. A continuous intravenous infusion of insulin offers advantages intraoperatively, while blood glucose is closely monitored, and the insulin infusion rate is dynamically adjusted according to blood glucose readings.^[36]

For patients taking glucose-lowering medications, some oral medications and non-insulin injections should be withheld, if time permits, on the day of surgery. For the patients receiving intravenous iodine contrast media for testing, metformin should be discontinued prior to or at the time of the examination and resumed at least 48 h after completion of the examination, and only if renal function is stable upon recheck.^[37] The DPP-4is and GLP-1 RAs affect glucose control through glucose-dependent mechanism, so they can be used during the perioperative period due to their low risk of hypoglycemia. SGLT-2is tend to cause hypovolemia and urinary tract infection, so it is necessary to discontinue it 48 h before PCI. For shorter, less invasive day surgeries, where patients can resume a normal diet on the day of surgery, some oral glucose-lowering medications can be retained, but sulfonylureas and glinides, which may promote insulin secretion, should be discontinued, as these medications are prone to causing hypoglycemia after fasting.^[36]

Emergency surgery carries inherent difficulties regarding ideal control of blood glucose preoperatively due to the critical nature of cases. Nevertheless, intraoperative and postoperative hyperglycemia should be controlled with continuous glucose monitoring to avoid hypoglycemia. For patients with comorbid ketoacidosis, glycemic management should be proactive, and an individualized decision on whether to postpone surgery will be tailored to the patient's overall physiological condition and the urgency of the surgery.

Multidisciplinary consultation

Multidisciplinary consultation^[38] and manage-

ment can be considered when CHD patients experience the following challenges:

(1) Diagnostic uncertainty and special situations: those who are found to have abnormal blood glucose levels with an unclear clinical classification for the first time; pregnant and lactating women with abnormal blood glucose.

(2) Treatment difficulty: those who present with recurrent hypoglycemia with unknown causes or after treatment by physicians; those whose blood glucose fluctuates greatly and is uncontrollable by physicians; those who have serious and uncontrollable adverse reactions to glucose-lowering medications; those who fail to achieve targets for blood glucose, blood pressure, and blood lipids despite long-term treatment.

(3) Serious complications: (a) acute complications of diabetes: severe hypoglycemia or hyperglycemia with or without impaired consciousness (diabetic ketoacidosis, hyperosmolar hyperglycemic state, or lactic acidosis). (b) Challenges in screening for chronic complications of diabetes (retinopathy, nephropathy, neuropathy, diabetic foot, or peripheral vasculopathy), the establishment of treatment plans, and the evaluation of treatment effectiveness; worsening of chronic complications of diabetes that requires emergency treatment: acute cardiovascular and cerebrovascular disease; diabetic nephropathy-induced renal insufficiency [$\text{eGFR} < 60 \text{ mL/min per } 1.73 \text{ m}^2$] or massive proteinuria; severe vision loss caused by diabetic retinopathy; intermittent claudication and ischemic pain, diabetic foot ulcers or severe foot deformities caused by diabetic peripheral vasculopathy.

(4) Other conditions or diseases requiring intervention at the discretion of the attending physician.

Long-term follow-up

During the follow-up of CHD patients, in addition to monitoring blood pressure and lipids, it is essential to perform long-term monitoring of blood glucose, including re-examination of fasting/postprandial blood glucose at each visit, and HbA_{1c} should be tested at least every 3 months.^[38]



Practice of Glucose-lowering Medications with proven Cardiovascular Benefits

Key message

(1) When GLP-1 RAs (liraglutide, semaglutide, and dulaglutide) and SGLT-2 is (empagliflozin, dapagliflozin, and canagliflozin) with proven cardiovascular benefits are used in clinical practice, contraindications should be excluded, and pay attention to dose titration, dose adjustment of other drugs at treatment initiation, and long-term monitoring and treatment of side effects during the treatment process.

(2) The combination of GLP-1 RAs and SGLT-2is has a synergistic effect by mechanism, yielding a reduction in the risk of cardiovascular events without increasing the risk of severe hypoglycemia.

GLP-1 RAs

Contraindications

GLP-1 RAs are contraindicated in patients who are allergic to GLP-1 RAs, pregnant or breastfeeding, and have a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. Additionally, GLP-1 RAs should be used with caution in individuals with gastroparesis or previous gastric surgery, a history of pancreatitis, or proliferative diabetic retinopathy, and the benefits and risks of treatment need to be evaluated.^[39]

Dose Titration of GLP-1 RAs

All GLP-1 RAs available in China (except for beaglutide and exenatide microspheres) can be used in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min); those with severe renal impairment (creatinine clearance 15 to < 30 mL/min) patients can use semaglutide, dulaglutide and liraglutide, but their use is not recommended for patients with end-stage renal disease (creatinine clearance < 15 mL/min).^[40]

Regarding dosing, it is recommended to gradually titrate GLP-1 RA to the cardiovascular benefit dose with the maximum tolerated dose. The LEADER trial^[12] confirmed that cardiovascular benefits with liraglutide 1.8 mg; the SUSTAIN-6 trial^[14] showed that semaglutide 0.5 mg or 1.0 mg (once-weekly) provided similar reductions in the risk of MACE and its components. The REWIND trial^[16] found that dulaglutide 1.5 mg conferred cardiovascular benefits.

Adjustment of Other Medications at Treatment Initiation

(1) Adjustment of other glucose-lowering medications: GLP-1 RAs and DPP-4is have overlapping mechanisms of action, and their combination is not recommended. Other glucose-lowering medications that need adjustment are mainly sulfonylureas and insulin. For patients receiving sulfonylurea therapy, discontinuation should be considered at the time of initiating GLP-1 RA therapy, especially when baseline HbA_{1c} is $\leq 7.5\%$ or the patient has experienced hypoglycemic episodes at any HbA_{1c} level. If HbA_{1c} is 7.6%-8.5%, sulfonylureas should be reduced by 50%. If HbA_{1c} is $> 8.5\%$, sulfonylureas can be maintained at the same dose. Subsequently, as the patient's HbA_{1c} level reaches the individual target value, it may be possible to discontinue sulfonylureas.^[39] For patients treated with insulin, it is recommended to reduce the basal insulin dose by 20%-30% if the baseline HbA_{1c} level is at or below the target before GLP-1 RA initiation, or if the patient is experiencing hypoglycemic episodes. For those using higher doses of insulin or multiple daily injections of insulin, cardiologists may consider delaying the initiation of GLP-1 RA therapy, and referring the patient to an endocrinologist for consideration of therapy transition.^[39]

(2) Adjustment of cardiovascular medications: semaglutide and liraglutide are primarily metabolized through proteolytic degradation. *In vitro* studies have shown that semaglutide and liraglutide have a very low potential for to have pharmacokinetic drug-drug interactions related to cytochrome P450 enzymes and plasma protein binding with other active substances. No clinically relevant absorption delays have been observed when used concomitantly with commonly used cardiovascular medications (e.g., digoxin, warfarin, atorvastatin, etc.). Therefore, dose adjustment is not necessary.

Common Adverse Reactions and Treatment Principles

GLP-1 RAs rarely causes hypoglycemia unless used concurrently with sulfonylureas or insulin. The most common adverse reactions of GLP-1 RAs are gastrointestinal distress, which is dose-dependent and can be alleviated with the extension of treatment. When patients experience gastrointestinal



al symptoms, a comprehensive evaluation should be performed: for short-term or mild gastrointestinal reactions, symptoms can be alleviated by consuming small, frequent meals and avoiding fried or greasy foods; for persistent or more severe gastrointestinal reactions, dose escalation of GLP-1 RA should be suspended, and the dose of GLP-1 RA should be reduced or switched to another GLP-1 RA according to the patient's condition, or even discontinue GLP-1 RA, until the adverse reactions resolve, and then consider resuming GLP-1 RAs therapy. Injection site reactions that may occur with the use of GLP-1 RAs include erythema, rash, and subcutaneous nodules, which may be prevented by rotating the injection sites.^[39]

Patient Monitoring and Follow-up

For patients receiving GLP-1 RAs treatment, monitoring for gastrointestinal adverse reactions and evaluating the long-term medication adherence is key during follow-up. After initiating treatment, if the patient can tolerate it, regardless of blood glucose control, GLP-1 RA can be adjusted to a dose level proven to improve cardiovascular outcomes.^[39]

SGLT-2is

Contraindications

Contraindications to SGLT-2is include: known allergic or other adverse reactions; pregnancy or lactation; eGFR < 20 mL/min per 1.73 m²; symptomatic hypotension or systolic blood pressure < 95 mmHg (1 mmHg = 0.133 kPa).^[41]

Target Doses of SGLT-2is

The target doses of SGLT-2i are as follows:^[41] dapagliflozin 10 mg/day, empagliflozin 10 mg/day, canagliflozin 100 mg/day, sotagliflozin 200 mg/day, and ertugliflozin 5 mg/day. Depending on the patient's baseline blood pressure, blood volume, blood glucose, and renal function, the drug dose may be reduced by half when initiating treatment.

Adjustment of Other Medications at Treatment initiation

(1) Adjustment of other glucose-lowering medications: sulfonylureas and insulin increase the risk of hypoglycemia. Therefore, when initiating SGLT-2is

therapy, it is recommended to reduce or discontinue sulfonylureas and reduce the dose of insulin.^[42]

(2) Adjustment of cardiovascular medications: SGLT-2is can induce osmotic diuresis and may lead to hypotension in susceptible patients. Therefore, it is recommended to adjust the dose of renin-angiotensin-aldosterone system inhibitors and reduce the diuretics dose according to blood pressure/renal function during treatment.^[42] Pharmacokinetic studies suggest that canagliflozin and sotagliflozin may increase digoxin concentration, so monitoring is required during co-administration.

Common Adverse Reactions and Treatment Principles^[42]

(1) Urogenital tract infections: Most are mild to moderate bacterial or fungal infections, and conventional anti-infective treatment is effective. It is recommended that patients pay attention to personal genital hygiene, drink adequate water, and ensure regular urination to prevent such infections. (2) Non-hyperglycemia diabetic ketoacidosis: this condition is rare. Before initiating such medications, a comprehensive assessment of the patient's condition is recommended. Enhanced medication guidance and post-treatment monitoring should be implemented. If symptoms such as abdominal pain, nausea, vomiting, fatigue, or dyspnea occur, immediate testing of ketones and arterial blood acid-base status is necessary to establish a diagnosis. Once diagnosed, SGLT-2i should be immediately discontinued, and symptomatic treatment should be administered.

Patient Monitoring and Follow-up

Based on the adverse reactions that may occur during the administration of SGLT-2is, it is recommended monitoring eGFR, blood volume, blood pressure, urine routine, blood glucose, body weight and physical examination of the lower extremities, as well as arterial blood gas analysis, if necessary, after initiating SGLT-2i treatment.^[41]

Combination of GLP-1 RA and SGLT-2i

GLP-1 RA and SGLT-2i have cardiovascular protective mechanisms independent of glucose lowering effects, their mechanisms are complementary, which underlies the feasibility of combining the two



medications. A meta-analysis of RCTs showed that,^[43] compared with monotherapy, the combination of SGLT-2i and GLP-1 RA significantly reduced HbA_{1c} and body weight in T2DM patients without increasing the risk of severe hypoglycemia. Another meta-analysis of cardiovascular outcome trials found that,^[44] the additive effect of SGLT-2i and GLP-1 RA combination therapy failed to reach statistical significance in reducing MACE events, although provided greater benefits than any monotherapy. A recent subgroup analysis of a real-world study reported^[45] a significant risk reduction of 47% and 44%, respectively, in all-cause mortality for combination therapy versus SGLT-2i and GLP-1RA alone.

Medication Other Than Glucose-lowering Medications for CHD Patients with T2DM

Key message

For CHD patients with concomitant T2DM, in addition to glucose-lowering medications, attention should also be paid to other essential CHD medications, including antiplatelet therapy, antihypertensive therapy, lipid-lowering therapy, and anti-myocardial ischemia therapy.

Antiplatelet therapy

Patients with CCS require long-term administration of low-dose aspirin. If aspirin is not tolerated, clopidogrel may be considered as an alternative. For patients ACS or after PCI, dual antiplatelet therapy (aspirin + clopidogrel/ticagrelor) for at least 12 months is recommended.^[6]

Antihypertensive therapy

The lowering of target blood pressure to < 130/80 mmHg is recommended in patients with CVD and T2DM. The target can be revised to < 140/90 mmHg if the intensive treatment to achieve the ideal goal is intolerable. The preferred antihypertensive medications are angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Combination antihypertensive therapy is indicated in patients with blood pressure $\geq$ 160/100 mmHg, 20/10 mmHg above the target blood pressure, or those who fail to achieve the target with monotherapy.^[6]

Lipid-lowering therapy

Moderate-intensity statins are preferred as lipid-lowering medications in patients with CHD and T2DM.^[46] However, pay attention to monitoring blood glucose. The primary goal is low-density lipoprotein cholesterol (LDL-C) < 1.4mmol/L and LDL-C reduction of at least 50%. The secondary goal is non-high-density lipoprotein cholesterol (non-HDL-C) < 2.2 mmol/L.^[6,46]

Anti-ischaemic therapy^[6]

(1) Beta blockers: beta blockers are the first-line drugs for treating exertional angina and myocardial infarction, with a target resting heart rate of 55-60 beats/min. Since this class of medications may compromise the patient's ability to respond to hypoglycemic episodes, medication indications should be determined with caution. (2) Nitrates: They are the first-line drugs for treating various types of anginas, and their long-term use is not recommended after coronary revascularization treatment or in patients whose angina has been well controlled. (3) Calcium antagonists: They are the first-line medications for treating angina with or without coronary artery spasms. Combination of a non-dihydropyridines calcium antagonist with a beta blocker may have an impact on heart rate, which requires close attention. Dihydropyridines calcium antagonists should be used in long-acting formulations whenever possible.

PROSPECTS

Despite the breakthrough progress in glucose-lowering treatment for patients with cardiovascular diseases, there are still many challenges facing clinical practice. First, there is little evidence-based medicine for blood glucose management in ACS patients. Hence, more clinical studies are urgently needed to explore the fundamentals of management strategies, such as the timing of glucose-lowering initiation, the optimal glucose-lowering regimens, and treatment goals. Second, international studies have demonstrated the benefits of GLP-1 RA in non-diabetic obese patients with cardiovascular diseases,^[47] including a small number of Asian participants. Large-scale studies in Chinese popula-



tions are still needed to further validate these benefits. Additionally, besides GLP-1 RA and SGLT-2i, the effectiveness and safety of different classes of glucose-lowering medications and different combination regimens in patients with cardiovascular disease warrant further elaboration. Finally, there is limited evidence on glycemic management in patients with CHD and T2DM across different age groups in China, particularly in elderly patients. Further clinical trials and real-world studies are required to explore and accumulate evidence for these aforementioned issues.

Conflict of Interests

None.

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