Chinese Expert Consensus on Medication Safety in Polypharmacy in Type 2 Diabetics with Chronic Kidney Disease

Diabetes is a serious public health problem worldwide. The prevalence of chronic kidney disease （CKD） secondary to type 2 diabetes mellitus（T2DM） is growing with the increase of T2DM prevalence. There is no comprehensive guideline on medication safety in polypharmacy in patients with T2DM-related CKD. This consensus provides guidance on safety issues in polypharmacy for clinical pharmacists and Chinese patients with T2DM-related CKD，and a summary of the information on usage and dosage，and related pharmaceutical characteristics of drugs as well as medication for special populations for supporting clinical medical workers in delivering standardized medication services.

Contents

1. Methods

1.1 Consensus making steps and criteria

The development of this consensus was mainly based on the following criteria: the definition of clinical practice guidelines published by the American Institute of Medicine in 2011, the evidence generated through a systematic review, and the optimal guidance proposed after the evaluation of the pros and cons of various alternative intervention modalities; the World Health Organization Handbook for Guideline Development issued by the World Health Organization (WHO) in 2013 [1]; the Basic Methods and Procedures for Making / Revising the Clinical Diagnosis and Treatment Guidelines issued by the Chinese Medical Association in 2016 [2]. And guideline plans and formal guideline documents would be produced in accordance with the reporting entries for health care practice guidelines [3].

1.2 Clinical questions, evidence search rationale and recommendations formation

1.2.1 Clinical questions The clinical questions were collected from clinical practice and relevant literature pre-test, and first-line clinicians and clinical pharmacists experienced in the diagnosis and treatment of type 2 diabetes mellitus (T2DM) combined with chronic kidney disease (CKD) were recruited and interviewed over 2 rounds of questionnaires. Clinical questions for inclusion in

this consensus and an inductive summary of the current approach to diagnosis and treatment were finalized by online survey and discussion meetings among experts involved in the writing of this consensus.

1.2.2 Guideline search and clinical evidence search system A search of PubMed, EMBase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform and Chinese Biomedical Literature Database (CBM), and guideline publishing websites [including the UK National Institute for Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), WHO official site（ https://www. who. int/ ）and the National Health Commission of the People's Republic of China official site（ https://www. nhc. gov. cn/ ）]. The clinical evidence was retrieved from the time when the library was built to 2022-05-08, the restricted language was English or Chinese, and “type 2 diabetes mellitus, renal disease, nephropathy, nephrosis, nephroma, the kidney disease, renal dysfunction, combination, combination medication, polydrug, polypharmacy” was used as the search term. The search included patients with T2DM and CKD, of whom age > 65 years was defined as elderly patients. Search results of 2,262 Chinese and English literatures were obtained after de duplicating, and 76 safety related literatures were obtained after spermatozoa screening. After clarifying the search strategy and inclusion and exclusion criteria of literatures, two groups of consensus panel members independently conducted literature screening according to the title, aim and full texts in the step-by-step order, and then the information of included literatures was extracted according to a predesigned information extraction form. Disagreements were resolved by discussion through consultation with the opinions of a third party of evidence-based methodology experts.

1.2.3 Evaluation of levels of evidence The consensus panel evaluated the evidence and the evaluation tool was the Clinical Evidence Level Grading and Recommendation Grade from Oxford Centre for Evidence Based Medicine (OCEBM) [3]. The grade of recommendation for this consensus was graded according to the strength of recommendation from the OCEBM and GRADE, and the strength of recommendation was formed based on a comprehensive consideration including quality of evidence, trade-off of benefits, patient willingness, values, cost of intervention, and accessible resources and graded as A, B, C, and D. A total of 76 references were included, including 70 references (92.11%) with recommendation grade I and 6 references (7.89%) with recommendation grade II, as detailed in Table 1 [4-79].

1.2.4 Formation of consensus recommendations An evidence review group was responsible for the review of evidence and drafting the evidence summary. The quality of evidence was based on the OCEBM evidence grade evaluation. After members of the expert panel reached consensus on recommendations through the Delphi process, guideline consensus was ultimately adjudicated and approved by the guideline Steering Committee. Peer review mainly consisted of review of the questions, review of evidence tables and a complete recommendation scheme (conducted in the manner of a guideline group meeting), with the secretary group responsible for recording feedback on the comments and all changes.

1.2.5 Consensus registration This expert consensus was registered with the Global Practice Guidelines Registry Platform, http://www. guidelines-registry. cn/ domestic version) (Registration Number: IPGRP-2021CN261).

Table 1. The level of evidence graded by the OCEBM recommended in the Chinese Expert Consensus on Medication Safety in Polypharmacy in Type 2 Diabetics with Chronic Kidney Disease

Level of recommendation	Level of evidence	Definition	Reference	Quantity of literature (articles)	Proportion of literature (%)
A	1a	Systematic review of the homogeneeity randomized controlled trials	[4-44]	41	53.95
	1b	A single randomized controlled trial	[45-73]	29	38.16
	1c	"All or nothing" evidence	—	0	
B	2a	Systematic review of homogeneous cohort studies	—	0	
	2b	A single cohort study (including low-quality RCTs, e.g., follow-up rate <80%)	[74-79]	6	7.89
	2c	Outcome based study	—	0	
	3a	Systematic review of homogenous case-control studies	—	0	
	3b	A single case-control study	—	0	
C	4	Case series (with low-quality cohort studies and case-control studies)	—	0	
D	5	Expert	—	—	

	opinion without rigorous evaluation, or based solely on physiology and basic research		
合计	—	76	100.00

2. Profiles of T2DM combined with CKD

2.1 Epidemiology

Diabetes mellitus has become a serious global public health problem, with a global prevalence of diabetes mellitus of approximately 9.3% (463 million people) in 2019, which is expected to increase to 10.9% (700 million people) in 2045 [80]. Sustained high blood glucose levels cause systemic vascular damage affecting the heart, eyes, kidneys, and nerves and leading to various complications. Among them, CKD is a serious comorbidity of diabetes, and diabetic kidney disease (DKD) is the most common one [81]. CKD is a clinical syndrome characterized by persistent abnormalities in renal structure and / or renal function, with a worldwide incidence of CKD ranging from 8% to 16% [82-83]. More than 40% of patients with diabetes may develop CKD, and the majority of patients have early CKD (CKD stages 1 to 2); some patients will progress to end-stage renal disease requiring dialysis and / or transplantation [80]. According to age stratified analysis, the prevalence of CKD is found to be as high as 58.7% in T2DM patients ≥ 65 years old, with a more advanced CKD stage [84].

2.2 Current status of domestic and foreign guidelines or consensus of polypharmacy in T2DM combined with CKD

There has not been a more comprehensive clinical polypharmacy safety guideline for T2DM patients with CKD at home and abroad, and some of the guidelines that have been issued only consider one comorbidity, with limited specific recommendations on how to manage patients with coexistent multiple diseases. There are 15 judgment criteria published nationally and internationally regarding potentially inappropriate medication (PIM) for older people, but only the Beers provides a potentially inappropriate medication for older people [84] (AGSBeers Criteria ®), in which a small number of adverse drug-drug interactions (ADI) content are involved. Therefore, a consensus on the safety of clinical polypharmacy in patients with T2DM and CKD needs to be made and promulgated, to avoid or reduce the damage caused by ADI when polypharmacy is used and improve the level of safe medication.

2.3 Targets and strategies of treatment for diabetes and CKD

Patients with diabetes and CKD should be treated with a comprehensive treatment strategy and aimed at reducing the risk of cardiovascular disease and the progression of renal disease as the

main treatment goals, with strict control of cardiovascular risk factors including hypertension, hyperglycemia, abnormal serum lipids, smoking, obesity, etc. , effective remission of proteinuria, avoidance of nephrotoxic drugs, and adjustment of drug doses to delay CKD progression [85]. Glomerular filtration rate (GFR) is one of the important indexes for evaluating renal function, and the staging of renal function in CKD is performed based on estimating the glomerular filtration rate (eGFR). It was found that declines in urinary albumin / creatinine ratio (UACR) and EGFR were both independent risk factors for end-stage renal disease and cardiovascular mortality, and the two were synergistic [86]. Staging of renal function was referred to the Staging Criteria for Clinical Practice Guidelines 2012 edition, produced by the Kidney Disease Improving Global Organization (KDIGO), as detailed in Table 2 [87].

Table2. Characteristics of stages of CKD in type 2 diabetes

CKD classification based on cause (C), eGFR (G) and albuminuria (A)				UACR Categories (Description and Range)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30mg/g <3mg/mmol	30-300mg/g 3-30mg/mmol	>300mg/g >30mg/mmol
eGFR Categories (Description and Range)	G1	Normal or high	≥90 ml•min^{-1}•（1.73 m^2）$^{-1}$	1，if CKD is diagnosed	treatment，1	treatment，2
	G2	Mildly decreased	60-89 ml •min^{-1} •（1.73 m^2）$^{-1}$	1，if CKD is diagnosed	treatment，1	treatment，2
	G3a	Mildly to moderately decreased	45-59 ml •min^{-1} •（1.73 m^2）$^{-1}$	treatment，1	treatment，2	referral，3
	G3b	Moderately to severely decreased	30-44 ml•min^{-1}•（1.73 m^2）$^{-1}$	treatment，2	referral，3	referral，3
	G4	Severely decreased	15-29 ml•min^{-1}•（1.73 m^2）$^{-1}$	referral，3	referral，3	referral，4
	G5	Kidney failure	<15 ml•min^{-1}•（1.73 m^2）$^{-1}$	referral，4	referral，4	referral，4

Note: CKD= chronic kidney disease, eGFR= estimated glomerular filtration rate, UACR= urinary albumin/creatinine ratio; The numbers in the table are the guide of follow-up frequency (number of times per year); The background color represents the progression risk of CKD: green is low risk, yellow is medium risk, orange is high risk, and red is extremely high risk. Green can reflect CKD with normal eGFR an UACR level only in the presence of other kidney damage markers, such as polycystic kidney disease or kidney biopsy abnormalities in imageology, with follow-up measurements once annually; It requires caution, and measurements at least once per year in yellow; It requires measurements twice per year in orange; It requires measurements three times per year in red; It requires measurements four times per year in dark red.

2.3.1 Hypoglycemia therapy Glycemic control retards progression of CKD, and for patients with prevention of complications as the primary goal, recommended target values for glycated hemoglobin (HbA1c) control can be appropriately relaxed to: HbA1c < 6.5% or HbA1c < 7.0%; for patients with multiple comorbidities or at high risk of hypoglycemia, HbA1c can be at the higher recommended target values, such as: HbA1c < 7.5% or HbA1c < 8.0% [80]. Glucose lowering on target alleviates the aggravation or progression of proteinuria and reduces the proportion of patients who develop CKD stage 3, and massive proteinuria can be reversed to microalbuminuria or normoproteinuria in patients [88-89]. Hypoglycemic agents mainly include insulin, biguanides, sulfonylureas, glinides, αglycosidase inhibitors, thiazolidinediones (TZD) class, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium glucose cotransporter 2 inhibitors (SGLT2I) and glucagon like peptide 1 receptor agonists (GLP-1RA). Patients with type 1 diabetes mellitus (T1DM) require insulin therapy, whereas for those with T2DM, there are many treatment options. Because clearance of insulin and other drugs is reduced in patients with CKD, such populations are more prone to hypoglycemia, and hypoglycemic drug classes and doses may need to be adjusted with the level of renal function.

2.3.2 Antihypertensive treatment Controlling hypertension in patients with CKD may not only slow the progression of kidney injury but also reduce the risk of cardiovascular disease. Antihypertensive treatment in diabetes patients with CKD, the blood pressure lowering targets are systolic blood pressure (SBP) ≤ 140 mm Hg (1 mm Hg = 0.133 kPa) and diastolic blood pressure (DBP) ≤ 90 mm Hg at urinary albumin excretion rate (AER) < 30 mg / 24 h; at AER > 30 mg / 24 h, the blood pressure lowering targets are SBP ≤ 130 mm Hg and DBP ≤ 80 mm Hg [90]. Hypertensive patients with CKD without proteinuria may be treated with 1 or 2 of the following drugs: angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB), calcium channel blockers (CCB), thiazide diuretics, and if unable to reach the control glycemic level, continue the joint use of α- Receptor blockers, β- Receptor blockers, or mineralocorticoid receptor antagonists (MRA), etc; Combination of ACEI or ARB with or without CCB is preferred in hypertensive patients with CKD with proteinuria, and for those whose glycemic level cannot be controlled to the desired level, α- Receptor blockers, β- Receptor blockers, thiazide diuretics, MRA, etc may be used jointly; Patients with severe hypertension may choose a combination of 2 or more antihypertensive drugs [91].

2.3.3 Lipid regulation therapy There is an association between dyslipidemia and the risk of CKD patients with diabetes, and lipid regulation by statins can reduce cardiovascular disease events and mortality [92]. Studies have shown that statins are safe and effective in regulating lipids and preventing cardiovascular disease (CVD) events at the end of CKD and after transplantation [93].

2.3.4 Urate lowering therapy Hyperuricemia is a risk factor for the development of CKD and is associated with all-cause mortality in CKD, and lowering serum uric acid levels ameliorates kidney injury [94]. Allopurinol readily accumulates in the body in renal insufficiency, increases the risk of toxicity, and is contraindicated in patients with CKD stage 5; No dose adjustment is necessary for febuxostat in patients with mild to moderate renal dysfunction or even end-stage CKD, and febuxostat can slow the eGFR decline in asymptomatic hyperuricemia patients with CKD stage 3 and CKD stage 4 [95]. Benzbromarone is not recommended in patients with CKD stage 4 and above and is contraindicated in patients with nephrolithiasis. To avoid toxic drug accumulation caused by impaired renal function mediated improper drug metabolism and

excretion, urate lowering drugs should be rationally selected according to the stage of renal function [96].

3. Risks and recommendations for monitoring of co-medications in patients with diabetes and CKD

3.1 Risks and monitoring recommendations of hypoglycemic agents in patients with diabetes and CKD

Clinical findings show that glucose lowering up to goal reduces the incidence of the primary renal endpoint by 20% in patients with early-stage of diabetes or CKD, and can reverse pre-existing macroalbuminuria to microalbuminuria or normoproteinuria in patients [97]. Patients with T2DM and CKD are suitable for individualized selection of oral hypoglycemic agents according to renal function status and dose adjustment according to the degree of renal impairment, as detailed in Table 3 [98-109].

Table 3. The risks and monitoring recommendations of hypoglycemic agents in patients with diabetes and CKD

Drug classification	**Recommendations related to kidney benefits**	**Representative drugs**	**glomerular filtration rate eGFR [ml · min-1 · (1.73m2)$^{-1}$]**					**risks and adverse reactions**	**Precautions and monitoring suggestions**
			≥60	45~59	30~44	15~29	＜15		
biguanides	For T2DKD patients, metformin is recommended as the first choice for blood glucose control when there is no contraindication (2020)	Metformin	√	dose reduction	Use with caution /×[22]	×	×	Metformin may accumulate and cause lactic acidosis in case of renal insufficiency	1、Monitoring eGFR, and timely adjust the dosage of metformin according to eGFR。2、Metformin should be stopped in severe infection, acute heart failure, respiratory failure, AKI and other stress states [99]
SGLT2i	SGLT2i has an	Dapagliflozin	√	√	√	Use with	×	Adverse reactions related	1、Patients with high risk of ketoacidosis should avoid using such drugs as much as

	independent hypoglycemic renal protective effect, significantly reducing renal risk[100]					caution[a]		to genitourinary system infection and blood volume reduction. Invokana increases the risk of amputation and fracture of lower limbs[14]	possible [101] 2、Pay attention to the increased risk of urinary and reproductive system infection [45] 3、Studies on the efficacy and safety of SGLT2i in renal transplant patients are lacking, SGLT2i in not recommended for these cases because of the possible increased risk of infection
		Empagliflozin	√	√	×[102]	×	×		
		Invokana	√	√	√	Use with caution[a]	×		
glucagon like peptide 1 receptor agonists (GLP-1RA)	GLP-1 receptor agonist can significantly reduce urinary albumin[103]	Exenatide	√	√	√	×	×	Gastrointestinal reaction is a common adverse reaction of GLP-1 receptor agonist	1、It should start from a small dosage and gradually increase the dosage to reduce gastrointestinal reaction 2、Not recommended for ESRD patients 3、Patients with medullary thyroid carcinoma, multiple endocrine neoplasia type 2 and history of acute pancreatitis should not use GLP receptor agonist.
		Risenatide	√	√	√	×	×		
		Liraglutide	√	√	√	√	×		
		Dulaglutide	√	√	√	√	×		
		Smeaglutide	√	√	√	√	×		
DPP-4 inhibitors	DPP-4 inhibitor can significantly reduce urinary albumin[104]	Linagliptin	√	√	√	√	√	Gastrointestinal adverse reactions, infections (mainly include nasopharyngitis, urinary tract infection, upper respiratory tract infection), allergies and elevated liver enzymes	1、Monitor the liver enzymes of patients, and do not adjust the dose for mild liver damage 2、Timely adjust the dose according to the renal function level. The dose of saxagliptin should be halved when 30<eGFR<45, and reduced to 1/4 of the conventional dose when eGFR<30 3、The dose of saxagliptin and vildagliptin should be halced when eGFR<45 4、The dose of alogliptin should be halved when 30<eGFR<60, and reduced to 1/4 of the conventional dose when eGFR<30[105])
		Sitagliptin	√	√	dose reduction	dose reduction	dose reduction		
		Saxagliptin	√	√	dose reduction	dose reduction	dose reduction		
		Alogliptin	√	dose reduction	dose reduction	dose reduction	dose reduction		
		vildagliptin	√	√	dose reduction	dose reduction	dose reduction		
insulin	There is no renal benefit, but insulin can be the first choice							Because the degradation and excretion of insulin are significantly reduced during renal insufficiency and	1、In the early stage of DKD, the insulin demand may increase due to the increase of insulin resistance [33]. It is recommended that the dosage of insulin be increased as appropriate when it is used in the early stage of DKD (Rave et al., 2001) 2、In patients with middle and late stage

	of hypoglycemic drugs for DKD patients during pregnancy.								ESRD, it may lead to accumulation in the body, with the risk of hypoglycemia and fluid retention	DKD, especially those with CKD G3b and below, the insulin demand will decrease due to the reduction of insulin clearance by the kidney, and the risk of hypoglycemia will also increase. Care should be taken when insulin and insulin secretagogues are used together 3、Short acting or quick acting dosage forms are preferred, blood glucose is closely monitored, and insulin dosage is adjusted in time 4、Elderly patients should give priority to basic insulin to avoid hypoglycemia。 5、Patients with DM - CKD need to be reassessed according to the eGFR level, and individualized dose adjustment
insulin secretagogues	No kidney benefit recommendation	sulfonylureas	Glibenclamide[b]	√	×	×	×	×	Risk of hypoglycemia	Sulfonylureas: Attention should be paid to strengthening blood glucose monitoring, and try to use preparations with short half-life[45]
			Glimepiride[b]	√	dose reduction	×	×	×		
			Gliclazide[b]	√	dose reduction	dose reduction	×	×		
			Glipizide[b]	√	dose reduction	dose reduction	×	×		
			Gliquidone	√	√	√	Use with caution	Use with caution		
		Glinides	Nateglinide[c]	√	√	√	√	√		Nateglinides: 1. Attention should be paid to strengthening blood glucose monitoring 2 The peak drug concentration of nateglinide in hemodialysis patients decreases, and the dosage may need to be adjusted[88]
			Repaglinide[c]	√	√	√	√	dose reducti		

							on		
α glycosidase inhibitors	No kidney benefit recommendation	Acarbose	√	√	Use with caution	Use with caution[d]	×	Gastrointestinal reactions, risk of hypoglycemia when combined with other medications	Acarbose and Miglitol are forbidden when eGFR<25 ml • min-1 • (1.73 m2) - 1, Voglibose should be used with caution when eGFR<30 ml • min-1 • (1.73 m2) - 1
		Miglitol	√	√	Use with caution[d]	Use with caution[d]	×		
		Voglibose	√	√	Use with caution	×(Singhsakul et al., 2019)	×		
Thiazolidinediones	No kidney benefit recommendation	Rosiglitazone	√	√	√	√	√	Risk of water and sodium retention, causing an increase in plasma volume	It is forbidden for patients with cardiac function grade II or above of New York Heart Association[109]
		Pioglitazone	√	√	√	√	√		

Notes: √ represents that it can be used at normal doses, ×indicating disabled, ×indicating no relevant content; eGFR= estimated glomerular filtration rate, T2DM = type 2 diabetes, SGLT2i= sodium-glucose cotransporter 2 inhibitor, GLP-1= glucagon-like peptide 1, DPP-4= dipeptidyl peptidase 4, TZD= thiazolidinedione, ESRD= end-stage renal disease, and DKD= diabetic nephropathy; [a] indicates that dagligrin is not recommended to improve glycemic control in adult T2DM patients with eGFR <45 ml · min-1 · (1.73 m2) -1, but can be continued to reduce chronic kidney disease adults with decreased eGFR and reduce the risk of end-stage kidney disease, except for dialysis patients; Cagligrin is not recommended in improving glycemic control in adult T2DM patients with eGFR <30 ml • min-m. 1 (1.73 m2) -1, but can be continued to reduce sustained eGFR decline and reduce the risk of end-stage renal disease in adults with chronic renal disease risk, except in dialysis patients; [b] represents sulfonylureas; [c] represents glenae; [d] represents that acarbose and maglitol are disabled at eGFR <25 ml · min-1 · (1.73 m2) -1

3.2 Risks and monitoring of combination hypoglycemic agents in patients with diabetes and CKD

It is recommended that when combining multiple hypoglycemic agents simultaneously, the risk of hypoglycemia may be increased, and the main agents include insulin, sulfonylurea, and nonsulfonylurea insulin secretagogues, etc. The risks and monitoring recommendations for commonly used combinations of glucose lowering drugs in the clinic are detailed in Table 4 [110-120].

Table 4 Risks and monitoring suggestions of some commonly used hypoglycemic drugs in diabetic CKD patients

Combination of hypoglycemic drugs	Risk of Combination	Medication precautions and recommendations
Metformin + SGLT2i	Increased risk of reproductive system infections and fractures, with reports of AKI [110]	1. First-line combination of drugs in T2DM with CKD 2. Renal function status needs to be taken into account when choosing the type and dose of SGLT2i [111] 3. Invokana may increase the risk of lower limb amputation [112]
Metformin + GLP-1 receptor agonist	Increased gastrointestinal adverse effects such as nausea, vomiting, and diarrhea [110]	1. To reduce the occurrence of gastrointestinal adverse reactions, GLP-1 receptor agonists should be started at small doses and gradually increased 2. The adverse effects are gradually reduced with longer duration of use [105, 111].
Metformin + sulfonylureas/ glinides	Increased hypoglycemia, body mass, and possible cardiovascular risk [110, 113]	1. Require regular monitoring of body mass, blood glucose and renal function 2. Patients with mild renal insufficiency should choose gliquidone if using sulfonylureas [114]
Metformin + α glucosidase inhibitors	Increased gastrointestinal adverse effects such as nausea and abdominal discomfort [115]	1. α- glucosidase inhibitors can be started with a small dose, and gradually increased to avoid adverse effects 2. If hypoglycemia occurs, glucose or honey can be given [111]
Metformin + TZD	Increased risk of congestive heart failure and fracture [110]	Should be used with caution in elderly T2DM patients with ASCVD, cardiac insufficiency and osteoporosis [114]
Insulin + sulfonylureas/ glinides	Increased risk of hypoglycemia [116]	Regular blood glucose monitoring is needed to avoid the risk of hypoglycemia.
Insulin + TZD	Increased body mass, which can lead to water and sodium retention and increased risk of heart failure and fractures [117-118]	1. Monitor body mass and control diet 2. The combination in the elderly or in those with cardiac insufficiency should be closely monitored, to avoid water and sodium retention leading to congestive heart failure; The combination in patients with osteoporosis should with caution [105]
Insulin+ SGLT2i	Increased risk of urogenital infections [119-120]. Risk for diabetic ketoacidosis may be increased due to excessive reduction of insulin dosages [116]	When who hace already taken basal insulin, the amount of insulin may be appropriately reduced to the risk of hypoglycemia, but the dose should not be reduced too quickly.

Notes: AKI= acute kidney injury, ASCVD= atherosclerotic cardiovascular disease

3.3 Risks and monitoring recommendations of combinations of hypoglycemia drugs and antihypertensive and lipid regulating drugs in patients with diabetes mellitus and CKD

It is inevitable and very common to combine glucose lowering drugs and other drugs in patients with diabetes mellitus and CKD, and polypharmacy may increase the risk of ADI, which in part will lead to serious consequences. In view of this, the risk of polypharmacy in such patients is of concern, and management measures are proposed to avoid or reduce the damage from drug-drug interactions when polypharmacy is combined.

There is an association among blood pressure, dyslipidemia, and cardiovascular disease events and mortality in diabetic patients with CKD [94]. For hypertensive patients with CKD with proteinuria, ACEI / ARB may be used as the first choice of antihypertensive agent, although the risk of co-administration with glucose lowering drugs should be kept in mind; For example, gemfibrozil can be used for lipid regulating therapy in patients with diabetes and CKD, and has irreversible inhibitory effects on CYP2C8 and is prone to drug interactions with other drugs, as detailed in Table 5 [121-124].

Table 5 Risks and monitoring suggestions of the use of hypoglycemic drugs with antihypertensive and lipid-lowering drugs

hypoglycemic drugs	Combined drugs	Risk of interaction and adverse reaction	Medication recommendations
Sulfonylureas: glibenclamide, etc	Antihypertensive drugs: ACEI [121] (captopril, enalapril, etc.)	Increased insulin sensitivity, leading to severe hypoglycemia	Patients should be informed about the risk of hypoglycemia in order to be prepared for the event
Glinides: Repaglinides	Antihypertensive drugs: ACEI [121] (captopril, enalapril, etc.)	Increased risk of hypoglycemia when combined	The dose of repalinides should be reduced and the frequency of blood glucose monitoring should be increased when combined
TZD: rosiglitazone, pioglitazone	Lipid-lowering drugs: Beite (gemfibrozil) [122]	Gemfibrozil has a strong CYP2C8 inhibition effect, rosiglitazone and pioglitazone are mainly metabolized by CYP2C8; When used with gemfibrozil, the AUC of rosiglitazone and pioglitazone increases by 2.3 times and 3.4 times respectively	When starting or stopping the combination, changes in diabetes treatment may be needed based on clinical response.
Glinides: repaglinide	Lipid-lowering drugs: Beite (gemfibrozil) [122]	Regglinide is mainly metabolized by CYP2C8 and CYP3A4, AUC of Regglinide increases by 8 times when combined with gemfibrozil, and its hypoglycemic effect is significantly enhanced and prolonged [123]	The combination use was prohibited [124]

Note: ACEI= angiotensin-converting enzyme inhibitor, AUC= the area under the subject operating characteristic curve

3.4 Risk and monitoring recommendations of hypoglycemic and other drug combinations in patients with diabetes and CKD

In addition to strict control of cardiovascular and renal disease risk factors such as blood glucose, blood pressure, and lipids, patients with diabetes and CKD might complicate other chronic diseases, including heart failure, thromboembolism, infection, etc. , and need to be alert to the risk of using other drugs and polypharmacy in patients with CKD, as detailed in Tables 6-9 [125-130].

Table 6. The risks and monitoring recommendations of hypoglycemic drugs combined with other related drugs

Drug(s)	Combined drug(s)	Drug interaction mechanism	Suggestions
Metformin	iodinated contrast agent	Patients with contrast agents often have a transient GFR reduction. Metformin is mainly excreted by glomerular filtration, and the use of contrast agent can easily lead to the accumulation of metformin in the body	For patients with eGFR>60, Metformin can be temporarily stopped on the day of receiving iodinated contrast agent examination. For patients with 60>eGFR>45, stop using metformin can be stopped 48 hours before receiving iodinated containing contrast agent examination [125].
α - Glycosidase inhibitors: Acarbose	Digoxin	Diarrhea after taking acarbose can reduce the absorption, AUC and blood drug peak concentration of digoxin [52].	The dose of digoxin needs to be adjusted in combination
	Colestyramine	Colestyramine can adsorb acarbose and reduce its effect.	The combination should be avoided
Sulfonylureas	fluconazole	Fluconazole can inhibit CYP2C9 activity, slow down the metabolism of sulfonylureas, and increase the risk of hypoglycemia. [127]	Monitor blood glucose and adjust the dosage of sulfonylureas.
	Rifampicin	Rifampicin induces CYP2C9 activity, accelerates the metabolism of sulfonylureas, and leads to the increase of blood glucose.	Monitor blood glucose and adjust the dosage of sulfonylureas.
Glinides: Repaglinide	Clopidogrel	The metabolite of Clopidogrel can significantly inhibit CYP2C8, the metabolism enzyme of repaglinide, and increase its blood concentration. [122]	Avoid using together.
	CYP3A4 inhibitors: ketoconazole, itraconazole	The blood concentration of Repaglinide can be increased in combination	Reduce the dose of Repaglinide or increase the frequency of blood glucose monitoring when combined.
Dipeptidyl peptidase IV	CYP3A4/5 strong	The major metabolic enzyme CYP3A4/5	Reduce the dosage of sargliptin to

(DPP-4) inhibitor: Shagliptin	inhibitors: Ketoconazole, azanavir, etc.	of saxagliptin will be inhibited, and the plasma concentration of Shagliptin will be increased [128].	2.5mg per day [129].
	CYP3A4/5 strong inducer: Rifampicin etc.	The major metabolicenzyme CYP3A4/5 is saxagliptin will be induced	The two agents should be used at an interval of 24 hours. It is not recommended to adjust the dosage of Shagliptin [130].
TZDs: Rosiglitazone Pioglitazone	CYP2C8 inducer: Rifampicin	Rosiglitazone and pioglitazone are mainly metabolized by CYP2C8, and their AUC may be reduced when combined with CYP2C8 inducers such as rifampicin [130].	When starting or stopping the combination, it may be necessary to change the diabetes treatment according to the clinical response.

Table 7. Recommended dose of statins in T2DM patients with CKD

Drug(s)	Recommended dosage (mg/d)	Eliminate	Dose adjustment for mild to moderate renal insufficiency	Dose adjustment for severe renal insufficiency (mg/d)
Simvastatin	5-40	Liver	No dose adjustment required	Use with caution, intial dose: 5 mg/d
Pravastatin	10-40	Liver/ Kidney	No dose adjustment required	Initial dose: 10, maximum dose: 10-20 mg/d
Lovastatin	20-60	Liver	No dose adjustment required	Maximum dose: 20 mg/d
Fluvastatin	20-80	Liver	No dose adjustment required	Forbidden
Pitavastatin	1-4	Liver/ Kidney	No dose adjustment required	Initial dose: 1 mg/d, maximum dose: 2 mg/d
Atorvastatin	10-80	Liver	No dose adjustment required	No dose adjustment required
Rosuvastatin	5-40	Liver/ Kidney	No dose adjustment required	Initial dose: 5 mg/d, maximum dose: 10 mg/d

Table 8. Anticoagulant use in elderly T2DM patients with impaired renal function

Drug(s)	CrCL ≥ 60ml/min	CrCL 45~ 59 ml/min	CrCL 30 ~ 44 ml/min	CrCL 15 ~ 29 ml/min	CrCL ＜15 ml/min
Low molecular heparin	Usual dose	Usual dose	Usual dose	Usual dose	50% initial dose
Dabigatran	Usual dose	Dose adjustment	Dose adjustment	Forbidden	Forbidden
Apixaban	Usual dose	Usual dose	Usual dose	Dose adjustment	Forbidden
Edoxaban	Usual dose	＜50%, dose adjustment	Dose adjustment	Dose adjustment	Forbidden
Rivaroxaban	Usual dose	＜50%, dose adjustment	Dose adjustment	Dose adjustment	Forbidden
Heparin	Usual dose	Usual dose	Usual dose	Usual dose	Usual dose

Warfarin	Usual dose	Usual dose	Usual dose	Usual dose	Usual dose

Note: CrCL=, endophytic creatinine clearance rate

Table 9. Dose adjustment of nonsteroidal anti-inflammatory drugs in elderly T2DM patients with impaired renal function

Drug(s)	CrCL ⩾ 60ml/min	CrCL 10 ~ 50 ml/min	CrCL ＜10 ml/min
Paracetamol	Adjust the interval of medication, q4h	q6h	q8h
Ibuprofen	Initial dose	Initial dose	Avoid
Diclofenac	50% ~100%	25%～50%	＜25%
Meloxicam	Initial dose	50%	Avoid
Celecoxib	Initial dose	Avoid	Avoid
Parecoxib	Initial dose	Avoid	Avoid
Flurbiprofen axetil	Dose adjustment	Forbidden	Forbidden

4. Characteristics of drug treatment and multi-factorial risk control in elderly patients

4.1 Characteristics of drug treatment in elderly patients with diabetes mellitus and CKD

Based on the characteristics of elderly physiological conditions and multiple drug use in patients with diabetes mellitus and CKD, elderly patients with diabetes mellitus and CKD also have the following drug use risks.

- In diabetic elderly patients with CKD, the significant reduction of serum albumin will change the volume of distribution of drugs and affect their clearance, and polypharmacy is more likely to cause adverse effects [131].
- Unlike other populations, glycemic control goals in older adults with diabetes mellitus needs more care to avoid hypoglycemia. According to the Expert Consensus on Glycated Hemoglobin (HbA1c) Control Goals and Attainment Strategies for Chinese Adults with Type 2 Diabetes [5] and the Chinese Guideline for the Management and Treatment of Diabetes in the Elderly (2021 Edition) [132], benefits may be achieved when HbA1c targets are more liberal for older patients, such as the appropriate HbA1c target values of < 7.5% in elderly diabetic patients with CKD stages 1 to 3a, < 8.0% in those with stage 3b and above, and < 8.5% in elderly diabetic dialysis patients without other end-stage chronic diseases [133]. Special vigilance for hypoglycemia is warranted in patients using drugs with a higher risk of hypoglycemia (e.g., insulin, sulfonylureas, glinides, etc.).
- Elderly patients with diabetes and CKD are also usually combined with cardiovascular disease as well as cognitive dysfunction and so on, so the prognosis of elderly patients with

diabetes and CKD is worse than that of patients with T2DM or CKD alone.

- Elderly patients with diabetes and CKD should be aware of the risk of acute kidney injury (AKI). Many drugs have the risk of renal injury, such as certain antimicrobials, nonsteroidal anti-inflammatory drugs, certain Chinese herbs, etc. Acute kidney injury can also be induced by comorbid cardiovascular disease, sepsis, and acute hyperglycemia and ketoacidosis. When these drugs are used, the dosage and course of medication should be strictly mastered, while renal function monitoring should be enhanced.

4.2 Elderly patients with diabetes mellitus and CKD drug treatment multi-factorial risk control

Elderly patients with diabetes mellitus and CKD who have a multi-factorial risk during the use of concomitant medication with hypoglycemic drugs should carefully review, collate, evaluate, and list the control planning.

- Conduct disease progression risk assessment and management, and develop multiple medication risk control plans.
- Evaluate the medication regimen plausibility and safety risks according to the physiological characteristics, drug metabolism characteristics, and medication adherence of elderly patients [134-135].
- Develop individualized treatment goals to stratify patient medication use. Instruct patients to take their medication correctly, and effectively establish communication and feedback system.

4.3 Common drug risk management for elderly patients with diabetes mellitus and CKD

- Elderly patients having a reduced sensitivity in response to β- receptor blockers and an adverse effect on glucose metabolism by the intrinsic sympathomimetic activity of the drug class itself suggest the use of selective β 1-blockers or β- receptor blockers with the function of α 1-receptor blockade. At the same time, regular assessment and management of blood pressure and heart rate were performed. To avoid masking hypoglycemic symptoms, β-receptor blockers should be used in caution in patients with a history of recurrent hypoglycemic episodes [136].
- In patients with concomitant ischemic heart disease, anticoagulant and antiplatelet aggregation therapy is recommended and novel glucose lowering drugs may be selected as appropriate.
- When patients with combined CKD stage 3 have heart failure, ACEI, ARB and β- receptor blockers might be used appropriately; if symptoms do not resolve, add an MRA. When patients have depressed ejection fraction, sacubitril may be used instead of ACEI / ARB, or use a novel MRA such as finerenone et al [137].
- Diabetic patients with CKD, when using ACEI / ARB class rennin-angiotensin system blockers, can continue to use when there is a small increase in serum creatinine but the increase is < 30% from baseline and in the context of euvolemic condition [138].
- In elderly diabetic patients with comorbid hypertension, complicated with kidney disease or

impaired renal function, lowering BP should avoid the combination of nonsteroidal anti-inflammatory drugs, diuretics in antihypertensive drugs, ACEIs, and ARBs to reduce the occurrence of adverse events such as hyperkalemia and AKI [139].

- Routine supplementation of vitamin D or ω- 3 fatty acids in T2DM patients with normal renal function or with mild renal impairment do not reduce CKD incidence or delay eGFR decline, and therefore is not recommended [140].
- In patients with CKD presenting with anemia and hemoglobin (Hb) < 100 g / L, treatment with erythropoietin or combination of iron is recommended.
- Prophylactic hydration may be administered when CKD grade G3b patients require contrast media for imaging diagnosis, from 3 to 4 h before contrast media to 4- 6 h after: 0. 9% sodium chloride solution 1 ml / kg intravenously every hour. Keep under close observation during application and avoid heart failure [141].

5. Clinical frequently asked questions and recommendations for special concomitant medications in patients with diabetes and CKD

5.1 In patients with diabetes and CKD, what is the effect of aspirin use on the risk of bleeding?

【Recommendations】

- Caution is recommended for the use of aspirin in patients with diabetes mellitus complicated by CKD [6-8, 46-47, 74]. (1a, A)
- Whether the benefits outweigh the risks of bleeding with aspirin for the primary prevention of cardiovascular disease in diabetic patients with CKD remains inconclusive [10-12]. (1a, A)
- Routine use of aspirin in non-elderly diabetic patients for primary prevention of cardiovascular events is not recommended [12-13]. (1a, A)
- For the prevention of cardiovascular disease in elderly patients with diabetes, it is recommended to start with low-dose aspirin and make an individualized assessment [14-16, 48, 132]. (1a, A)

Evidence: A Meta-analysis suggested that prophylactic use of low-dose aspirin in CKD patients may prevent the occurrence of cardiovascular events in CKD to some extent, but increase the risk of bleeding more than 1-fold in CKD patients, and similar results have been demonstrated in multiple RCT studies [6-8, 46-47, 74]. Therefore, low-dose aspirin should be used with caution in CKD patients at higher bleeding risk. A 2011 meta-review showed that aspirin reduces the risk of major adverse cardiovascular events (MACE) in diabetic patients without cardiovascular disease, while there was also a trend towards higher rates of bleeding and gastrointestinal complications [10]. Whereas two Meta reviews in 2019 [11] and 2022 [9] seemed to draw opposite conclusions in the evaluation of aspirin use in CKD patients. After evaluating the risks and benefits of aspirin use for primary prevention of CVD in patients with CKD, it was found that patients had an approximately 50% increased risk of CVD major bleeding events and more than a 1-fold increase in small bleeding events, without clear evidence of benefit. Recommendations for primary prevention with aspirin are age ≥ 50 years combined with at least 1 major risk factor and no high risk of bleeding,

and aspirin is not recommended for patients at low cardiovascular risk [12-13]. The results of a Meta-analysis [14] in 2019 showed a 9% reduction in the risk of MACE but an increase in the risk of major bleeding by 24% in the subgroup aged over 60 years, thus suggesting the use of low-dose aspirin as the primary prevention strategy for CVD in patients with diabetes. Multiple RCT studies have also suggested that the use of aspirin as primary prevention for older adults (with or without diabetes mellitus) aged > 70 years carries a greater risk than benefit, and whether aspirin should be used as primary prevention in older patients needs to be evaluated clinically specifically [15-16, 48,132].

5.2 In T2DM patients with CKD, metformin combined with SGLT2i, does it affect renal function?

【Recommendations】

- There is a renal benefit of SGLT2i combination with metformin [45, 49-50, 75]. (1b, B)
- In T2DM patients with mild to moderate CKD（eGFR 30~60ml·min^{-1}·（1.73 m^2）$^{-1}$）, dual therapy with metformin and SGLT2i is recommended to reduce the incidence of adverse renal outcomes [49-50]. (1b, B)
- In T2DM patients with eGFR 30-90 ml · min^{-1} · (1.73m^2) $^{-1}$ and concomitant albuminuria, dual treatment with metformin and SGLT2i is recommended to attenuate the loss of renal function, prevent end-stage renal disease, and reduce the mortality of renal disease [45]. （1b，B）

Note: As indicated in the US Food and Drug Administration (FDA) instructions, SGLT2i is not recommended for adult T2DM patients with eGFR < 30 ml · min^{-1} · (1.73 m^2) $^{-1}$ [where dapagliflozin eGFR < 45 ml · min^{-1} · (1.73 m^2) $^{-1}$] to improve glycemic control, but may continue to be prescribed to lower eGFR and reduce the risk of end-stage renal disease, with the exception of dialysis patients. The State Food and Drug Administration of the People's Republic of China (SFDA) stipulates that metformin is contraindicated in patients with eGFR < 45 ml · min^{-1} · (1.73 m^2) $^{-1}$, whereas the FDA specifies that it is contraindicated in patients with EGFR < 30 ml · min^{-1} · (1.73 m^2) $^{-1}$.

Evidence: Multiple Meta-analyses have indicated that additional treatment with SGLT2i plus metformin, compared with metformin monotherapy, significantly and consistently reduced HbA1c in T2DM patients [17-24], without increasing the risk of serious adverse events [25]. Mentioned in a 2021 Meta-analysis that SGLT2i significantly reduced the risk of renal events [26], similar conclusions were also presented in several large cohort and RCT studies [4, 51-52, 76]. In a 2021 retrospective study, it was mentioned that the decline in eGFR levels after SGLT2i use could be abolished by the combination of metformin, so there was a renal benefit with the two drug combination [75]. A 2018 post hoc analysis of a phase 2 / 3 study in patients with T2DM with renal impairment suggested that dapagliflozin could be used to treat patients with CKD stage 3a [eGFR ≥ 45 ml · min^{-1} · (1.73 m^2) $^{-1}$ and < 60 ml·min^{-1}· (1.73 m^2) $^{-1}$] [53]. In addition, more than 50% of patients in the EMPA-REG study [45], the DECLARE-TIMI study [49], the CREDENCE study [50], and the SCORED study [54] were treated with metformin in combination with SGLT2i, and each study demonstrated significant benefit in attenuating loss of renal function, preventing end-stage renal disease, and reducing renal mortality, as well as reducing the SGLT2i applicable range to

eGFR ≥ 30 ml·min^{-1}·(1.73 m^2)$^{-1}$.

5.3 In patients with T2DM and CKD, are SGLT2i combinations associated with an increased risk of urinary and genital infections compared with metformin monotherapy when using metformin-based regimens?

【Recommendations】

- When using SGLT2i alone or in combination with metformin in patients with T2DM, both of them should be paid more attention to the risk of germline infection and should be selected carefully [27-28, 77] (1a). The significantly increased risk of germline infections when empagliflozin is administered to female patients suggests careful selection and use [77] and a switch to other agents may be considered if necessary. (1a, A)
- Patients with T2DM and CKD who choose DGLT2i need to be concerned about the high risk of germline infection. (B)
- The risk of urethral infection with SGLT2i is a matter of debate [21, 25] and there are trade-offs when they are chosen. （B）

Evidence: There is currently debate as to whether the combination of SGLT2i with metformin increases the risk of urinary and genital infections. Multiple Meta-analysis studies have suggested that SGLT2i increase the risk of urinary tract infections and genital infections compared with metformin alone [17-18, 21]; Similar conclusions were also presented in a retrospective cohort study in 2022, where SGLT2i used as adjunct to metformin were associated with a higher risk of reproductive and urinary tract infections compared to TZD used in combination with DPP-4 inhibitors, SU class glucose lowering agents and metformin [77]. However, several Meta-analyses have also suggested that the incidence of urinary tract infections associated with SGLT2i combinations with metformin was similar to that associated with metformin alone, although the incidence of genital infections was slightly higher in the combination group [19-20, 22]. A national Meta-analysis including 9 RCT studies with 3422 patients showed that compared with metformin alone, the combination of SGLT2i increased the risk of developing genital infection during treatment in patients with T2DM, but there was no significant difference in the risk of urinary infection [24]. A 2017 Meta-analysis including 3 RCT studies showed that SGLT2i therapy combined with metformin had no statistically significant difference in the relative risk of urinary tract infection and genital system infection compared with metformin alone [20]. However, results from a Meta-analysis including four RCT studies, 3749 patients, in 2019 showed that SGLT2i combination with metformin compared with metformin or SGLT2i monotherapy, the RR (95% CI) of urinary tract infection for combination therapy was 1.12 (0.77, 1.61) and 0. 97 (0.69, 1.37), respectively; Compared with metformin and SGLT2i monotherapy, and the RR (95% CI) of genital system infection for combination therapy was 2.22 (1.33, 3.72) and 0.69 (0.50, 0. 96), respectively. This result suggested that the increased risk of infection in the urinary tract and reproductive system mainly stems from SGLT2i [18]. A Meta-analysis of the dose and safety of empagliflozin suggested that female patients taking empagliflozin had a significantly higher incidence of genital and urinary tract infections than male patients [27]. Conversely, a 2020

Meta-analysis including 51 RCT studies with 24 371 patients showed that SGLT2i significantly increased the risk of genital infection in T2DM patients, but the risk was independent of the dosage [28]. Subsequently in 2021 the team further explored the overall efficacy of different doses for T2DM patients and showed that high-dose of SGLT2i were more likely to achieve glycemic control targets compared to low-dose of SGLT2i, along with better control in blood pressure and body quality [29]. The risk of urinary and genital infections associated with SGLT2i use in combination with metformin in T2DM patients with renal dysfunction has not been reported.

5.4 ACEIs combined with ARBs in the DKD population, is there an increased risk of hyperkalemia and AKI?

【Recommendations】

- It is recommended that monotherapy with ACEI or ARB is clinically preferred, after gradually adding up to the maximum dose and then adding / switching other drugs to achieve the desired therapeutic goal, and the combination is not recommended [32]. (1a, A)
- Two drug combinations can reduce proteinuria in DKD by dual blockade of the rennin-angiotensin-aldosterone system (RAAS), but the clinical benefit is limited to reduction of proteinuria, and the benefit on GFR is uncertain. There is a certain risk of hyperkalemia and AKI simultaneously [31-35]. （1a，A）

Evidence: ACEI and ARB belong to the RAAS inhibitors and single agent use is effective in controlling blood pressure and reducing urinary protein levels. Multiple Meta-analyses [31-33] showed that the combination of the two drugs significantly reduced the level of proteinuria in diabetic patients, but did not improve the progression of end-stage renal disease, nor did it improve all-cause and cardiovascular mortality [31-33]. Studies have found that in patients with DKD, losartan combined with lisinopril increased the risk of hyperkalemia and AKI, suggesting that the combination of both drugs increased the risk of adverse events [34]. For blood potassium, five Meta-analyses [31-33] all reported that the combination of ARB and ACEI caused a significant increase in blood potassium, but one Meta-analysis in Chinese [56] indicated that the combination of ARB and ACEI did not increase the risk of hyperkalemia. Jennings et al [32] mentioned in their Meta-analysis results of 10 RCT studies that RAAS dual blockade would cause a mean increase in serum potassium of 0.2 mmol / L. In addition, 1 meta-analysis including 42 RCT studies found that DKD patients with macroalbuminuria (> 300 mg / day) had a higher risk of hyperkalemia than those with microalbuminuria (30-300 mg / day) [31]. A Meta-analysis including 32 RCT studies similarly showed that patients with severe DKD (GFR < 60 ml / min or UACR > 1 000 mg / g) had a higher incidence of hyperkalemia and AKI after combination therapy, whereas patients with mild (GFR > 60 ml / min or UACR ≤ 1 000 g / g) had a similar prevalence of hyperkalemia and AKI as monotherapy [33].

5.5 Increased incidence of edema after TZD class drug treatment in T2DM patients with CKD?

【Recommendations】

- Treatment with metformin combined with TZDs increases the risk of edema development

compared with metformin alone [36-39]. (1a, A)

- Suggest that patients at high risk of edema treated with a TZD plus metformin use a small dosage (e. g., pioglitazone 7.5 mg / day) as the starting therapeutic dosage to reduce the risk of edema development [57, 78]. （2a，C）

Evidence: Metformin and TZD class drugs are commonly used for oral therapeutics for T2DM. Often in the clinic, when metformin alone does not achieve the ideal glucose lowering effect, consider combination medication to achieve better glucose lowering effect. At present, 2 domestic Meta-analyses [36-37] and 1 foreign systematic review [38] consistently showed that combination therapy of the two drugs could reduce blood glucose and HbA1c more effectively, while improving lipid metabolism and insulin resistance, but the incidence of simultaneous edema was significantly higher than that of metformin monotherapy. Edema is a known adverse effect associated with TZD class drugs, and its higher incidence of edema up to 11.7% has been reported in both monotherapy and combination with metformin therapy. In addition, a 2018 Meta-analysis investigating the association between oral hypoglycemic agents and the risk of macular edema [39], which included 13 studies, suggested that oral hypoglycemic agents may not be associated with the incidence of macular edema [OR (95% CI) = 1.77 (0. 93, 3.37)]. But TZD class [OR (95% CI) = 2.19 (1.49, 3.21)] was a risk factor for macular edema, and the use of rosiglitazone [OR (95% CI) = 3.12 (1.30, 7.49)] increased the risk for macular edema. In response to the reported influence of TZD class on the risk of edema, a 2018 clinical study with stratified assessment based on routine clinical data and individual trial data (n = 22 379) suggested that female gender and obesity might be among the influencing factors on the risk of edema [78]. The dosage of TZDs as another contributing factor to the risk of edema was mentioned in an RCT on dose-effect [57]: compared with standard and high-dose therapy, low-dose pioglitazone was found to have a significantly lower incidence of peripheral edema in the low-dose (7.5 mg / D) pioglitazone group than in the standard dose group (15 mg / D) (3.7% vs.26.8%, P = 0.001 4), on the basis of lowering blood glucose, regulating lipid metabolism, and improving insulin resistance.

5.6 In patients with diabetes and renal impairment, does the addition of a mineralocorticoid receptor antagonist (MRA) to an ACEI / ARB basic medication increase the risk of developing hyperkalemia?

【Recommendations】

- Low to moderate dose of novel MRA combined with ACEI / ARB is suggested to reduce proteinuria and less cause hyperkalemia in patients with diabetes mellitus associated with renal dysfunction [58]. (1a, C)
- The risk of hyperkalemia can be reduced by thiazides or loop diuretics when used in combination with ACEI / ARB by MRA in patients with diabetes and renal dysfunction [59]. (1a, C)
- In patients with diabetes and renal dysfunction who are at high risk for hyperkalemia, blood potassium management is recommended with ACEI / ARB in combination with Finerenone, while routine blood potassium monitoring is necessary [60-61]. （1a，C）

Evidence:

(1) Several RCT studies have demonstrated that MRA combined with ACEI / ARB could

obviously reduce proteinuria levels in patients with DKD and effectively slow the progression of DKD [40-41, 58, 62]. In patients with persistent microalbuminuria on long-term ACEI / ARB therapy, there was a significant renal benefit from the addition of MRA [63]. Combination use increases a patient's risk of hyperkalemia, leading to discontinuation or dose reduction [62, 64, and 79]. But for most patients, the increase in serum potassium is in a predictable and manageable range. Most hyperkalaemias are asymptomatic, not accompanied by ECG changes, and can be managed by dietary counseling and the short-term use of sodium potassium exchange resin [59]. In patients who withdraw from the study due to hyperkalemia, serum potassium can gradually return to baseline levels after discontinuation of MRA [41, 63].

(2) Multiple studies suggested that low to moderate dose of MRA as an add-on therapy to RAAS inhibitors did not observe hyperkalemia or consequent withdrawal of participants from the trial while showed benefits of lowering blood pressure, reducing urinary protein, and conferring cardiovascular [58, 65-67], most likely because patients were carefully selected, such as excluding patients with a history of hyperkalemia, close follow-up, liberal use of loop or thiazide diuretics as needed, and the relatively short duration of the study. A similar low incidence may not be seen by general clinicians in the routine use of this treatment [68].

(3) Finerenone has not yet been approved in our country. Serum potassium levels and eGFR should be measured before starting treatment. Finerenone therapy may be initiated if serum potassium is ≤ 4.8 mmol / L according to the EU and FDA instructions. If serum potassium is > 4.8 to 5.0 mmol / L, starting Finerenone therapy may be considered, with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum potassium levels. Treatment should not be initiated if serum potassium is > 5.0 mmol / L. Finerenone starting dosage varied according to patient renal function, with eGFR ≥ 60 ml · min^{-1} · (1.73 m^2) $^{-1}$ patient, starting dose at 20 mg / time, 1 time / D, with eGFR ≥ 25 ml · min^{-1} · (1.73 m^2) $^{-1}$ and < 60 ml · min^{-1} · (1.73 m^2) $^{-1}$ patient, starting dose at 10 mg / time, 1 time / D, and those with an eGFR < 25 ml · min^{-1} · (1.73 m^2) $^{-1}$, Finerenone is not recommended.

(4) International large-scale studies such as FIGARO-DKD have shown that in patients with DKD and eGFR > 25 ml · min^{-1} · (1.73 m^2) $^{-1}$, who already have RAAS inhibitors, the addition of Finerenone further improves composite renal and cardiovascular outcomes, decreased proteinuria, and also a small decrease in systolic blood pressure. Routine potassium monitoring in patients with CKD and T2DM is considered appropriate to manage the risk of hyperkalemia, being able to minimize the impact of hyperkalemia. Diuretics or SGLT2i use can reduce risk. Emerging data suggest newer potassium binders may reduce this risk [60, 69].

5.7 In patients with diabetes and CKD, how should they be managed with potassium lowering agents when hyperkalemia is present?

【Recommendations】

- Diabetic patients with CKD who have hyperkalemia can be treated with potassium conjugates for potassium lowering therapy [42]. (1a, A)
- Calcium polystyrene sulfonate (CPS) is recommended for the treatment of hyperkalemia in diabetic patients with CKD when using potassium - like conjugates, especially combined with thiazide diuretics [42]. (1a, A)
- In patients with acute hyperkalemia (when serum potassium is < 6 mmol / L), zirconium

cyclosilicate sodium (SZC) is an optional drug [43]. (1a, A)

- Patiromer reduces serum potassium in T2DM patients with CKD hyperkalemia independent of insulin use [70]. (1b, C)
- When combined with ACEI / ARB, patiromer's medium - and low-dose potassium lowering therapy may be recommended when available [71]. （1b，C）

Evidence: a Cochrane systematic review of potassium binders for hyperkalemia in CKD suggested that there were no statistical differences in the changes of serum potassium, SBP or DBP levels between CPS and sodium polydisulfide propane sulfonate (SPS) groups [42]. In combination with thiazide diuretics, SPS increased the risk of nausea compared to CPS [72]. SZC is the drug of choice in patients with acute hyperkalemia due to its ability to lower serum potassium levels more rapidly, with a recommended starting dose of 10 g three times / D, administered orally, and administered for a maximum of 48 h [43]. And in patients with chronic hyperkalemia, patiromer seems to be the drug of choice [44]. In a retrospective study, patiromer reduced serum potassium in hyperkalemia patients with T2DM and CKD, independent of insulin use [70]. In the AMETHYST-DN（NCT01371747) study [71], patiromer was used with ACEI / ARB alone or in combination with or without spironolactone in patients with DKD, and the results showed that (1) Patiromer (18.6g / D) at moderate doses may cause serum potassium changes in mild hyperkalemia (> 5.0 ~ 5.5 mmol / L); (2) Low dose (8.4 g / D) and moderate dose of patiromer caused changes in serum potassium in moderate hyperkalemia (> 5.5 ~ < 6.0 mmol / L); (3) When applied to diabetic patients with CKD and hyperkalemia, low and moderate dose patiromer did not affect blood glucose. The long-term efficacy and safety follow-up in the AMETHYST-DN study also found that: in heart failure patients with DKD with ACEI / ARB induced hyperkalemia, the use of patiromer was well tolerated with significant efficacy [73].

This article has no conflict of interest.

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